International Labour Organization

Diagnostic and exposure criteria for occupational diseases

Guidance notes for diagnosis and prevention of the diseases in the ILO List of Occupational Diseases (revised 2010)

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▶ Foreword

At its 307th Session (March 2010), the ILO Governing Body approved the list of occupational diseases as revised by the Meeting of Experts on the Revision of the List of Occupational Diseases (Geneva, 27–30 October 2009), which replaces the preceding list annexed to Recommendation No. 194. This new list, which can be referred to as the "ILO List of Occupational Diseases (revised 2010)", is designed to assist countries in the prevention, recording, notification and, if applicable, compensation of diseases caused by work.

In the report of the Meeting of Experts and the discussion of the Governing Body on the new list, the development of guidance on diagnosis and prevention of occupational diseases was considered to be a priority for the application of the list.

This document is a response of the Office to the proposals of the 2009 Meeting of Experts and part of its efforts to promote the application of the new list. A core group of internationally recognized experts was called upon to help in collecting information on national diagnostic criteria and in formulating guidance notes on the diagnosis and prevention of the occupational diseases specified in the ILO List of Occupational Diseases (revised 2010).

The guidance notes reflect the collective wisdom and experts' view of more than 40 international experts who have participated in the technical and consultant meetings on the content creation process, drafting of chapters, sections, or paragraphs, reviewing or commenting on the contents of the guidance notes. The contributions of all the experts, drafters, reviewers and contributors to the drafting, revision and validation of this document are much appreciated. Dr Shengli Niu, Prof Claudio Colosio, Dr Michele Carugno, and Dr Anil Adisesh have reviewed, validated, finalized, and edited the guidance notes submitted by the individual drafters.

The guidance notes provide information and criteria to be considered in the diagnosis and prevention of the diseases included in the ILO List of Occupational Diseases (revised 2010). It is intended for the use of competent authorities, social security institutions, workers' compensation funds, occupational safety and health professionals, physicians, employers and workers, and persons in charge of recording, notification, prevention, and compensation programmes for occupational diseases.

I should note that the responsibility for opinions and criteria presented in this publication rests solely with the experts who contributed to the drafting and review, and that the publication of this document does not constitute an endorsement by the ILO or the institutions with which the experts, drafters, reviewers, and contributors are affiliated.

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Chief

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▶ Preface

According to the Protocol of 2002 to the Occupational Safety and Health Convention, 1981 (No. 155), the term "occupational disease" covers any disease contracted as a result of an exposure to risk factors arising from work activity. The Employment Injury Benefits Recommendation, 1964 (No. 121), Paragraph 6(1), defines occupational diseases in the following terms: "Each Member should, under prescribed conditions, regard diseases known to arise out of the exposure to substances and dangerous conditions in processes, trades or occupations as occupational diseases."

Two main elements are present in the definition of occupational disease:

- the causal relationship between exposure in a specific working environment or work activity and a specific disease; and
- the fact that the disease occurs among a group of exposed persons with a frequency above the average morbidity of the rest of the population.

The causal relationship is established on the basis of clinical and pathological data, occupational background and job analysis, identification and evaluation of occupational risk factors and of the role of other risk factors.

As a general rule, the symptoms and signs alone are not sufficiently characteristic to enable an occupational disease to be diagnosed as such without the knowledge of the pathological changes engendered by the physical, chemical, biological or other factors encountered in the exercise of an occupation.

Identification of occupational diseases has an impact not only on provisions of the employment injury benefits, but also on national and on enterprise level preventive programmes. The ILO has had a long history in identification of diseases as occupational in origin for the purpose of their prevention and compensation. In 1919, the year of the creation of the ILO, anthrax and lead poisoning were declared as occupational diseases at the first International Labour Conference. In 1925, Convention No. 18 on Workmen's Compensation established the first ILO List of Occupational Diseases. In 1934, Convention No. 18 was revised and a new Workmen's Compensation Convention (No. 42) was adopted with a new ILO List of Occupational Diseases. In 1964, the International Labour Conference adopted the Employment Injury Benefits Convention (No. 121), which was appended with a list of occupational diseases in Schedule I. This Schedule was amended in 1980.

The List of Occupational Diseases Recommendation, 2002, (No. 194) adopted by the International Labour Conference in 2002 annexed a list of occupational diseases which was revised in 2010. The revised 2010 ILO List of Occupational Diseases represents the most recent ILO work in this regard. Recommendation No. 194 encourages ILO Member States to establish their national lists of occupational diseases for the purposes of prevention, recording, notification and, if applicable, compensation, and to comprise in their national lists, to the extent possible, the diseases contained in the Annex to the Recommendation. This 2010 ILO List includes both specific occupational diseases arising from work activities and open items that allow the recognition of a disease not listed as occupational in origin where a direct link is established scientifically, or determined by methods appropriate to national conditions and practice, between the exposure arising from work activities and the disease contracted by the worker.

The 2010 ILO List is structured with four sections:

1) Occupational diseases caused by exposure to agents arising from work activities (chemical, physical, biological agents and infectious or parasitic diseases)
2) Occupational diseases by target organ systems (respiratory diseases, skin diseases, musculoskeletal disorders, and mental and behavioural disorders)
3) Occupational cancer
4) Other diseases

When the 2010 ILO List was adopted by the ILO Governing Body at its 307th session in March 2010, guidance on diagnosis of occupational diseases was considered to be needed for the practical implementation of the new list and for the prevention of the diseases in the list. As a response, soon after the adoption of the 2010 ILO List, a core group of internationally recognized experts was called upon to help the Office in collecting and compiling useful information which could be used as reference material to help in the identification and diagnosis of occupational diseases. The group was initially formed by the members of the WHO Global Working Group on Occupational Health in ICD-11 and was composed of experts who worked at national and international levels on the identification, recognition and diagnosis of occupational diseases. The 2010 ILO List of Occupational Diseases includes about 100 specified types or groups of diseases caused by hazardous agents, diseases classified by target organ systems or included under the categories of occupational cancer and other diseases. More than 40 experts have worked throughout a timespan of ten years on this activity. Most of the experts contributed their expertise and knowledge on a voluntary basis.

Experts in the core group were assigned to prepare guidance notes on the diagnosis and prevention of the diseases included in the 2010 ILO List of Occupational Diseases based on their expertise, experience and professional work activities. Several meetings of the core experts group were held to agree on the framework and the templates to be used as the guidance notes on the diagnosis of the diseases specified in the 2010 ILO List. The experts were asked to prepare the draft notes preferably in consultation with their working teams in their affiliated institutions or through their professional technical networks. The draft notes were reviewed and discussed at group meetings or through e-mail. The convenors of the core experts group coordinated and arranged the review, by the group, of the work submitted by the individual experts. The criteria proposed by the drafters were double-checked, and validated before the finalization of the guidance notes, and the diseases discussed in the guidance notes were identified with their corresponding codes in both the ICD-10 and ICD-11.

This publication is intended to assist ILO Member States in the recognition of the diseases specified in the 2010 ILO List as occupational in origin and in their inclusion in the national lists for the purpose of their prevention, recording, notification and, if applicable, compensation.

A guidance note was prepared for each type or group of the disease items specified in the 2010 ILO List according to the following structure:

1) For occupational diseases caused by exposure to agents arising from work activities:
    a. General characteristics of the causal agent
    b. Occupational exposures
    c. Toxicological profile (for chemical agents) or biological mechanisms (for physical and biological agents), main health effects and diagnostic criteria
    d. Key actions for prevention
    e. Further reading

2) For occupational diseases by target organ systems:
   a. Short profile of the aetiopathogenesis
   b. Occupational exposures
   c. Main health effects and diagnostic criteria
   d. Key actions for prevention
   e. Further reading
3) For occupational cancer:
   a. General characteristics of the causal agent
   b. Occupational exposures
   c. Carcinogenic mechanisms, main health effects and diagnostic criteria
   d. Key actions for prevention
   e. Further reading
4) For specific diseases caused by occupations or processes, the structure mentioned under the above 2) was used.

In the diagnostic criteria part, when appropriate, a minimum duration of exposure (defined as the minimum period of time needed by the noxious agent to cause the disease) and a maximum latent period (defined as the time window between the beginning of the occupational exposure and the disease onset, unless otherwise specified) were proposed based on the experience of the experts in the core group. The experts in the core group also agreed that, when there was a difference between proposals, the shortest minimum duration of exposure and the longest maximum latent period would be preferred.

In the "Further reading" sections, the key reference materials that were consulted to support the drafting of the guidance notes have been listed. More detailed information on the topics concerned can be found in these references.

The guidance notes are based on information from authoritative sources and the collective wisdom of the drafters, reviewers and contributors and are edited by the Office. The individual viewpoints presented in this publication are ultimately those of the experts and not of their institutions or the International Labour Organization.

Part I.

ILO List of Occupational Diseases[1] (revised 2010)

1 In the application of this list the degree and type of exposure and the work or occupation involving a particular risk of exposure should be taken into account when appropriate.

1 Occupational diseases caused by exposure to agents arising from work activities

1.1 Diseases caused by chemical agents

1.1.1 Diseases caused by beryllium or its compounds
1.1.2 Diseases caused by cadmium or its compounds
1.1.3 Diseases caused by phosphorus or its compounds
1.1.4 Diseases caused by chromium or its compounds
1.1.5 Diseases caused by manganese or its compounds
1.1.6 Diseases caused by arsenic or its compounds
1.1.7 Diseases caused by mercury or its compounds
1.1.8 Diseases caused by lead or its compounds
1.1.9 Diseases caused by fluorine or its compounds
1.1.10 Diseases caused by carbon disulfide
1.1.11 Diseases caused by halogen derivatives of aliphatic or aromatic hydrocarbons
1.1.12 Diseases caused by benzene or its homologues
1.1.13 Diseases caused by nitro- and amino-derivatives of benzene or its homologues
1.1.14 Diseases caused by nitroglycerine or other nitric acid esters
1.1.15 Diseases caused by alcohols, glycols or ketones
1.1.16 Diseases caused by asphyxiants like carbon monoxide, hydrogen sulfide, hydrogen cyanide or its derivatives
1.1.17 Diseases caused by acrylonitrile
1.1.18 Diseases caused by oxides of nitrogen
1.1.19 Diseases caused by vanadium or its compounds
1.1.20 Diseases caused by antimony or its compounds
1.1.21 Diseases caused by hexane
1.1.22 Diseases caused by mineral acids
1.1.23 Diseases caused by pharmaceutical agents
1.1.24 Diseases caused by nickel or its compounds
1.1.25 Diseases caused by thallium or its compounds
1.1.26 Diseases caused by osmium or its compounds
1.1.27 Diseases caused by selenium or its compounds
1.1.28 Diseases caused by copper or its compounds
1.1.29 Diseases caused by platinum or its compounds
1.1.30 Diseases caused by tin or its compounds
1.1.31 Diseases caused by zinc or its compounds
1.1.32 Diseases caused by phosgene
1.1.33 Diseases caused by corneal irritants like benzoquinone
1.1.34 Diseases caused by ammonia
1.1.35 Diseases caused by isocyanates
1.1.36 Diseases caused by pesticides
1.1.37 Diseases caused by sulphur oxides
1.1.38 Diseases caused by organic solvents
1.1.39 Diseases caused by latex or latex-containing products

1.1.40 Diseases caused by chlorine

1.1.41 Diseases caused by other chemical agents at work not mentioned in the preceding items where a direct link is established scientifically, or determined by methods appropriate to national conditions and practice, between the exposure to these chemical agents arising from work activities and the disease(s) contracted by the worker

1.2 Diseases caused by physical agents

1.2.1 Hearing impairment caused by noise

1.2.2 Diseases caused by vibration (disorders of muscles, tendons, bones, joints, peripheral blood vessels or peripheral nerves)

1.2.3 Diseases caused by compressed or decompressed air

1.2.4 Diseases caused by ionizing radiations

1.2.5 Diseases caused by optical (ultraviolet, visible light, infrared) radiations including laser

1.2.6 Diseases caused by exposure to extreme temperatures

1.2.7 Diseases caused by other physical agents at work not mentioned in the preceding items where a direct link is established scientifically, or determined by methods appropriate to national conditions and practice, between the exposure to these physical agents arising from work activities and the disease(s) contracted by the worker

1.3 Biological agents and infectious or parasitic diseases

1.3.1 Brucellosis

1.3.2 Hepatitis viruses

1.3.3 Human immunodeficiency virus (HIV)

1.3.4 Tetanus

1.3.5 Tuberculosis

1.3.6 Toxic or inflammatory syndromes associated with bacterial or fungal contaminants

1.3.7 Anthrax

1.3.8 Leptospirosis

1.3.9 Diseases caused by other biological agents at work not mentioned in the preceding items where a direct link is established scientifically, or determined by methods appropriate to national conditions and practice, between the exposure to these biological agents arising from work activities and the disease(s) contracted by the worker

2 Occupational diseases by target organ systems

2.1 Respiratory diseases

2.1.1 Pneumoconioses caused by fibrogenic mineral dust (silicosis, anthraco-silicosis, asbestosis)

2.1.2 Silicotuberculosis

2.1.3 Pneumoconioses caused by non-fibrogenic mineral dust

2.1.4 Siderosis

2.1.5 Bronchopulmonary diseases caused by hard-metal dust

2.1.6 Bronchopulmonary diseases caused by dust of cotton (byssinosis), flax, hemp, sisal or sugar cane (bagassosis)

2.1.7 Asthma caused by recognized sensitizing agents or irritants inherent to the work process

2.1.8 Extrinsic allergic alveolitis caused by the inhalation of organic dusts or microbially contaminated aerosols, arising from work activities

2.1.9 Chronic obstructive pulmonary diseases caused by inhalation of coal dust, dust from stone quarries, wood dust, dust from cereals and agricultural work, dust in animal stables, dust from textiles, and paper dust, arising from work activities

2.1.10 Diseases of the lung caused by aluminium

2.1.11 Upper airways disorders caused by recognized sensitizing agents or irritants inherent to the work process

2.1.12 Other respiratory diseases not mentioned in the preceding items where a direct link is established scientifically, or determined by methods appropriate to national conditions and practice, between the exposure to risk factors arising from work activities and the disease(s) contracted by the worker

2.2 Skin diseases

2.2.1 Allergic contact dermatoses and contact urticaria caused by other recognized allergy-provoking agents arising from work activities not included in other items

2.2.2 Irritant contact dermatoses caused by other recognized irritant agents arising from work activities not included in other items

2.2.3 Vitiligo caused by other recognized agents arising from work activities not included in other items

2.2.4 Other skin diseases caused by physical, chemical or biological agents at work not included under other items where a direct link is established scientifically, or determined by methods appropriate to national conditions and practice, between the exposure to risk factors arising from work activities and the skin disease(s) contracted by the worker

2.3 Musculoskeletal disorders

2.3.1 Radial styloid tenosynovitis due to repetitive movements, forceful exertions and extreme postures of the wrist

2.3.2 Chronic tenosynovitis of hand and wrist due to repetitive movements, forceful exertions and extreme postures of the wrist

2.3.3 Olecranon bursitis due to prolonged pressure of the elbow region

2.3.4 Prepatellar bursitis due to prolonged stay in kneeling position

2.3.5 Epicondylitis due to repetitive forceful work

2.3.6 Meniscus lesions following extended periods of work in a kneeling or squatting position

2.3.7 Carpal tunnel syndrome due to extended periods of repetitive forceful work, work involving vibration, extreme postures of the wrist, or a combination of the three

2.3.8 Other musculoskeletal disorders not mentioned in the preceding items where a direct link is established scientifically, or determined by methods appropriate to national conditions and practice, between the exposure to risk factors arising from work activities and the musculoskeletal disorder(s) contracted by the worker

2.4 Mental and behavioural disorders

2.4.1 Post-traumatic stress disorder

2.4.2 Other mental or behavioural disorders not mentioned in the preceding item where a direct link is established scientifically, or determined by methods appropriate to national conditions and practice, between the exposure to risk factors arising from work activities and the mental and behavioural disorder(s) contracted by the worker

3 Occupational cancer

3.1 Cancer caused by the following agents

3.1.1 Asbestos

3.1.2 Benzidine and its salts

3.1.3 Bis-chloromethyl ether (BCME)

3.1.4 Chromium VI compounds

3.1.5 Coal tars, coal tar pitches or soots

3.1.6 Beta-naphthylamine

3.1.7 Vinyl chloride

3.1.8 Benzene

3.1.9 Toxic nitro- and amino-derivatives of benzene or its homologues

3.1.10 Ionizing radiations

3.1.11 Tar, pitch, bitumen, mineral oil, anthracene, or the compounds, products or residues of these substances

3.1.12 Coke oven emissions

3.1.13 Nickel compounds

3.1.14 Wood dust

3.1.15 Arsenic and its compounds

3.1.16 Beryllium and its compounds

3.1.17 Cadmium and its compounds

3.1.18 Erionite

3.1.19 Ethylene oxide

3.1.20 Hepatitis B virus (HBV) and hepatitis C virus (HCV)

3.1.21 Cancers caused by other agents at work not mentioned in the preceding items where a direct link is established scientifically, or determined by methods appropriate to national conditions and practice, between the exposure to these agents arising from work activities and the cancer(s) contracted by the worker

4 Other diseases

4.1 Miners' nystagmus

4.2 Other specific diseases caused by occupations or processes not mentioned in this list where a direct link is established scientifically, or determined by methods appropriate to national conditions and practice, between the exposure arising from work activities and the disease(s) contracted by the worker

Part II.

Guidance notes for diagnosis and prevention of the diseases specified in the ILO List of Occupational Diseases (revised 2010)

1. Occupational diseases caused by exposure to agents arising from work activities

1.1. Diseases caused by chemical agents

1.1.1 Diseases caused by beryllium or its compounds	ICD Code T56.7 +Z57
General characteristics of the causal agent	Beryllium (Be), CAS number 7440-41-7, is a chemical element with one stable isotope (^{9}Be) and a mean atomic mass of 9.01 Da. It is situated in Group 2 (2-A; Alkali earths) of the periodic table and has only one oxidation number (II). Beryllium is the lowest density metal in the periodic table (1.85 g·cm^{-3}). Metallic beryllium is steel-grey in colour. It is mechanically strong (with high tensile strength), and light-weight. It is non-sparking, non-magnetic, has excellent thermal conductivity, is corrosion resistant, and has one of the highest melting points of the light metals (1,287°C). A surface layer of beryllium oxide will protect the underlying metal from further oxidation in air and water. Unprotected metal reacts with acids to yield soluble Be (II) tetra-hydrated and oligomeric oxygen-bridged species, which in turn undergo extensive hydrolysis in water to yield acidic solutions. Soluble beryllium salts taste sweet, hence the previous alternative chemical name of the element, glucinium. Beryllium occurs in the environment only in the form of its compounds. Its commonest ores are beryl (double silicate of aluminium and beryllium) and bertrandite (beryllium hydroxosilicate). Very pure gem-quality beryls are known as blue-green aquamarine and green emerald. Beryllium extraction from beryl and bertrandite ores is known to take place industrially only in the USA, China and Kazakhstan. In 2020, the USA was the largest manufacturer and exporter of beryllium. Processing uses corrosive chemicals and high temperatures to produce beryllium hydroxide. The elemental metal is obtained by electrolysis of beryllium hydroxide or by thermal reduction with magnesium. In the chemical industry beryllium compounds are used as Lewis acids in catalysts. Beryllium oxide is the bulk constituent of ceramic materials with electrical conducting properties employed in high technology applications. It is the starting material to produce beryllium metal, that is used primarily as a hardening agent in alloys (it is no longer used in fluorescent lamps). *Beryllium-copper* (up to 4% beryllium) is the most common beryllium-containing alloy, prepared by fusing beryllium oxide with copper. It is characterized by high electrical conductivity, wide temperature tolerance, high elasticity and fatigue strength, and corrosion resistance. Because of these properties, copper-beryllium alloys are used extensively in industry: • in mechanical parts subject to high wear or extreme vibration, e.g. in bearings, cams, gears, and corrosion-resistant springs in automobiles, • in electrical contacts, switches, relays and connectors, • in high-end industries and applications (especially defence industries), such as aerospace, electronics, radar, telecommunications, computers, civil and military nuclear appliances, • in the manufacture of: - high strength non-sparking tools, - casts for moulding metal, glass, and plastic items, - some alloys for dental use, - consumer goods such as sports equipment (golf clubs and bicycle frames), - ceramics installed in microwave ovens. *Beryllium-aluminium* (<1-60% beryllium) is used in high technology applications, such as aircraft, scientific devices on spacecraft, defence avionics, packaging, high resolution medical and industrial X-ray equipment. *Beryllium-nickel* (0.275-7% beryllium) has high tensile strength and has age-hardening characteristics. Among its uses are diamond drill-bit matrices, watch balance wheels and airplane brakes.
Occupational exposures	Occupational exposure to beryllium dusts and fumes occurs in all phases of metal extraction and refining. In the preparation of its alloys into usable goods (processing by melting, grinding, welding, drilling), and in the decommissioning and recycling of items and waste materials. Recycling of end-life manufactured goods for valuable constituents can be a source of high exposure, especially in the informal sector, where precautions may not be taken. About 1% to 15% of workers using beryllium are thought to be exposed to levels that are unsafe. Since beryllium is predominantly used as an alloy with copper, aluminium and nickel, the importance of co-exposure with other metals like these has to be considered (for each metal, see the corresponding item).

1.1.1 Diseases caused by beryllium or its compounds — ICD Code T56.7 +Z57

Toxicological profile, main health effects and diagnostic criteria

Short toxicological profile	Beryllium induces immunologic reactions in exposed and sensitized individuals, by triggering a type IV hypersensitivity response to beryllium antigen in T lymphocytes. White blood cells accumulate around beryllium-containing solid particles (e.g. beryllium oxide and alloys, the most important being beryllium-copper alloy) without being able to phagocytise and clear them from tissue. Lung mononuclear cell inflammation and granuloma formation is maintained by the accumulation in lung tissue of CD4 memory T cells specific for beryllium. Granulomas most often form in the lung, since inhalation is by far the most common entry route of beryllium dusts. However, very fine beryllium particles can travel through the body by the lymphatic route to organs such as the liver and the skin, where granulomas may progressively enlarge. The dividing lines between acute irritant effects, beryllium sensitization, and chronic beryllium disease are unclear. Progression from exposure to sensitization, and to chronic beryllium disease partly depends on genetic susceptibility. Beryllium causes dermatitis and lung diseases, which include acute berylliosis, chronic beryllium disease and lung cancer. The IARC recognizes beryllium and beryllium compounds as a Group 1 carcinogen (see item 3.1.16).

Name of the diseases and ICD code: **Acute beryllium disease** *(Specific disease code)* **+T56.7 +Z57**

Berylliosis (lung) (J63.2), Acute bronchitis and pneumonitis (J68.0), Upper respiratory inflammation (J68.2), Pulmonary oedema (J68.1), Acute conjunctivitis (H10.2), Allergic contact dermatitis (L23), Irritant contact dermatitis (L24)

Short description of the disease

Acute beryllium disease is now far rarer than in the 20th century. The acute effects typically involve the skin and the respiratory system. The eye can be affected with either conjunctivitis or contact sensitization. Contact dermatitis can be either irritant or allergic. The acute respiratory effects can range from a mild inflammation of the nasopharynx, trachea and bronchi to a severe pneumonitis, presumed to be of chemical origin. Acute beryllium disease may be part of a spectrum of sensitization to beryllium since the skin manifestations often precede the onset of pneumonitis, suggesting a delayed type hypersensitivity. Signs and symptoms include malaise and weight loss, dyspnoea, fever, cough (sometimes with haemoptysis); breathlessness may be present with infiltrates seen on chest X-ray. Avoiding further exposure often leads to resolution, but there may be some chronic lung fibrosis.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms:
  - Acute beryllium disease can affect the skin, mucous membranes and respiratory tract causing dermatitis, rhinitis, pharyngitis, tracheobronchitis, and pneumonitis.
  - Acute pneumonitis is potentially the most serious consequence of acute exposure to very high levels of soluble beryllium salts. The main presenting symptom is shortness of breath; malaise, anorexia, and weight loss are also common findings.
  - The clinical course of acute beryllium disease is very variable. It may range from mild, self-limiting illness, to persistent chronic disease, or rapidly progressive and fatal disease. Fibrosis may develop among individuals surviving an acute episode.
  - Ulceration and subcutaneous granulomas develop if small beryllium crystals penetrate the skin.
- Examinations:
  - Chest auscultation may reveal crackles or wheezes.
  - Chest X-ray may show increased broncho-vascular markings, diffuse bilateral alveolar infiltrates or severe bilateral pulmonary oedema.

Exposure assessment

- History of occupational exposure: confirmed occupational exposure to beryllium or its salts (exposures are typically very high). If available, monitoring of workplace air concentrations. Acute respiratory symptoms leading to pneumonitis might require concentrations as high as 25 µg/m^3. On the other hand, sensitization can occur at beryllium levels lower than 0.02 µg/m^3. The blood Beryllium Lymphocyte Proliferation Test (BeLPT) is an in-vitro measure of the beryllium antigen-specific cell-mediated immune response, and is a marker of past exposure.
- Minimum duration of exposure: in sensitized individuals, even a single exposure can lead to health effects.
- Maximum latent period: a few days following very high pulmonary short-term exposure, or weeks following prolonged exposure at lower concentrations (depending on the intensity of exposure). For skin manifestations, two weeks from first exposure to occurrence of the dermatitis, except in the case of heavy exposures, when an irritant reaction may be immediate. One month for granulomas.

For allergic and irritant contact dermatoses, refer to item 2.2.1 and 2.2.2, respectively.

1.1.1 Diseases caused by beryllium or its compounds — ICD Code T56.7 +Z57

Name of the diseases and ICD code: **Chronic beryllium disease (CBD)** *(Specific disease code)* **+T56.7 +Z57**

Chronic berylliosis (J63.2), Hepatic granulomas (K75), Granulomatous nodular skin lesions (L92.8)

Short description of the disease

Chronic beryllium disease (CBD) was first described in the USA in fluorescent lamp workers. It consists of a chronic granulomatous disorder affecting lungs, liver and skin, caused by a cell-mediated sensitization to beryllium (a type IV hypersensitivity reaction). It follows the inhalation of fumes and respirable dusts of beryllium salts, oxides and alloys. There is no evidence that treatment changes the natural history of subclinical CBD. While removal from further exposure is advised, there is no evidence whether this improves outcome, and after hypersensitivity to self-tissues is established, a progression to CBD can occur years after exposure has ceased. Beryllium poisoning can produce hepatomegaly, hepatonecrosis, and granulomas, with beryllium containing nodules similar to the lesions observed in sarcoidosis.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: CBD is characterized by dyspnoea on exertion, weight loss, non-productive cough, fatigue, chest pain, anorexia, and weakness. Symptoms progress in severity over a long period. Advanced cases display clubbing of the fingers and a combination of fibrosis and active interstitial inflammation. *Cor pulmonale* can develop and is a cause of death in very advanced cases.
- Examinations:
  - Crackles on chest auscultation.
  - Impaired performance in exercise testing.
  - Restrictive or mixed obstructive/restrictive changes in lung function.
  - Reduction of carbon monoxide diffusing capacity (D_{LCO}).
  - Chest X-ray might reveal a reticulonodular infiltrate.
  - CT scan may identify parenchymal nodules, septal lines, ground glass opacities and hilar or mediastinal adenopathy.
  - Abdominal ultrasonography and liver biopsy may show evidence of granulomas.
  - Increased total white cells with CD4+ T lymphocyte predominance on bronchoalveolar lavage (BAL). BeLPT can be undertaken on lavage fluid.
  - Histological evidence of non-caseating granulomas in bronchial tissue on either transbronchial biopsy or thoracoscopic lung biopsy.
  - Positive BeLPT (CBD is characterized by a Type IV, cell-mediated delayed hypersensitivity reaction).

New tests are under evaluation including beryllium stimulated neopterin test and beryllium specific cytokine proliferation tests.

Classification

Three diagnostic groups have been proposed:

1. Beryllium sensitization:
   a. Evidence of a beryllium-specific immune response as indicated by
      i. abnormal blood BeLPT or
      ii. positive beryllium skin patch test.
   b. No evidence of granuloma on lung biopsy.
2. Subclinical CBD:
   a. Evidence of a beryllium-specific immune response (see 1.a).
   b. Histopathological changes on lung biopsy consistent with CBD such as
      i. non-caseating granulomas, and
      ii. mononuclear cell infiltrate.
   c. No respiratory symptoms or physiological abnormalities.
3. Clinically evident CBD:
   a. 2.a + 2.b and
   b. signs and symptoms as described above.

1.1.1 Diseases caused by beryllium or its compounds ICD Code T56.7 +Z57

Exposure assessment

- History of occupational exposure: confirmed occupational exposure to beryllium, and workplace monitoring data, if available.
- Minimum duration of exposure: beryllium sensitization may occur as early as a few months after initial exposure.
- Maximum latent period: On average, CBD develops six to ten years after exposure, but has been reported to occur as early as three months after initial exposure, or with a latency up to 40 years.

Name of the diseases and ICD code: **Occupational lung cancer due to beryllium**
(Specific disease code) **+T56.7 +Z57**

Lung cancer (C34)

Refer to item 3.1.16.

Key actions for prevention	The technological uses of beryllium are unlikely to be eliminated in the foreseeable future, and might expand in the production of high technology end products. Because beryllium is persistent in the body, the most effective prevention of beryllium-related disease is avoidance of exposure by adopting the most stringent level of precaution. This is made easier by the fact that the manipulation of beryllium often occurs in manufacturing shops of high technology industry, where the products are protected from contamination through the workers' use of full-cover suits, facemasks and gloves. The protection of workers stems from the avoidance of skin and eye contact. Therefore, extraction, metallurgy, lower-level manufacturing and recycling are the industrial sectors where higher exposure can occur and need particular attention from safety and health professionals. Proximity or indirect exposure of workers may result in hazardous levels. "Take home" contamination of work clothing can expose families, effluents from plants can expose the general population, and both can cause disease. To assess exposure to airborne beryllium dusts, measurement by air sampling of the personal breathing zone is preferred to area /background sampling. Various occupational exposure limits are suggested or enforced in different countries. In 2018, the USA Occupational Health and Safety Administration reduced the Permissible Exposure Limit for beryllium to 0.2 µg/m^3, but it is possible that chronic beryllium disease will occur at exposures lower than this. The American Conference of Governmental Industrial Hygienists (ACGIH) recommends a non-mandatory 8hr time-weighted average Threshold Limit Value (TLV-TWA) in air of 0.05 µg/m^3, and this is used in a number of countries. Health surveillance using the blood beryllium lymphocyte proliferation test (BeLPT) is widely recommended as a biomarker of exposure. The sensitivity of a single test is mediocre, but improves with repeated testing. The interpretation of a single positive BeLPT is problematic, and if facilities are available, bronchoalveolar lavage (BAL) and transbronchial biopsy of any lesions could be undertaken. A single positive BAL BeLPT is considered diagnostic of beryllium sensitization. Following sensitization, removal from further exposure is advised, but there is little evidence that this improves outcome.

Further reading

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1.1.1 Diseases caused by beryllium or its compounds — ICD Code T56.7 +Z57

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For the chemical entities listed below an entry exists in the collection of International Chemical Safety Cards (ICSC) hosted in the ILO website

Name	Synonyms	ICSC
Beryllium	Glucinium	0226
Beryllium oxide	Beryllia, Beryllium monoxide	1325
Beryllium sulphate		1351
Beryllium nitrate		1352
Beryllium carbonate	Beryllium basic carbonate	1353
Beryllium chloride		1354
Beryllium fluoride	Beryllium difluoride	1355

▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
1.1.1	Toxic effects of beryllium and its compounds	T56.7	NE61 & XM4QG7
1.1.1	Berylliosis (acute/chronic)	J63.2	CA60.6
1.1.1	Acute bronchitis and pneumonitis	J68.0	CA81.0
1.1.1	Upper respiratory inflammation	J68.2	CA81.2
1.1.1	Pulmonary oedema	J68.1	CA81.1
1.1.1	Conjunctivitis	H10.2	9A60.Z
1.1.1	Allergic contact dermatitis	L23	EK00
1.1.1	Irritant contact dermatitis	L24	EK02
1.1.1	Skin ulceration	L98.4	ME60.Z
1.1.1	Granulomatous nodular skin lesions	L92.8	EE8Y
1.1.1	Hepatic granulomas	K75	DB97.1
1.1.1	Lung cancer	C34	2C25.Z
	Occupational exposure to risk factors	Z57	QD84.Y

1.1.2 Diseases caused by cadmium or its compounds	ICD Code T56.3 +Z57
General characteristics of the causal agent	Cadmium (Cd), CAS number 7440-43-9, is the chemical element with atomic number 48 in the periodic table of the elements. It has several stable isotopes between ^{106}Cd and ^{116}Cd, with ^{114}Cd and ^{112}Cd being the most abundant (24% and 29%, respectively). Its mean atomic mass is 112.4 Da. Cadmium belongs to Group 12 (2-B; Transition metals) in the element families and features only the oxidation number II. Cadmium is a silver-white, malleable metal, which has a low melting point (327°C) and is highly resistant to corrosion, although its standard reduction potential is at -0.40 V due to the protection afforded by the superficial oxide layer. Cadmium metal dissolves in mineral acids with the production of flammable hydrogen gas, and its dust reacts exothermically with hydrogen azide, sulphur, selenium and tellurium and oxidants. These reactions present a fire and explosion hazard. Cadmium has many chemical and physical similarities to zinc and occurs together with zinc in several minerals. It is a by-product of smelting zinc and some lead ores. The main cadmium compounds are cadmium acetate, cadmium sulphide, cadmium sulpho-selenide, cadmium stearate, cadmium oxide, cadmium carbonate, cadmium sulphate, and cadmium chloride. Exposure of the general population to cadmium has occurred through ingestion of contaminated rice and other foods, and possibly through drinking-water. Cigarettes contain relatively high levels of cadmium, which derives naturally from the metal accumulated by the leaves and stems of tobacco grown in soil containing cadmium. This source contributes significantly to the non-occupational exposure of smokers.
Occupational exposures	About 80% of cadmium industrial usage is represented by manufacturing of nickel-cadmium batteries. Other uses include electroplating (mainly of iron and steel), paint pigments, and stearate heat stabilization in polyvinyl chloride (PVC) plastics. Cadmium can also be found as an impurity in other metals (zinc, lead and copper), in fossil fuels (coal, oil, gas, peat and wood), in cement, and in phosphate fertilizers. This latter source may be as high as 300 grams per ton of extracted phosphate and the use of such material in the production of fertilizers results in contamination of agricultural soils. Among the inorganic salts of cadmium, the most industrially important is cadmium stearate, followed by cadmium sulphide and cadmium sulphoselenide, which are used as yellow and red pigments in plastics and other materials. Cadmium sulphide is also used in photo- and solar cells. Cadmium chloride is the main chemical form of cadmium used in electroplating, and has a minor use as a fungicide, colorant for pyrotechnics, an additive in tinning solutions, and mordant in dyeing and printing textiles. Minor uses include the production of special photographic films and the manufacture of specialised mirrors and coatings for electronic vacuum tubes. Cadmium oxide is used in electroplating, in the preparation of PVC heat stabilizers, and as a component of silver alloys, phosphors, semiconductors, and glass-ceramic glazes. Cadmium fumes are generated in potentially toxic concentrations in the production of cadmium alloys, in welding, and oxyacetylene cutting of cadmium coated steel and rivets. Also in the smelting, melting, and refining of metals that contain cadmium. Cadmium accumulates in food crops and drinking water (in which it remains soluble at pH levels around neutral), and ingestion often adds to occupational exposures. Absorption of cadmium from the gut increases in iron deficiency, and workers with poor diets and menstruating females are at higher risk of toxicity. Summarizing, workers may be exposed to cadmium, in occupational settings, through the inhalation of oxide fumes generated during heating or welding of cadmium-containing materials, or inhalation of particles of metal, oxide and pigment dust. The highest occupational exposures to cadmium occur in industries involving smelting and refining of metals, metal machining, battery manufacture, electroplating, plastics, ceramics, paint, and welding operations.

1.1.2 Diseases caused by cadmium or its compounds — ICD Code T56.3 +Z57

Toxicological profile, main health effects and diagnostic criteria

Short toxicological profile	Cadmium does not have any physiological function, and exerts toxicity by a number of different mechanisms, particularly affecting mitochondria. It is known to increase oxidative stress by acting as a catalyst in the formation of reactive oxygen species, increasing lipid peroxidation, and depleting glutathione and protein-bound sulfhydryl groups. Cadmium stimulates the production of inflammatory cytokines and down-regulates the protective function of nitric oxide formation. Once absorbed from the respiratory and gastrointestinal tracts, cadmium binds to metallothionein, an abundant protein carrier of transition metal ions and semi-metals. Circulating cadmium (bound to glutathione and metallothionein) accumulates over time in the body and some is permanently retained in the kidney. In consequence, the kidneys (in particular kidney tubules) are the main target of cadmium toxicity. Due to its similarity to calcium, absorbed cadmium accumulates in the bones. Cadmium is excreted in urine, largely as cadmium-metallothionein complex, but the rate of excretion is low. This results in a very long biological half-life of about fifteen to thirty years. Inhalation of cadmium fume gives respiratory symptoms accompanied by fever and systemic malaise, and high exposures can result in death. Thus, the lungs are a target organ in acute high-level exposures to inhaled cadmium fumes, while the kidneys and the skeletal systems are mainly affected by chronic toxic effects of cadmium exposure. Cadmium and cadmium compounds have been classified by IARC as carcinogenic to humans (Group 1) (see item 3.1.17).

Name of the diseases and ICD code: **Acute diseases caused by cadmium or its compounds**
(Specific disease code) **+T56.3 +Z57**

Acute chemical bronchitis and pneumonitis (J68.0), Reactive airways dysfunction syndrome (RADS) (J68.3), Acute chemical pulmonary oedema (J68.1)

Short description of the disease

Inhalation of cadmium fumes causes profound damage to the respiratory system; rhinitis, tracheo-bronchitis, pneumonitis, reactive airways dysfunction syndrome (RADS) and pulmonary oedema. Symptoms may appear 4 to 10 hours after exposure. Initial symptoms resemble a flu-like illness, with chills, fever, and myalgia. Later symptoms include chest pain, cough, and dyspnoea. Bronchospasm and haemoptysis may also occur. It has been estimated that an 8-hour exposure to 5 mg/m^3 may be lethal. The immediately dangerous to life or health level (IDLH) is estimated at 1 mg/m^3 per 8 hours. Ingestion of large amounts of cadmium may occur accidentally by hand-mouth contact from cadmium-contaminated hands or food. As little as 10 mg is sufficient to cause severe erosion of the gastrointestinal tract, while more than 100 mg is considered to be lethal.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: following inhalation, symptoms develop within 4-24 hours – cough, dyspnoea, chest pain, dryness and irritation of the nose and throat, headache, dizziness, memory loss, weakness, pain in the back and limbs, fever, chills, metallic taste, and sweating. The presentation may resemble typical "metal fume fever" (i.e., thirst, chills muscle-aches, shivering and fever, headache and nausea), followed in some cases by pseudo-influenza symptoms progressing to pulmonary oedema or respiratory failure. Sufficient cadmium exposure can lead to decreased glomerular filtration rate (GFR) and chronic renal failure manifested by: aminoaciduria, glycosuria, hypercalciuria, hyperphosphaturia, polyuria, and reduced buffering capacity for acids. Death following acute inhalation is usually due to pulmonary oedema with onset 4-7 days after exposure. Subjects who survive acute cadmium poisoning may recover without residual damage, although permanent respiratory function impairment has been reported. Following ingestion, the principal symptoms of acute poisoning appear within 15-30 minutes: abdominal pain, diarrhoea, nausea, vomiting, and muscle cramping, vertigo, bone pain, loss of consciousness, convulsions and even coma.
- Examinations: chest X-ray, pulmonary function tests, arterial blood gas analysis, full blood count, and electrocardiogram (ECG) can assist in diagnosis. During the initial flu-like symptoms, pulmonary function tests are usually normal. Although there is likely to be an inflammatory lung infiltrate of polymorphonuclear leukocytes, the chest radiograph should also be clear. A peripheral blood leucocytosis is usually present. If the disorder progresses, respiratory function becomes compromised and infiltrates or other changes appear on the chest radiograph. Histologic findings in the lungs after such exposures include hyperaemia of the trachea and bronchi, pulmonary oedema, intra-alveolar haemorrhage, fibroblastic proliferation, hyperplasia of alveolar lining cells, and thrombosis of small blood vessels. Blood or urine cadmium levels are elevated, as well as levels in tissues such as lung, liver, kidney. The tissue concentrations of cadmium may help in the forensic examination of fatalities resulting from either acute or chronic poisoning.

1.1.2 Diseases caused by cadmium or its compounds ICD Code T56.3 +Z57

Exposure assessment

- History of occupational exposure: confirmed intense occupational exposure to cadmium fumes and dusts.
- Minimum duration of exposure: few minutes.
- Maximum latent period: 48 hours.

Name of the diseases and ICD code: **Chronic diseases caused by cadmium or its compounds**
(Specific disease code) **+T56.3 +Z57**

Pulmonary emphysema (J68.4)

Short description of the disease

Most cases of acute lung injury resolve without permanent effects. However, long-term respiratory effects are observed following chronic exposure to cadmium fumes and dusts, mainly chronic obstructive pulmonary disease and emphysema.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: chronic cough, dyspnoea, and sputum production; wheezes, decreased intensity of breath sounds, and prolonged expiration on physical examination.
- Examinations:
  - Airflow limitation on pulmonary function testing that is not fully reversible and is most often progressive.
  - Radiographs of patients with chronic bronchitis typically show only nonspecific peri-bronchial and peri-vascular markings. Plain radiographs are insensitive for the diagnosis of emphysema; they show hyperinflation with flattening of the diaphragm or peripheral arterial deficiency in about half of cases. Computed tomography (CT) of the chest, particularly using high-resolution CT, is more sensitive and specific than plain radiographs for diagnosis. In advanced disease, pulmonary hypertension may be suggested by enlargement of central pulmonary arteries on radiographs, and Doppler echocardiography provides an estimate of pulmonary artery pressure.
  - Elevated urinary and blood cadmium concentration. Note that cadmium excretion in urine increases only when the binding capacity of kidney metallothionein is exceeded. Therefore, cadmiuria suggests very high exposures, and signs of early nephrotoxicity are also usually present (see below).
  - The determination of cadmium concentrations in lung, liver, and kidney may be useful in forensic examination of fatalities resulting from either acute or chronic poisoning.

Exposure assessment

- History of occupational exposure: confirmed long-term occupational exposure to high airborne concentrations of cadmium (fumes and dusts). For example, airborne cadmium concentrations significantly exceeding the American Conference of Governmental Industrial Hygienists (ACGIH) 8hr Time-Weighted Average (TWA) Threshold Limit Value (TLV) of 2 µg/m^3.
- Minimum duration of exposure: usually 10 years.
- Maximum latent period: six years.

Anosmia (R43.0)

Short description of the disease

Anosmia is a common finding in chronic cadmium poisoning that results from damage to the olfactory epithelium, for which cadmium has a strong affinity. In addition, once bound to glutathione and metallothionein in the olfactory epithelium, cadmium can cross the blood brain barrier and accumulate in the brain.

Available data show a correlation between olfactory impairment and cadmium concentrations in blood and urine. This is a specific toxic effect on the olfactory epithelium and is not correlated with direct irritation.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: a decrease or loss in olfaction results in a changed perception of flavour, which includes both smell and taste. The presence of other respiratory manifestations due to cadmium poisoning should be assessed, together with potential tubular proteinuria, in most advanced cases.
- Examinations: olfactory abnormalities can be detected with formal testing, that usually rely on measuring detection thresholds of a specific odorant and on measuring the ability to identify odorants. Nasal endoscopy as well as CT scans could be performed with special attention to the olfactory cleft to rule out polyp disease or intra-cranial masses.

1.1.2 Diseases caused by cadmium or its compounds — ICD Code T56.3 +Z57

Exposure assessment

- History of occupational exposure: confirmed long-term occupational exposure to cadmium. A reduction in the olfactory function has been observed in conditions of particularly high exposures, corresponding to levels of urinary cadmium > 5 mg/g creatinine.
- Minimum duration of exposure: about 10 years.
- Maximum latent period: five years.

Nephropathy (N14.3), Chronic kidney disease (N18), Fanconi-like syndrome (E72.0)

Short description of the disease

The kidney is the main toxicological target of cadmium, independent of the route of absorption. Toxicity is the consequence of cadmium accumulation in the renal cortex. Cadmium binds to metallothionein in the liver and the complex is transported to the kidney, where it is released. The initial toxic effect of cadmium on the kidney is an increase in the excretion of low-molecular-weight proteins, such as retinol-binding protein, β_2-microglobulin and α_1-microglobulin. These are usually reabsorbed by the proximal renal tubule, and increased levels of excretion have been advocated as an indicator of early damage to the proximal tubule. The critical cadmium concentration in the renal cortex is in the order of 200 ppm (corresponding to a urinary cadmium excretion of about 10 µg/g creatinine). Changes in renal biomarkers can occur at lower levels in vulnerable individuals, such as people with diabetes, and renal effects can be detected even at 2 µg/g creatinine.

Cadmium causes, at a later stage, glomerular injury, with a resulting decrease in filtration. Fanconi-like syndrome is a more generalized dysfunction of the proximal tubular cells, which no longer efficiently re-absorb essential soluble components such as phosphates, amino-acids, urate, and glucose. This causes phosphaturia, glycosuria, aminoaciduria, uricosuria, and tubular proteinuria. The principal feature of Fanconi syndrome is bone demineralization (osteomalacia) caused by excessive excretion of phosphate (phosphate wasting).

Diagnostic criteria

Clinical manifestations

- Signs, symptoms and examinations:
  - Laboratory evidence of cadmiuria (if persistently increased above 5 µg/g creatinine).
  - Occupational cadmium exposure can lead to a small reversible increase in urinary enzymes, such as N-acetylglucosaminidase (NAG) and gamma-glutamyl-transpeptidase (GGT): these indicators are used to detect possible early effects of exposure in research studies.
  - As kidney dysfunction progresses, amino acids, glucose and calcium and phosphorus are also lost in urine. Kidney stones are frequently reported due to hypercalcuria and in severe cases uraemia may develop.
  - There is an almost linear increase in risk of tubular proteinuria with urinary cadmium when it exceeds 10 µg/g creatinine.
  - Cadmium concentrations in organ tissues (lung, liver, kidney and bones) may be seen elevated resulting from either acute or chronic poisoning.

Exposure assessment

- History of occupational exposure: confirmed long-term occupational exposure to cadmium. Airborne cadmium concentration > 2 µg/m^3. If available, biological monitoring:
  - Urine cadmium >5 µg/g creatinine.
  - Blood cadmium >5 µg/L.
  - Retinol binding protein ≥ 5.1 µmol/mol creatinine (i.e., 1000 µg/g creatinine). Note: retinol binding protein levels in urine may be useful in detecting early nephrotoxic effects. RBP estimation is preferred to β_2-microglobulin and α_1-microglobulin because it is more specific for renal tubular damage, and more stable for analytical purposes. However, robust longitudinal studies showing that such micro-proteinuria progresses to chronic kidney disease are absent, so there is uncertainty about what levels are of concern.
- Minimum duration of exposure: one year.
- Maximum latent period: 10 years.

1.1.2 Diseases caused by cadmium or its compounds — ICD Code T56.3 +Z57

Osteomalacia (M83.8), Osteoporosis (M80.8), Itai-itai disease (T56.3)

Short description of the disease

Cadmium has been recognized as the cause of a specific bone demineralisation with accompanying severe bone pain, and sometimes vertebral collapse and consequent neurological impairment. In the early 20th century a cluster of cases, known as 'Itai-itai' disease occurred in Japan, particularly in elderly females consuming a diet largely constituted by rice and fish that were contaminated with cadmium.

Consequently gender, age and poor nutrition are thought to be risk factors. The disease has not been observed in occupationally exposed workers and the amount of information is thus poor for osteomalacia in the occupational setting. However, when tubular nephropathy is present, alterations in calcium metabolism may contribute to changes in bone mineral density, other mechanisms may be important such as stimulation of osteoclast activity.

Bone lesions are usually a late manifestation of severe chronic environmental cadmium poisoning. They are characterized by osteomalacia, osteoporosis and spontaneous fractures.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: skeletal deformities, decreased height, difficulty in walking, stooped posture, waddling gait, pain in the low back and extremities, and pain induced by spinal percussion, as a result of skeletal changes and deformities.
- Examinations: bone abnormalities found at X-ray examinations. Bone mineral density measurements showing low abnormal values. Presence of clinical and biochemical effects of kidney damage (see above).

Exposure assessment

- History of occupational exposure: confirmed long-term occupational exposure to high concentrations of cadmium and, if available:
  - Biological monitoring: evidence of urine cadmium concentrations exceeding 5 µg/g creatinine.
  - Workplace air monitoring: airborne cadmium concentration > 2 µg/m^3.
- Minimum duration of exposure: several years.
- Maximum latent period: 12 years.

Name of the diseases and ICD code: **Chronic diseases caused by cadmium or its compounds**
(Specific disease code) **+T56.3 +Z57**

Lung cancer (C34), Kidney cancer (C64), Prostate cancer (C61)

Cadmium and cadmium compounds cause cancer of the lung. Positive associations have been observed between exposure to cadmium and cadmium compounds and cancer of the kidney and of the prostate.

For detailed information on these disorders, refer to item 3.1.17.

Key actions for prevention	Due to its recognized carcinogenic activity, cadmium is progressively being eliminated from the industrial and manufacturing uses for which substitutes have been found, especially for electrical batteries, PVC plasticizers and red/yellow pigments in consumer goods. Cadmium electro-finishing of iron and steel parts in car manufacturing, such as in bumpers and in other aesthetic finishing, is being replaced or eliminated by changes in car design. However, its use continues for specialised applications such as hydraulic actuators. The electroplating industry can process items in enclosed tanks from which little or no worker exposure is expected, and compliance with stringent environmental regulations has resulted in lower cadmium concentrations in waste water. In activities where exposure to cadmium can occur, the use of personal protective equipment may be necessary (e.g. respiratory protective equipment to prevent inhalation, as well as gloves and coveralls to prevent splashes and skin contact with corrosive electroplating solutions). Worker exposure in the manufacture of nickel-cadmium batteries is decreasing, with improvements in occupational hygiene, and as these batteries are superseded by more environmentally friendly forms of electric power storage. However, workers involved in waste recovery from electric and electronic appliances, as well as in cadmium smelting and recovery from iron and steel scrap, should adopt the same prevention measures to avoid or minimize exposure. This is of particular importance for commercial activities in the informal sector.

1.1.2 Diseases caused by cadmium or its compounds	ICD Code T56.3 +Z57
Key actions for prevention	Several international or national agencies and institutional databases report limits of exposure of cadmium concentrations that have been observed to provide reasonable level of protection for workers' health. We report some of them as examples: • ILO International Chemical Safety Cards (ICSC) database - Cadmium: 0.01 mg/m^3 as 8hr TLV-TWA. - Cadmium chloride: 0.002 mg/m^3 as TLV-TWA. - Cadmium oxide: 0.002 mg/m^3 as TLV-TWA. • ACGIH - A TLV-TWA of 0.01 mg/m^3 for "total" particulate, and of 0.002 mg/m^3 for the respirable particulate fraction are recommended for occupational exposure to cadmium and its compounds. The 0.01 mg/m^3 "total" particulate TLV is intended to minimize the potential for development of preclinical kidney dysfunction. The respirable particulate TLV is intended to minimize the potential for lower respirable tract accumulation of a cadmium burden that could induce lung cancer. The TLVs should significantly reduce the potential for metal fume fever in cadmium-exposed workers. - ACGIH recommends monitoring of cadmium in urine as a specific test for chronic exposure to cadmium. Cadmium concentration of 5 µg/g of creatinine is recommended as a biological exposure index (BEI). The BEI is intended to prevent the potential for renal dysfunction in workers. The recommended BEI is equivalent in international System of Units (SI) to 5 µmol/mol of creatinine. - ACGIH recommends monitoring of cadmium in blood as a specific indicator of the recent exposure to cadmium. Cadmium concentration of 5 µg/L is recommended as a BEI for the monitoring of cadmium exposure. Cadmium concentration in blood primarily reflects recent exposure and is complementary to the cadmium measurements in urine, which primarily reflect chronic exposure. The BEI is intended to prevent the potential for renal dysfunction in workers. • SCOEL - The Scientific Committee on Occupational Exposure Limits (SCOEL) of the European Commission proposed an occupational exposure limit (8hr TWA) of 1 µg/m^3 (i.e., 0.001 mg/m^3) for the inhalable fraction of cadmium and a Biological Limit Value (BLV) of 2 µg/g creatinine in urine.

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1.1.2 Diseases caused by cadmium or its compounds ICD Code T56.3 +Z57

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For the chemical entities listed below an entry exists in the collection of International Chemical Safety Cards (ICSC) hosted in the ILO website

Name	Synonyms	ICSC
Cadmium		0020
Cadmium chloride	Cadmium dichloride	0116
Cadmium oxide	Cadmium monoxide	0117
Cadmium sulfide	Cadmium monosulphide; cadmium sulphide; cadmium monosulfide	0404
Cadmium acetate	Acetic acid, cadmium salt bis(acetoxy) cadmium	1075
Cadmium sulfate	Cadmium sulphate	1318

▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
1.1.2	Toxic effects of cadmium or its compounds	T56.3	NE61& XM0V73
1.1.2	Acute chemical bronchitis and pneumonitis	J68.0	CA81.0
1.1.2	Reactive airways dysfunction syndrome (RADS)	J68.3	CA81.Y
1.1.2	Acute chemical pulmonary oedema	J68.1	CA81.1
1.1.2	Pulmonary emphysema	J68.4	CA21.Z
1.1.2	Anosmia	R43.0	MB41.0
1.1.2	Nephropathy	N14.3	GB55.1
1.1.2	Chronic kidney disease	N18	GB61.Z
1.1.2	Fanconi-like syndrome	E72.0	5C60.Z
1.1.2	Osteomalacia	M83.8	FB83.2Y
1.1.2	Osteoporosis	M80.8	FB83.1Z
1.1.2	Itai-Itai disease	T56.3	NE61 & XM0V73
1.1.2	Lung cancer	C34	2C25.Z
1.1.2	Kidney cancer	C64	2C90.Z
1.1.2	Prostate cancer	C61	2C82.Z
	Occupational exposure to risk factors	Z57	QD84.Y

1.1.3 Diseases caused by phosphorus or its compounds	ICD Code T57.1 +Z57
General characteristics of the causal agent	Phosphorus (P) is a chemical element with atomic number 15 in the periodic table. It is essentially mono-isotopic, although there is a short-lived artificial radioactive isotope (^{31}P), that is widely used in biological research. This is a beta-emitter with a half-life of 14.3 days. The atomic mass of phosphorus is 31.9 Da. It is placed in Group 15 (V-A) of the periodic table, and its principal oxidation numbers are -III (phosphine), 0 (elemental), III (phosphite) and V (phosphate). Phosphorus (-III) and Phosphorus (0) are those of the highest toxicological concern. Phosphorus is an abundant element, essential to life on earth because of its involvement in biological structures and processes. The most important are: DNA and RNA structures, phospholipids of cell membranes, high-energy nucleoside di-phosphates and triphosphates, nucleoside phosphates, and phosphorylated protein agents in cell signalling. Elemental phosphorus, which is not present as such in nature, exists in three main allotropic forms. *White phosphorus* (or yellow phosphorus; P_4) is highly reactive, and spontaneously ignites in air, oxidizing to phosphoric anhydride, which in turn reacts with ambient water to form phosphoric acid and poly-phosphoric acid anhydrides. It is soluble in organic solvents. This allotrope of phosphorus caused significant occupational diseases for nearly 100 years, until its use in match-manufacture was restricted or banned in the early 20th century. *Red phosphorus* is a much more stable and less toxic polymeric allotrope, used in most industrial applications requiring elemental phosphorus. *Black phosphorus* is an even more stable allotropic form, with potential uses in nanotechnology; only limited information is presently available on its toxicity. Phosphorus ores consist mainly of monomeric or polymeric phosphate, such as apatite and phosphorite (forms of calcium phosphate), essentially of biological origin. Phosphate ores are present in concentrated, industrially exploitable forms only in limited areas of the earth (China, Russia, Morocco, and Florida, Idaho, Tennessee, and Utah in the USA). Extensive mining started in the late 19th century. Inorganic phosphorous compounds include phosphoric acid, phosphorus pentoxide, phosphorus pentachloride, phosphorus pentasulphide, phosphorus chloride, phosphorus oxychloride, and phosphine gas. Phosphine (or hydrogen phosphide, PH_3) is a colourless, flammable gas produced industrially by the reaction of phosphoric acid and metals, or by heating phosphoric chloride. It is generated naturally by the anaerobic decomposition of dead tissues. Pure phosphine auto-ignites above 38°C, and forms an explosive mixture in air at concentrations greater than 1.8% by volume. Phosphorus is present in several organic chemicals of major importance, e.g. organophosphorus pesticides (refer to item 1.1.36 for further details), chemical warfare agents, and organophosphate flame-retardants, although the latter have been phased out in many countries because of their toxicity.
Occupational exposures	Phosphorus and its compounds have many different uses in modern industry. These include bulk uses in the production of fertilizers, detergents, and animal foods, and the preparation of fine chemicals (such as pharmaceuticals, pesticides, lubricants), ammunitions and incendiary devices. For each class of phosphorus compounds and for each industrial use, there are different scenarios for exposure, and occupational concerns for safety and health. Inorganic phosphates are widely used as fertilizers in agriculture but are of little toxicological concern. Organic phosphate esters are widely used in industry as lubricant additives, fire retardants, plasticizers and chemical intermediates. They are found in the rubber, plastics, paper, varnish and metal industries and as ingredients in pesticides and cleaning compounds. Their potential for occupational toxicity is highly variable. White phosphorus is still used in the manufacture of rodenticides, such as aluminium phosphide. Red phosphorus is used in the manufacture of matches. Black phosphorous is little used in industry at present. Phosphine is a gas heavier than air, produced when strong acids are in contact with phosphide-containing metals or in specific metallurgical reactions. It is used in the synthesis of organophosphines and other organic phosphorous derivatives, as a fumigant for grains in grain elevators, and on-board ships as a pesticide for insects and rodents. Other uses are as an intermediate in the synthesis of organo-phosphines and organic phosphonium derivatives, and as a dopant to introduce phosphorus into silicon crystals, in the manufacture of microelectronic devices for the semiconductor industry. Following industrial accidents, rescue workers and health care workers must be vigilant to avoid accidental contamination.

1.1.3 Diseases caused by phosphorus or its compounds ICD Code T57.1 +Z57

Toxicological profile, main health effects and diagnostic criteria

Short toxicological profile	Because phosphorus is lipid-soluble, it is rapidly absorbed and distributed in the body following inhalation, ingestion, and contact causing skin-burns. White phosphorus causes multiple local and systemic toxic effects. It impairs mitochondrial (ATP) production, impairs protein synthesis, and causes cell necrosis. The inhibition of very low density lipoprotein (VLDL) synthesis leads to accumulation of triglycerides in the liver and hepatotoxicity. Local effects include severe burns to the skin and mucosa upon contact, burns to the upper airways and severe pulmonary inflammation following inhalation, and burns to the gastro-intestinal tract after ingestion. Systemic effects include multi-organ toxicity (hepatotoxicity, renal, gastrointestinal and cardiovascular), that may be delayed in onset for one to seven days, and are accompanied by multiple metabolic effects. Fatal poisoning usually results from acute hepatic failure and cardiovascular collapse. "Phossy jaw" is a condition caused by chronic inhalation and ingestion of white phosphorus, and accumulation in the bone. Historically, it was a major disease of workers engaged in match-production. Phosphoric anhydride (phosphorus pentoxide) and phosphoric acid cause painful burns to the skin and mucosa upon contact, especially in the concentrated form of poly-phosphoric acid (PPA) used in chemical applications. The halogen derivatives of phosphoric acid (phosphorus chlorides and oxy-chlorides) cause respiratory tract irritation and painful burns to the skin and mucosa upon contact. Phosphine causes methaemoglobinemia upon inhalation, similar to alkyl-phosphines.

Name of the diseases and ICD code: **Acute diseases caused by phosphorous or its compounds**
(Specific disease code) **+T57.1 +Z57**

Irritant respiratory effects (J68), Acute poisoning with phosphine gas (J68), Pulmonary oedema (chemical) (J68.1), Burns and corrosions of external body surface (T20-T25), Irritant contact dermatitis (L24), Acute toxic hepatitis (K71.2)

Short description of the disease

White phosphorus ignites spontaneously in air producing fumes, which cause skin, eye and respiratory tract irritation, with potential progression to pulmonary oedema. Similar effects are caused by phosphoric acid, phosphorus pentoxide, phosphorus pentachloride, phosphorus chloride, and phosphorus oxychloride.

Inhalation of phosphorus pentoxide, phosphorus pentachloride, or phosphine gas can cause a delayed pulmonary oedema, characterized by a maximum latency period of 72 hours. Although pure phosphine is odourless, a garlic or fish-like odour may be perceived at concentrations in the order of 0.3 ppm due to impurities in commercially prepared materials. Solid phosphorus (white phosphorus) can cause burns to the skin on direct contact and such burns must be decontaminated as rapidly as possible by washing with copious amounts of water, and where necessary, debridement. The burns are slow to heal. Liver injury may follow the inhalation or ingestion of white phosphorus. The latent period is usually short, no more than a few hours, but clinical manifestations may be delayed from one to seven days.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms:
  - Intermittent, low concentrations of phosphine gas (usually up to 0.3 ppm) are associated with mild headaches.
  - Higher acute exposures to phosphorus and its compounds are associated with skin and mucous membrane irritation, breathing difficulties, cough, and delayed onset pulmonary oedema.
  - Following exposure to phosphine gas, vomiting, nausea, dizziness and cough are amongst the most frequently reported symptoms. The breath of the poisoned subject often smells of garlic.
  - Very high skin exposures cause skin burns. Very high respiratory exposures cause airway burns and pulmonary oedema, and ingestion causes burns of the gastrointestinal tract and bleeding. These are followed by multi-organ toxicity and extensive metabolic disturbances, including hepatotoxicity, acute kidney injury (e.g. acute tubular necrosis), cardiac arrythmias, cardiovascular collapse, central nervous system effects, and disseminated intravascular coagulation. Symptoms and signs include abdominal pain, tachycardia, hypotension, lethargy, convulsions and coma.

1.1.3 Diseases caused by phosphorus or its compounds — ICD Code T57.1 +Z57

- Examinations:
  - For skin lesions, an ultraviolet light source such as a Wood's lamp can help identify contaminated areas, because phosphorus fluoresces under ultraviolet radiation. For further details on clinical features of irritant contact dermatitis, refer to item 2.2.2.
  - Lung function tests might be normal in the initial phases of inhalation toxicity, but are typically compromised later on.
  - Following ingestion, stool examination might show phosphorescence; smoking vomitus and stools may be observed.
  - With hepatotoxicity, hepatic enzymes are elevated (aspartate transaminase - AST, alanine transaminase - ALT), along with bilirubin levels. Abdominal ultrasound and CT scan may demonstrate liver damage. Hepatic histological changes include microvesicular steatosis and necrosis; in the long term, fibrosis may develop.
  - In severe toxicity, profound metabolic disturbance occurs, e.g. hypoglycaemia, hypocalcaemia, and cardiac arrythmias.
  - Acute kidney injury is accompanied by elevations in serum creatinine and electrolyte disturbances (e.g. hyperkalaemia). Urinalysis may show evidence of acute tubular necrosis: haematuria and casts.
  - Abnormalities in full blood count and in prothrombin time may be present. Intravascular haemolysis (with Heinz bodies) and methaemoglobinemia are unusual complications.

Exposure assessment

- History of occupational exposure: confirmed occupational exposure to very high concentrations of white phosphorous and its compounds, including phosphine. Note that maximum concentration of phosphine gas that can be tolerated for several hours without serious effects is around 7 ppm, and for 30–60 minutes is 100–200 ppm. A level of 2000 ppm is rapidly fatal.
- Minimum duration of exposure: for irritant effects, pulmonary oedema, burns, corrosive effects, and irritant contact dermatitis, a few seconds may be sufficient. When considering acute poisoning with phosphine gas, fatalities are possible with exposures of 30-60 minutes at concentrations above 290 ppm. For acute toxic hepatitis, a few minutes might be sufficient.
- Maximum latent period: a few minutes for acute poisoning with phosphine gas; 1-2 hours for local irritant/corrosive effects; up to 72 hours for pulmonary oedema (12 hours if not delayed) and for up to seven days for acute toxic hepatitis and other systemic effects.

Name of the diseases and ICD code: **Chronic diseases caused by phosphorous or its compounds**
(Specific disease code) **+T57.1 +Z57**

Necrosis of the maxilla and mandible ('phossy jaw') (K10.2)

Short description of the disease

This is a well-known effect of chronic inhalation of very high concentrations of white phosphorus, characterized by necrosis of the maxilla and mandible. Historically, cases occurred in the manufacture of matches, until the use of white phosphorous was banned. Prior to the antibiotic era, death was commonly due to septicaemia.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: profuse salivation, loosening of the teeth, lesions of the oral mucosa, sinus formation and bone sequestration.
- Examinations: appropriate imaging studies, X-rays and CT scans can demonstrate bone sequestration.

Exposure assessment

- History of occupational exposure: confirmed prolonged exposure to white phosphorus at high concentrations.
- Minimum duration of exposure: about one year.
- Maximum latent period: 12 months.

1.1.3 Diseases caused by phosphorus or its compounds — ICD Code T57.1 +Z57

Hepatotoxicity with hepatic necrosis (K71.1)

Short description of the disease

Chronic hepatic injury due to white phosphorous has been reported. The histological picture is characterised by microvesicular steatosis and necrosis. Chronic injury may cause periportal fibrosis.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: anorexia, nausea, vomiting, malaise, aversion to smoking, fever, enlarged and tender liver, jaundice.
- Examinations:
  - One of the hallmarks of hepatocellular necrosis due to phosphorus toxicity is elevation of aminotransferase levels and increased bilirubin levels in the blood and urine.
  - Alterations in full blood count and prothrombin time are usually found.
  - Abdominal ultrasound and CT scan may demonstrate hepatic damage.
  - Liver biopsy can show histological changes including microvesicular steatosis, necrosis and periportal fibrosis.

Exposure assessment

- History of occupational exposure: confirmed prolonged occupational exposure to phosphorous and its compounds at high concentrations.
- Minimum duration of exposure: few months.
- Maximum latent period: two years.

Key actions for prevention	Protection of workers against workplace exposure to phosphorus and its compounds can be achieved using the hierarchy of controls: elimination, substitution, engineering controls and personal protective equipment. An example of primary prevention in the late 19th and early 20th century history was the *substitution* of white phosphorus with red phosphorus in the fabrication of matches, and later *elimination* by the use of phosphorus-free materials. In particular, white phosphorous use in the manufacture of matches was banned by the 1906 Berne Convention [formally, the *International Convention respecting the Prohibition of the Use of White (Yellow) Phosphorus in the Manufacture of Matches*]. In the following decades, most European countries issued national prohibitions motivated by the hazardous and toxic properties of white phosphorus to workers and consumers. This Convention is considered to be a forerunner of the constitution of the International Labour Organization. Easy access to organophosphate pesticides makes them a common choice for intentional self-poisoning in agricultural workers. The most acutely toxic organophosphate pesticides are being superseded by less hazardous classes of chemicals (see item 1.1.36). Particular care needs to be taken in the use of metal phosphides for fumigation operations. *Source enclosure:* semiconductor doping with phosphine, for example, is conducted in enclosed units to protect the reagents and the products from the action of air and moisture. This leads to the protection of workers as a collateral benefit. The use of face masks, respirators and protective clothing as *personal protective equipment* (PPE) is the least effective measure in the hierarchy of controls. This is still commonly employed for workers engaged in agricultural crop protection, and storage of grain etc., when the use of very toxic chemicals, such as phosphine, metal phosphides and organophosphate pesticides is necessary. Emergency rescue and health care workers must be appropriately trained to recognise phosphorus toxicity, and undertake appropriate decontamination and exposure control measures. The group of experts considered that the following limits in workplace air concentrations provide reasonable levels of protection for workers' health, and are used in a number of countries: • White phosphorus: 0.1 ppm as 8hr TWA. • Phosphine: 0.3 ppm as 8hr TWA. Note that the 8-hour occupational exposure limit for phosphine in different countries lies between 0.023 and 0.3 ppm, and short-term exposure limit (STEL) values range between 0.1 and 1 ppm.

1.1.3 Diseases caused by phosphorus or its compounds ICD Code T57.1 +Z57

Further reading

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For the chemical entities listed below an entry exists in the collection of International Chemical Safety Cards (ICSC) hosted in the ILO website

Name	Synonyms	ICSC
Parathion	O,O-Diethyl-O-(4-nitrophenyl) phosphorothioate; Phosphorothioic acid O,O-diethyl O-(4-nitrophenyl) ester; Ethyl parathion	0006
Diazinon	O,O-Diethyl-O-(2-isopropyl-6-methylpyrimidin-4-yl) phosphorothioate; Phosphorothioic acid O,O-diethyl O-(6-methyl-2-(1-methylethyl)-4-pyrimidinyl) ester	0137
Glyphosate	N-(Phosphonomethyl)glycine	0160
Hexamethylphosphoric triamide	Hexamethylphosphoramide; Hexamethylphosphamide; HMPA	0162
Malathion	Diethyl(dimethoxythiophosphorylthio)succinate; S-1,2-bis(Ethoxycarbonyl) ethyl O,O-dimethylphosphorodithioate; Butanedioic acid, {(dimethoxyphosphinothioyl)thio}-, diethyl ester	0172
Methamidophos	O,S-Dimethyl phosphoramidothioate; Phosphoramidothioic acid, O,S-dimethyl ester	0176
Monocrotophos	Dimethyl (E)-1-methyl-2-(methylcarbamoyl) vinyl phosphate; Phosphoric acid, dimethyl 1-methyl-3-(methylamino)-3-oxo-1-propenyl ester, (E)-	0181
Phosphamidon	2-Chloro-2-diethylcarbamoyl-1-methylvinyl dimethyl phosphate; 2-Chloro-3-(diethylamino)-1-methyl-3-oxo-1-propenyl dimethyl phosphate; Dimethyl phosphate ester 2-chloro-N,N-diethyl-3-hydroxycrotonamide; O,O-Dimethyl-O-(2-chloro-2-diethylcarbamoyl-1-methylvinyl) phosphate	0189
Phosphorus oxychloride	Phosphoryl chloride; Trichlorophosphorus oxide; Trichlorophosphine oxide	0190
Temephos	O,O,O',O'-Tetramethyl O,O'-thiodi-p-phenylene bis(phosphorothioate); O,O'-(Thiodi-4,1-phenylene) bis(O,O-dimethylphosphorothioate); Phosphorothioic acid, O,O'-(thiodi-4,1-phenylene) O,O,O',O'-tetramethyl ester	0199
Ammonium phosphate dibasic	Diammonium hydrogen phosphate; Ammonium phosphate secondary	0217
Bensulide	O,O-Diisopropyl S-2-phenylsulfonylaminoethyl phosphorodithioate; Phosphorodithioic acid, O,O-bis(1-methylethyl)S-(2-((phenylsulfonyl)amino) ethyl)ester	0383
Carbophenothion	S-4-Chlorophenylthiomethyl O,O-diethyl phosphorodithioate; Phosphorodithioic acid, S-(((4-chlorophenyl)thio)methyl) O,O-diethyl ester	0410
Coumaphos	O-3-Chloro-4-methyl-2-oxo-2H-chromen-7-yl O,O-diethyl phosphorothioate; Phosphorothioic acid O-(3-chloro-4-methyl-2-oxo-2H-1-benzopyran-7-yl) O,O-diethyl ester; O,O-Diethyl O-(3-chloro-4-methyl-7-coumarinyl)phosphorothioate; O,O-Diethyl 3-chloro-4-methyl-7-umbelliferone thiophosphate	0422
Demeton-o-methyl	O-2-Ethylthioethyl O,O-dimethyl phosphorothioate	0429
Tris(2,3-dibromopropyl) phosphate	TBPP; 2,3-Dibromo-1-propanol phosphate; TDBPP	0433
Diethylthiophosphoryl chloride	Phosphorochloridothioic acid O,O-diethylester; Diethyl chlorothiophosphate; Diethyl phosphochloridothionate	0448
Aluminium phosphide	Aluminum phosphide	0472
Fenamiphos	Phenamiphos; Ethyl-3-methyl-4-(methylthio)phenyl(1-methylethyl) phosphoramidate	0483
Phosmet	O,O-Dimethyl S-phthalimidomethyl phosphorodithioate; Phosphorodithioic acid, S-((1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)methyl) O,O-dimethyl ester; O,O-Dimethyl phosphorodithioate S-ester with N-(mercaptomethyl) phthalimide	0543
Phosphorus pentachloride	Phosphorus perchloride; Phosphoric chloride	0544
Phosphorus pentoxide	Diphosphorus pentoxide; Phosphoric anhydride; Phosphorus pentaoxide	0545
Thiometon	S-2-Ethylthioethyl O,O-dimethyl phosphorodithioate; Phosphorodithioic acid, S-(2-(ethylthio)ethyl)O,O-dimethyl ester; Dithiomethon	0580

Name	Synonyms	ICSC
Thiophosphoryl chloride	Phosphorothionic trichloride; Trichlorophosphine sulfide; Phosphorous sulfochloride; Phosphorothioic trichloride	0581
Tributyl phosphate	Tri-n-butyl phosphate; Phosphoric acid, tributyl ester	0584
Trichlorphon	Dimethyl-2,2,2-trichloro-1-hydroxyethylphosphonate; Trichlorphene; (2,2,2-Trichloro-1-hydroxyethyl) phosphonic acid dimethyl ester; Chlorofos	0585
Zinc phosphide	Trizinc diphosphide	0602
Fenitrothion	O,O-Dimethyl O-4-nitro-m-tolyl phosphorothioate; O,O-Dimethyl O-(3-methyl-4-nitrophenyl) phosphorothioate; O,O-Dimethyl O-4-nitro-m-tolyl thiophosphate	0622
Methyl parathion	O,O-Dimethyl O-4-nitrophenyl phosphorothioate	0626
Phosphorus (yellow)	O,O-Dimethyl-p-nitrophenylthionophosphate	0628
Fenthion	Phosphorothioic acid, O,O-dimethyl O-(4-nitrophenyl) ester	0655
Triethyl phosphite	White phosphorus; Phosphorus tetramer	0684
Trimethyl phosphate	O,O-Dimethyl-O-(4-methylthio-m-tolyl) phosphorothioate; Phosphorothioic acid, O,O-dimethyl O-(3-methyl-4-(methylthio)phenyl) ester	0686
Cyclophosphamide	Phosphorous acid, triethyl ester	0689
Dichlorvos	Phosphoric acid trimethyl ester; Trimethyl orthophosphate	0690
Phosphine	2-Bis(2-chloroethyl)amino; N,N-Bis(2-chloroethyl)tetrahydro-2H-1,3,2-oxazaphosphorin-2-amine 2-oxide	0694
Phosphorus trichloride	2,2-Dichlorovinyl dimethyl phosphate; Phosphoric acid, 2,2-dichloroethenyl dimethyl ester; DDVP	0696
Triphenylphosphine	Phosphorus trihydride; Hydrogen phosphide	0700
Demeton-s-methyl	Trichlorophosphine; Phosphorous chloride	0705
Fonofos	Triphenylphosphorous	0708
Dimethoate	S-2-Ethylthioethyl O,O-dimethyl phosphorothioate; Phosphorothioic acid, S-(2-(ethylthio)ethyl)O,O-dimethyl ester	0741
Magnesium phosphide	O-Ethyl S-phenylethylphosphonodithioate	0744
Acephate	O,O-Dimethyl S-methylcarbamoylmethyl phosphorodithioate; Phosphorodithioic acid, O,O-dimethyl S-(2-(methylamino)-2-oxoethyl)ester; O,O-Dimethyl S-(2-(methylamino)-2-oxoethyl)phosphorodithioate	0748
EPN	Trimagnesium diphosphide	0753
Vamidothion	O,S-Dimethyl acetylphosphoramidothioate; Phosphoramidothioic acid, acetyl-, O,S-dimethyl ester N-(Methoxy(methylthio)phosphinoyl)acetamide	0758
Phosalone	S-6-chloro-2,3-dihydro-2-oxobenzoxazol-3-ylmethyl O,O-diethyl phosphorodithioate; Benzphos	0797
Azinphos-methyl	Phosphorodithioic acid 0,0-dimethyl S-((4-oxo-11,2,3-benzotriazin-3-(4H)-yl) methyl) ester; S-3,4-Dihydro-4-oxo-1,2,3-benzotriazin-3-ylmethyl) O,O-dimethyl phosphorodithioate	0826
Chlorpyrifos	O,O-Diethyl-O-(3,5,6-trichloro-2-pyridyl)phosphorothioate; O,O-Diethyl O-(3,5,6-trichloro-2-pyridinyl) phosphorothioic acid ester; Chlorpyrifos-ethyl	0851
Cyhalothrin	(RS)-alpha-Cyano-3-phenoxybenzyl (Z)-(1RS,3RS)-(2-chloro- 3,3,3-trifluoro-propenyl)-2,2-dimethylcyclopropanecarboxylate; Cyclopropanecarboxylic acid, 3-(2-chloro-3,3,3-trifluoro- 1-propenyl)-2,2-dimethyl-, cyano(3-phenoxyphenyl)methyl ester	0858
Lambda-cyhalothrin	3-(2-chloro-3,3,3-trifluoropropenyl)-2,2-dimethylcyclopropanecarboxylate a 1:1 reaction mixture of the (Z)-(1R,3R), (S) ester and (Z)-(1S,3S), (R) ester	0859
Demeton-methyl	3-(2-chloro-3,3,3-trifluoropropenyl)-2,2-dimethylcyclopropanecarboxylate;	0862
Demeton-s	a 1:1 reaction mixture of the (Z)-(1R,3R), (S) ester and (Z)-(1S,3S), (R) ester	0864
Dicrotophos		0872
Dioxathion (isomer mixture)	3-(2-chloro-3,3,3-trifluoropropenyl)-2,2-dimethylcyclopropanecarboxylate	0883
Ethion	a 1:1 reaction mixture of the (Z)-(1R,3R), (S) ester and (Z)-(1S,3S), (R) ester	0888

Name	Synonyms	ICSC
Mevinphos (isomer mixture)		0924
Naled	3-(2-chloro-3,3,3-trifluoropropenyl)-2,2-dimethylcyclopropanecarboxylate	0925
Tri-o-cresyl phosphate	a 1:1 reaction mixture of the (Z)-(1R,3R), (S) ester and (Z)-(1S,3S), (R) ester	0961
Tris(2-ethylhexyl) phosphate		0968
Fenchlorphos	3-(2-chloro-3,3,3-trifluoropropenyl)-2,2-dimethylcyclopropanecarboxylate	0975
Tetrapotassium pyrophosphate	a 1:1 reaction mixture of the (Z)-(1R,3R), (S) ester and (Z)-(1S,3S), (R) ester	0983
Sulfotep		0985
Phosphoric acid	3-(2-chloro-3,3,3-trifluoropropenyl)-2,2-dimethylcyclopropanecarboxylate	1008
Phorate	a 1:1 reaction mixture of the (Z)-(1R,3R), (S) ester and (Z)-(1S,3S), (R) ester	1060
Triphenyl phosphate		1062
Triphenyl phosphite	3-(2-chloro-3,3,3-trifluoropropenyl)-2,2-dimethylcyclopropanecarboxylate	1124
Calcium phosphide		1126
Disodium hydrogen phosphate	Disodium orthophosphate; Dibasic sodium phosphate	1129
Tetrasodium pyrophosphate	Sodium pyrophosphate; Pyrophosphoric acid, tetrasodium salt	1140
Crufomate	4-tert-Butyl-2-chlorophenyl methyl methylphosphoramidate; Amidophos	1143
T.E.P.P.	Tetraethyl pyrophosphate; Diphosphoric acid, tetraethyl ester; Tetraethyl diphosphate	1158
Trisodium phosphate (anhydrous)	Sodium phosphate, tribasic; Trisodium orthophosphate	1178
Sulprofos	O-Ethyl O-4-(methylthio)phenyl phosphorodithionic acid-S-propyl ester; O-Ethyl O-4-(methylmercapto)phenyl-S-n-propylphosphorothionothiolate	1248
Dibutyl phosphate	Dibutyl acid o-phosphate; Dibutyl hydrogen phosphate; Phosphoric acid dibutyl ester	1278
Chlorfenvinphos	O,O-Diethyl-O-{2-chloro-1-(2,4-dichlorophenyl)vinyl}phosphate; 2-Chloro-1-(2,4-dichlorophenyl)vinyldiethyl phosphate	1305
Fensulfothion	O,O-Diethyl O-(p-(methylsulfinyl)phenyl) phosphorothioate; O,O-Diethyl O-p-(methylsulfinyl)phenyl thiophosphate	1406
Diphosphorus pentasulfide	Diphosphorus pentasulfide; Phosphorus sulfide; Thiophosphoric anhydride	1407
Disulfoton	Dithiodemeton; O,O-Diethyl S-(2-ethylmercaptoethyl) dithiophosphate; O,O-Diethyl S-2-(ethylthio)ethyl phosphorodithioate	1408
Di(2-ethylhexyl) phosphate	Bis(2-ethylhexyl)hydrogen phosphate Bis(isooctyl)phosphate; Bis(isooctyl)phosphate; Dioctylphosphate; Bis(2-ethylhexyl)orthophosphoric acid	1412
Phenylphosphine	Phosphaniline	1424
Pentasodium triphosphate	Sodium tripolyphosphate; Sodium triphosphate; Triphosphoric acid, pentasodium, anhydrous	1469
Aluminium phosphate tribasic	Aluminophosphoric acid; Aluminium orthophosphate; Aluminium monophosphate	1538
Trimethyl phosphite	Phophorous acid, trimethyl ester; Trimethoxy phosphine; Methyl phosphite	1556
Dimethyl hydrogen phosphite	Dimethylphosphite; Dimethyl hydrogen phosphonate; Phosphorous acid dimethyl ester; Dimethylphosphonate	1599
Potassium dihydrogen phosphate	Potassium phosphate, monobasic; Phosphoric acid, monopotassium salt	1608
Methidathion	O,O-Dimethyl S-(2,3-dihydro-5-methoxy-2-oxo-1,3,4-thiadiazol-3-ylmethyl) phosphorodithioate; O,O-Dimethyl-S-(5-methoxy-1,3,4-thiadiazolinyl-3-methyl) dithiophosphate	1659
Ethoprophos	O-ethyl-S,S-dipropyl phosphorodithioate; Phosphorodithioic acid, O-ethyl S,S-dipropyl ester; Ethoprop	1660

Name	Synonyms	ICSC
Tris(2-chlorethyl) phosphate	Tri(beta-chloroethyl) phosphate; Tris(2-chloroethyl) orthophosphate; Ethanol, 2-chloro-, phosphate (3:1); TCEP	1677
Chlorethoxyfos	Phosphorothioic acid, O,O-diethyl O-(1,2,2,2-tetrachloroethyl) ester; O,O-Diethyl O-(1,2,2,2-tetrachloroethyl) phosphorothioate	1681
Chlormephos	Clormethylphos; S-(Chloromethy) O,O-diethyl phosphorodithioate; Phosphorodithioic acid, S-(chloromethyl) O,O-diethyl ester	1682

▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
1.1.3	Acute/chronic diseases caused by phosphorous or its compounds	T57.1	NE61 & XM6NP0
1.1.3	Irritant respiratory effects	J68	CA81.Z
1.1.3	Acute poisoning with phosphine gas	J68	CA81.Z
1.1.3	Pulmonary oedema (chemical)	J68.1	CA81.1
1.1.3	Burns and corrosions of external body surface	T20-T25	ND9Y
1.1.3	Irritant contact dermatitis	L24	EK02
1.1.3	Acute toxic hepatitis	K71.2	DB95.0
1.1.3	Hepatotoxicity with hepatic necrosis	K71.1	DB95.0
1.1.3	Necrosis of the maxilla and mandibular (‘phossy jaw’)	K10.2	DA06.0
	Occupational exposure to risk factors	Z57	QD84.Y

1.1.4 Diseases caused by chromium or its compounds	ICD Code T56.2 +Z57
General characteristics of the causal agent	Chromium (Cr), CAS number 7440-47-3, has the atomic number 24, and belongs to Group 6 (III-B, Transition Metals) in the periodic table of elements. Naturally occurring chromium is composed of three stable isotopes, with ^{52}Cr (83.8%) being the most abundant, and has an average atomic mass of 51.9961 Da. Elemental chromium is a hard, corrosion-resistant metal, blue-white to steel-grey in colour and shiny in appearance. Chromium exists in a series of oxidation states from -2 to +6 valence. In the environment, chromium occurs mostly as compounds, mainly in the stable chromium (III) oxidation state and, to a limited extent, in the strongly oxidizing chromium (VI) state. Chromium (VI) compounds may react with reducing (organic) matter to form the most stable chromium (III). Chromium (VI) is the chemical form of highest concern for occupational safety (chromium (III) is less toxic). The artificial isotope ^{51}Cr (half-life of 27.7 days) has laboratory applications in diagnostic tests. In biological systems, chromium mainly exists in transient forms in the physiological reduction of chromium (VI) to chromium (III). Chromium (III) may be an essential trace element in humans, is much less toxic than chromium (VI), and chromium (III) picolinate is used as a dietary supplement. In the workplace, chromium can be present in a wide range of alloys and inorganic chromium compounds, that differ widely in their toxic and carcinogenic effects. In terms of occupational toxicology, chromium compounds can be classified in three groups: 1. *Chromium metals and alloys:* elemental chromium metal, chromium-containing stainless steels, and other chromium-containing alloys. 2. *Trivalent chromium compounds:* chromic oxide (Cr_2O_3), chromic sulphate ($Cr_2[SO_4]_3$), chromic chloride ($CrCl_3$). 3. *Hexavalent chromium compounds:* chromium trioxide (CrO_3), the anhydride of chromic acid; chromates (e.g. Na_2CrO_4); di-chromates (e.g. sodium dichromate, Na_2CrO_4) and poly-chromates. These compounds may be sub-divided into two groups, according to their solubility in water: a. *Water-soluble* hexavalent chromium compounds: chromic acid and its anhydride. The monochromates and dichromates of sodium, potassium, ammonium, lithium, caesium, and rubidium. b. *Water-insoluble* hexavalent chromium compounds: zinc chromate, calcium chromate, lead chromate, barium chromate, strontium chromate, and sintered chromium trioxide
Occupational exposures	Chromium is one of the most widely used industrial metals. Several million workers worldwide are estimated to be exposed to chromium compounds. It is mainly used in three types of industries: • In the *metallurgical industry*, chromium is an important component of stainless steels and various metal alloys. In this context, the main use of chromium ores is in the preparation of ferrochrome (i.e., iron-chrome) from the mineral chromite. • In the *chemical industry*, chromium is used primarily in chrome plating, leather tanning, paint pigments (chromium compounds can be red, yellow, orange, and green, to be used in the textile industry for dyeing, silk treating, printing, and moth proofing wool), and wood treatment. Smaller amounts are used in catalysts, copy machine toners, corrosion inhibitors, drilling muds, magnetic tapes, photographic chemicals, safety matches, and water treatment. Traces of chromium are also present in concrete. • Refractory heat-resistant applications , uses of chromium include magnesite-chrome refractory firebrick for metallurgical furnace linings, and granular chromite for various other heat-resistant applications.

1.1.4 Diseases caused by chromium or its compounds	ICD Code T56.2 +Z57
Occupational exposures	Occupational sources of chromium include: • anti-algal agents, • antifreeze, • cement, • chrome alloy production, • chrome electroplating [soluble Cr(VI)], • copier servicing, • glass making, • leather tanning [soluble Cr(III)], • paints/pigments [insoluble Cr(VI)], • photoengraving, • porcelain and ceramics manufacture, • production of high-fidelity magnetic audio tapes, • tattooing, • textile manufacturing, • welding of alloys or steel, and • wood preservatives, e.g. acid copper chromate. Workers at greatest risk are involved in stainless steel welding, chromate production, chrome plating, and chrome pigment industries. Exposure is primarily to chromium (VI) via inhalation of aerosols. The main exposure route in occupational settings is through inhalation of fumes, dusts and vapours, and by direct skin absorption. Ingestion is relevant mainly in non-occupational contexts. It is important to recall that chromium (III) picolinate is used as a dietary supplement.
Toxicological profile, main health effects and diagnostic criteria	
Short toxicological profile	Uptake of chromium depends on the valence (III or VI) and watersolubility of the chromium-containing compound. Only about 0.5% to 1% of chromium (III) present in the diet is absorbed by the gastrointestinal tract. Chromium (VI) is more readily absorbed both by inhalation and oral routes. Absorbed chromium is distributed to all tissues of the body. Chromium (VI) is unstable, and is rapidly reduced by endogenous reducing agents to chromium (V), chromium (IV) and ultimately to stable chromium (III). Chromium is excreted primarily in the urine and to a lesser extent in faeces. In occupational exposures, chromium (VI) is far more toxic than chromium (III), because it is more readily absorbed. However, after chromium (VI) is absorbed, it is reduced to chromium (III) which is more persistent in the body. The process of reduction of chromium (VI) to chromium (III) in the body generates toxic reactive oxygen species. In chromium toxicity there are multiple effects, including disruption of the p53 signalling pathway, and induction of cell apoptosis. High-dose exposure to chromium compounds (e.g. following ingestion) can oxidise haemoglobin to methaemoglobin. The respiratory tract is the major target organ for chromium (VI) toxicity, following both acute and chronic inhalation. Perforation and ulceration of the nasal septum is a highly specific clinical sign of high occupational exposure to chromate aerosols. Insoluble inhaled chromium particles can remain in the lung for long periods. Acute exposure to chromium (VI) compounds can cause shortness of breath, cough, and wheeze. Following chronic exposure, bronchitis, pneumonia, and decreased pulmonary function have been noted. Respiratory sensitization may develop following inhalation of chromium (VI) compounds, as with nickel, although the precise mechanism for sensitization is unclear. Once sensitization has developed, subsequent low-level exposure to dusts, aerosols or welding fumes containing chromium (VI) causes generalized bronchospasm and typical features of asthma. Similarly, the respiratory tract is the major target organ for chromium (III) toxicity. Prolonged skin contact may lead to local irritation and sensitization. Occupational exposure to chromium (VI) compounds has been associated with effects on the nasal septum, and the eardrum.

1.1.4 Diseases caused by chromium or its compounds — ICD Code T56.2 +Z57

Short toxicological profile	Ingestion of chromium compounds can lead to gastrointestinal ulceration, gastrointestinal haemorrhage, and hypertrophic gastritis. Chromium (VI) compounds can cause mild to severe liver abnormalities. Ingestion of significant quantities of chromium (VI) compounds is reported to cause cardiovascular effects as part of sequelae leading to death and haematological effects such as decreased haemoglobin and increased total white blood cell counts. Renal effects after inhalation or oral exposure to chromium (VI) compounds have been reported. Occupational exposure to chromium (III) does not appear to be associated with renal effects. The IARC has classified chromium (VI) compounds as carcinogenic to humans (Group 1), with sufficient evidence for lung cancer in both animal experiments and human studies. There is also some evidence for upper-airway cancer. Chromium (III) as not classifiable as to its carcinogenicity to humans (Group 3). For further details refer to item 3.1.4.

Name of the diseases and ICD code: **Acute diseases caused by chromium or its compounds**
(Specific disease code) **+T56.2 +Z57**

Respiratory irritation (J68), Chemical bronchitis and pneumonitis (J68.0), Upper respiratory tract inflammation (J68.2), Chemical pulmonary oedema (J68.1), Reactive airways dysfunction syndrome (RADS) (J68.3), Irritant-induced occupational asthma (J68.3), Acute toxic liver disease (K71.9), Acute toxic renal failure with tubular necrosis (N17.0)

Short description of the disease

Clinical features are profoundly influenced by the route of absorption of the chemical, and most are related to chromium (VI) exposure although cases of chromium (III) poisoning are reported.

Diagnostic criteria

Clinical manifestations following inhalation

- Exposure to inhaled high concentrations of chromium (VI) compounds can lead to symptoms and signs of lung and upper respiratory tract irritation. These include sneezing, rhinorrhoea, epistaxis, nasal itching and soreness, redness of the throat, coughing, wheezing, inspiratory pain, bronchitis, pneumonia (or pneumonitis), decreased pulmonary function, bronchospasm, and typical asthmatic attacks which may recur on subsequent exposure. Intense exposure to chromic acid particulates may give rise to pulmonary oedema. An exposure for several days to chromic acid mist at concentrations of about 20 to 30 mg/m^3 for example can cause cough, headache, dyspnoea and sub-sternal pain.
- Inhalation of very high concentrations of chromium (VI) can result in gastrointestinal and neurological effects.
- Chromium (VI) exposure can result in renal effects in a dose-dependent manner in workers exposed to 4 to 20 µg/m^3 of chromium (VI) over 8-hour shifts.

Clinical manifestations following ingestion

- Although unlikely in occupational settings, involuntary ingestion of large amounts of chromium (VI) compounds (e.g. chromium sodium dichromate solution or ammonium dichromate) can lead to severe local effects, and systemic effects like haemolysis, metabolic acidosis, respiratory distress, and potentially death. Chromium (VI) compounds are powerful oxidants, and methaemoglobinemia has been reported in cases of severe poisoning, for example following ingestion. In methaemoglobinemia, the ferrous form of haemoglobin (Fe^{2+}) is oxidised to the non-functional ferric form (Fe^{3+}).
- Chromium VI ingestion may cause caustic burns in the mouth, pharynx, stomach and duodenum may occur as well as gastrointestinal necrosis and haemorrhage, diarrhoea, and severe dehydration. Early damage to the renal proximal tubule can be identified by low molecular weight proteinuria with increased urinary excretion of β_2-microglobulin and retinol-binding protein (RBP). In normal conditions these are re-absorbed by the proximal tubule. Very high doses of chromium (VI) cause damage to the proximal renal tubule and glomerulus with acute tubular necrosis identifiable on renal biopsy. In the most severe cases, there is renal failure with proteinuria, azotaemia and haematuria.
- Chromium (VI) compounds can cause liver damage and failure, characterized by diffuse necrosis, with jaundice, and increase in bilirubin, hepatic enzymes (AST, ALT) and serum lactic dehydrogenase. Pulmonary effects include haemoptysis and pulmonary oedema.

1.1.4 Diseases caused by chromium or its compounds — ICD Code T56.2 +Z57

Name of the diseases and ICD code: **Acute diseases caused by chromium or its compounds**
(Specific disease code) **+T56.2 +Z57**

Clinical manifestations following dermal contact

- Dermal exposure to chromium produces irritant and allergic contact dermatitis. Typical symptoms and signs include dryness, erythema, fissuring, papules, scaling, small vesicles, and swelling.
- Dermal exposure to chromium (VI) can cause burn. Broken skin, high temperatures, and occlusion by personal protective equipment facilitates absorption.

  Following dermal exposure to high concentrations of chromium (VI) compounds, several case studies have reported effects on the renal, haematological, cardiovascular, and gastrointestinal systems (e.g. with hyperaemia of the gastric mucosa). Some exposures resulted in deaths, although the magnitude of exposures were not quantified, and in most instances, subjects had pre-existing medical conditions that may have contributed to the reported effects.

Exposure assessment

- History of occupational exposure: confirmed occupational exposure to chromium compounds, through either inhalation of aerosols, dusts, and liquid, accidental ingestion, or dermal contact. If available, air concentrations of chromium compounds at the workplace, and urinary chromium measurements.
- Minimum duration of exposure: few minutes.
- Maximum latent period: 24 hours.

Chemical burns and corrosion of external body surfaces (T20-T25), Burns and corrosion of the respiratory tract (T27), Burns and corrosion of internal organs (T28.0-T28.2, T28.5-T28.7), Burns and corrosion of the eyes (T26), Conjunctivitis (H10.2), Keratitis (H16), Corneal ulcer (H16.0), Irritant contact dermatitis (L24)

Short description of the disease

Sub-acute and chronic low-dose chromium (VI) exposure primarily causes toxicity at the site of contact. Sub-acute exposure to chromium (VI) (aerosols, dusts, liquid), and its compounds, irritates or even corrodes the skin, and the mucous membranes of the eyes and respiratory tract.

Chronic exposure to chromium (VI) compounds can induce conjunctivitis, keratitis and painless erosive ulceration of the eyelids and the skin (chrome holes). Chronic exposure additionally occurs by ingestion.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms:
  - Skin symptoms include burning, numbness and pain. Signs include erythema, fissuring, papules, scaling, and small vesicles. In severe cases, the signs are those of chemical burns: swelling and blackened or denatured skin.
  - Following exposure of the eyes and adnexae, alteration, reduction or loss of vision can occur (the spraying of chromic acid can give rise to serious eye lesions).
  - Ingestion (including mucociliary clearance of inhaled particles) causes gastrointestinal irritation. Symptoms include oral discomfort/pain, vomiting, abdominal pain, indigestion, and diarrhoea. Signs include oral ulceration. Following ingestion, systemic effects may arise: e.g. irregular heartbeat or arrhythmias, altered blood pressure, shortness of breath, coughing, headache, dizziness, seizures, and muscle twitching.

For further details on clinical manifestations of irritant contact dermatitis, refer to item 2.2.2.

Exposure assessment

- History of occupational exposure: confirmed evidence of high occupational exposures to chromium or its compounds, with skin and mucosal contact. If available, urinary chromium levels and measurements of air concentrations of chromium compounds at the workplace.
- Minimum duration of exposure: a few minutes.
- Maximum latent period: 24 hours.

1.1.4 Diseases caused by chromium or its compounds ICD Code T56.2 +Z57

Name of the diseases and ICD code: **Chronic diseases caused by chromium or its compounds**
(Specific disease code) **+T56.2 +Z57**

Chronic obstructive pulmonary disease (COPD), Chronic bronchitis, Emphysema (J68.4)

Short description of the disease

Chronic inhalation exposure to chromium (VI) compounds results in chronic effects on the respiratory tract, with nasal itching and soreness, bronchitis, asthma, pneumonia and decreased pulmonary function.

Chronic inhalation of chromium (III) compounds causes a range of inflammatory changes in the respiratory tract, causing cough or dyspnoea, production of phlegm, and shortness of breath.

Diagnostic criteria

Clinical manifestations

- Symptoms and signs: chronic cough, dyspnoea, and sputum production; wheezes, decreased intensity of breath sounds, and prolonged expiration on physical examination.
- Examinations:
  - Pulmonary function testing shows airflow limitation that is not fully reversible and is most often progressive.
  - Radiographs of patients with chronic bronchitis typically show only nonspecific peri-bronchial and peri-vascular markings. Plain radiographs are insensitive for the diagnosis of emphysema; they show hyperinflation with flattening of the diaphragm or peripheral arterial deficiency in about half of cases. In advanced disease, pulmonary hypertension may be suggested by enlargement of central pulmonary arteries on radiographs. Enlargement of the hilar region and lymph nodes can be found in some cases of chromium exposure.
  - CT of the chest, particularly using high-resolution CT, is more sensitive and specific than plain radiographs for diagnosis of emphysema.
  - Doppler echocardiography provides an estimate of pulmonary artery pressure.

Exposure assessment

- History of occupational exposure: evidence of prolonged or repeated occupational exposure to chromium or its compounds through inhalation of aerosols, dusts, and liquids; and, if available, urinary chromium levels and measurements of air concentrations of chromium in the workplace.
- Minimum duration of exposure: ten years.
- Maximum latent period: five years.

Allergic contact dermatitis (L23)

Chromium is one of the most common skin sensitizers. It penetrates undamaged skin and oxidizes proteins giving rise to sensitizing antigens.

The low solubility of chromium (III) compounds makes them much less efficient contact allergens than chromium (VI) compounds.

For further details on clinical manifestations and exposure assessment criteria of allergic contact dermatitis refer to item 2.2.1.

Allergic occupational asthma (J45.0)

Workers may develop asthma following inhalation of chromium (VI) and sensitization, e.g. following low level exposures to dusts, aerosols or welding fumes.

After exposure to chromium (III) compounds, histological examination of the lung tissue has demonstrated mild nonspecific irritation.

For further details on clinical manifestations and exposure assessment criteria of allergic occupational asthma refer to item 2.1.7.

Allergic disorders of upper airways (J30.3, J30.4), Chronic rhinitis (J31.0)

Long-term exposure to chromium compounds may lead to allergic effects in upper respiratory tract and chronic rhinitis.

For further details on clinical manifestations and exposure assessment criteria of these disorders refer to item 2.1.11.

1.1.4 Diseases caused by chromium or its compounds — ICD Code T56.2 +Z57

Name of the diseases and ICD code: **Chronic diseases caused by chromium or its compounds**
(Specific disease code) **+T56.2 +Z57**

Septal ulceration of the nose (J34.0)

Short description of the disease

Deposition of chromium (VI) containing particulates or mist droplets on the nasal septum may cause painless ulceration of the cartilaginous portion and perforation.

Clinical manifestations

- Signs and symptoms:

  During the active inflammatory phase of ulceration, symptoms such as nasal itching, soreness, and rhinorrhoea may appear, together with nasal mucosal atrophy and epistaxis. Crusts containing necrotic debris from the cartilage of the septum form.

  In many cases, ulceration is followed, within a week or two, by perforation. Frequent nose picking may encourage this. Perforation typically occurs approximately 1.5 cm to 2 cm from the lower anterior part of the nasal septum. Lesions may be observed in the upper posterior part of the septum. Posterior perforations are usually asymptomatic while anterior ones are not. The periphery of the ulcer can remain active for several months, during which time the perforation may increase in size. Perforations may remain patent, or heal by the formation of vascular scar tissue. When inflammation / ulceration has subsided, symptoms are rare and affected subjects are often unaware that the septum remains perforated. Large perforations may result in deformation of the nasal architecture, and saddle nose deformity.

  Other potential causes of nasal perforation should be considered, such as: trauma (e.g. previous surgery, direct injury), inflammation (e.g. systemic lupus erythematosus,), infections (e.g. tuberculosis, syphilis), or neoplasm as well as inhalation of substances (e.g. cocaine, topical corticosteroids) should be considered.
- Examinations: thorough intranasal examination with anterior rhinoscopy is essential. Note that all crusting should be removed to attain a complete view of the septum. Topical nasal decongestants may help visual inspection by temporarily reducing swelling and exudate.

Exposure assessment

- History of occupational exposure: confirmed evidence of prolonged or repeated occupational exposure to chromium (VI) or its compounds through inhalation of aerosols, dusts, and liquid. If available, urinary chromium levels, and measurements of air concentrations of chromium (VI) in the workplace.
- Minimum duration of exposure: two weeks.
- Maximum latent period: 10 years.

Chrome ulcers (L98.4)

Short description of the disease

Chronic dermal exposure to chromium (VI) can cause skin ulcers that appear over a period of days. Over a few weeks, the ulcer heals producing a scar.

Clinical manifestations

- Signs and symptoms:

  Chrome ulcers (chrome holes) are deep, round, and clearly demarcated. They typically appear on the skin at finger joints, finger-webs, at the base of the nails, the backs of the hands and the forearm. Other body sites can also be affected. Ulcers are more likely if there is a cut, abrasion or any other defect in the skin.

  Over a period of days, a central crater develops, with an intense inflammatory reaction at the margins. The early lesion causes intensive itching at the affected site, particularly at night. Although deeply penetrating, they are usually painless or only slightly painful.

  Lesions tend to be clean and heal spontaneously, but may be troublesome if secondary infected. Healing takes a long time, leaving scars. Healing is in any case delayed if the lesion is left untreated.

Exposure assessment

- History of occupational exposure: confirmed extensive or repeated occupational exposure to chromium (VI) through direct skin contact. If available, urinary and blood chromium levels and measurements of air concentrations of chromium at the workplace.
- Minimum duration of exposure: less than one day.
- Maximum latent period: a couple of days.

1.1.4 Diseases caused by chromium or its compounds — ICD Code T56.2 +Z57

Name of the diseases and ICD code: ***Carcinogenic effects of exposure to chromium or its compounds***
(Specific disease code) ***+T56.2 +Z57***

Lung cancer (C34)

The IARC classifies chromium (VI) compounds (encountered in chromate production, chromate pigment production and chromium plating industries), as Group 1 carcinogens, causing cancer of the lung. Positive associations have been observed for cancers of the nose and nasal sinuses.

The mechanism of carcinogenesis is complex, and not fully elucidated. Chromium (VI) compounds generate oxidative stress, with the production of reactive oxygen species and hydroxyl radicals. The compounds are genotoxic, causing DNA strand breaks etc., and in cell and animal models various sister chromosomal aberrations are observed. Epigenetic effects such as DNA methylation are thought to be important. Individual characteristics also contribute to carcinogenesis: e.g. polymorphisms in chromium carrier mechanisms, endogenous enzymic reducing systems, adduct formation and the efficiency of DNA repair mechanisms.

For detailed information on these disorders, refer to item 3.1.4.

Key actions for prevention	The hierarchy of controls should be used to minimise exposure to chromium. Processes should be designed to minimise exposure, including adequate exhaust ventilation and the suppression of dust or mist containing chromium. Built-in control measures are preferred, requiring the least possible action by either process operators or maintenance staff. Spills of liquids or solids must be removed to prevent dispersion as airborne dust. Wet methods of cleaning should be used; and where this is not possible, the only acceptable alternative is vacuum cleaning. Where high concentrations cannot be avoided, personal protective equipment (PPE) may be employed. For example, dust masks, preferably with an efficiency of more than 99% in retaining particles of 0.5 µm size. Air-powered respirators may be needed in areas with high exposures. Providing laundering overalls daily may help in avoiding skin contamination. Hand and eye protection is generally recommended. Regular repair or replacement of all personal protective equipment (PPE) is recommended. The concentration in the work environment of chromium-containing dust and fumes should preferably be measured at regular intervals by both personal and area sampling. Where unacceptable concentrations are found, the sources of dust or fumes should be identified and controlled. At job entry, the various hazards associated with exposure to different chromium compounds, and risk mitigation measures should be explained. Careful washing of the skin after contact and care to avoid friction and sweating are important in the prevention and the control of primary irritation due to chromates. The need for high standards of personal hygiene should be emphasized. Regular health surveillance should include continued education, and visual inspection for chrome skin ulcers. Skin cuts and abrasions, however slight, should be cleaned immediately, and the use of a frequently renewed impervious dressing will enhance healing of any ulceration that may develop. Intravenous treatment with methylthioninium chloride (methylene blue) is used for methaemoglobinemia in severe poisoning caused by chromic acid and sodium chromate ingestion. In the past, EDTA ointment has been used in the treatment of chrome skin ulceration, and the prevention of perforations of the nasal septum. However, given the carcinogenic hazard presented by chromium compounds, it is poor practice to use antidotes to reduce symptoms caused by high exposure levels. Instead, exposures should be reduced to safe levels. With regard to the risk of allergic contact dermatitis after handling concrete containing chromium (VI) compounds, adding ferrous sulphate during mixing reduces chromium (VI) to chromium (III) and helps prevent cases among construction and concrete element pre-fabrication workers.

1.1.4 Diseases caused by chromium or its compounds	ICD Code T56.2 +Z57
Key actions for prevention	The group of experts considers that the following occupational exposure limits provide reasonable levels of protection for workers' health, and these are used in a number of countries: • Chromium (metals and alloys) and chromium (III) compounds: 0.5 mg/m^3 as 8hr TLV-TWA. • Most water-soluble chromium (VI) compounds: 0.05 mg/m^3 as 8hr TLV-TWA. • Most water-insoluble chromium (VI) compounds: 0.01 mg/m^3 as 8hr TLV-TWA. The ACGIH recommends the following 8hr TLV-TWA: • Metallic chromium 0.5 mg/m^3. • Hexavalent Cr (VI) water soluble compounds 0.0002 mg/m^3. • Water soluble trivalent Cr (III) compounds 0.003 mg/m^3. For exposure to chromium (VI) water soluble fume the ACGIH recommends the following biological exposure indices: • Total chromium in urine at end of shift, end of work-week 25 µg/L. • Total chromium in urine, increase during shift 10 µg/L.

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1.1.4 Diseases caused by chromium or its compounds ICD Code T56.2 +Z57

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For the chemical entities listed below an entry exists in the collection of International Chemical Safety Cards (ICSC) hosted in the ILO website

Group		Name	Synonyms	ICSC
Chromium metals and alloys		Chromium	Chrome	0029
Trivalent chromium compounds		Chromium hydroxide sulphate	Basic chrome sulphate; Monobasic chromium; sulphate	1309
		Chromium(III) chloride (anhydrous)	Chromic chloride; Chromium trichloride; Trichlorochromium	1316
		Chromic (III) hydroxide hydrate	Chromic (III) hydroxide hydrate	1455
		Chromic(III) nitrate nonahydrate	Chromic nitrate; Chromium trinitrate; Nitric acid; chromium(III) salt	1530
		Chromic(III) oxide	Chromic oxide; Dichromium trioxide	1531
		Chromic(III) chloride hexahydrate	Chromic chloride hexahydrate; Chromium trichloride hexahydrate	1532
Hexavalent chromiumcompounds	Water-soluble	Chromium(VI) oxide	Chromic trioxide; Chromic acid; Chromic anhydride	1194
		Ammonium dichromate	Diammonium dichromate (VI); Dichromic acid; diammonium salt; Ammonium bichromate	1368
		Sodium dichromate (anhydrous)	Disodium dichromate (VI); Dichromic acid; disodium salt; Disodium dichromium heptaoxide	1369
		Sodium chromate	Disodium chromate (VI); Chromic acid; disodium salt; Disodium chromium tetraoxide	1370
		Potassium dichromate	Dipotassium dichromate (VI); Dichromic acid; dipotassium salt; Potassium bichromate	1371
		Tert-butyl chromate	bis(tert-Butyl)chromate; Chromic acid; di-tert-butyl ester	1533
		Chromyl chloride	Chromic oxychloride; Dichlorodioxochromium; Chromium dichloride dioxide	0854
	Water-insoluble	Lead chromate	Chromic acid, Lead (II) salt (1:1), Plumbous chromate	0003
		Zinc chromate	Chromic acid, Zinc salt (1:1); Chromium zinc oxide; Zinc tetraoxychromate	0811
		Strontium chromate	C.I. Pigment yellow 32; Chromic acid strontium salt	0957
		Barium chromate	Barium chromate (VI); Barium chromate (1:1); Chromic acid, barium salt 1:1; C.I. 77103; C.I. Pigment yellow 31	1607

▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
1.1.4	Toxic effects of chromium or its compounds	T56.2	NE61 & XM9YJ8
1.1.4	Respiratory irritation	J68	CA81.Z
1.1.4	Chemical bronchitis and pneumonitis	J68.0	CA81.0
1.1.4	Upper respiratory tract inflammation	J68.2	CA81.2
1.1.4	Chemical pulmonary oedema	J68.1	CA81.1
1.1.4	Reactive airways dysfunction syndrome (RADS), Irritant-induced occupational asthma	J68.3	CA81.Y
1.1.4	Acute toxic renal failure with tubular necrosis	N17.0	GB60.Z
1.1.4	Acute toxic liver disease	K71.9	DB95.Z
1.1.4	Chemical burns and corrosions of external body surface	T20-T25	ND9Z
1.1.4	Burns and corrosions of respiratory tract	T27	NE01
1.1.4	Burns and corrosions of internal organs	T28.0-T28.2, T28.5-T28.7	NE0Z
1.1.4	Burns and corrosions of eyes	T26	NE00
1.1.4	Conjunctivitis	H10.2	9A60.Z
1.1.4	Keratitis	H16	9A73
1.1.4	Corneal ulcer	H16.0	9A76
1.1.4	Irritant contact dermatitis	L24	EK02
1.1.4	Allergic contact dermatitis	L23	EK00
1.1.4	Allergic occupational asthma	J45.0	CA23.0
1.1.4	Chronic obstructive pulmonary disease (COPD), Chronic bronchitis, Emphysema	J68.4	CA81.Y
1.1.4	Chronic rhinitis	J31.0	CA09.0
1.1.4	Nose septal ulceration	J34.0	CA0K.Y
1.1.4	Chrome ulcers	L98.4	ME66.Y
1.1.4	Allergic disorders of upper airways	J30.3, J30.4	CA08.03
1.1.4	Lung cancer	C34	2C25.Z
	Occupational exposure to risk factors	Z57	QD84.Y

1.1.5 Diseases caused by manganese or its compounds	ICD Code T57.2 +Z57
General characteristics of the causal agent	Manganese (Mn), CAS number 7439-96-5, is the element with atomic number 25 in the periodic table of the elements, is essentially mono-isotopic, and its atomic mass is 54.9 Da. Manganese is classified in Group VII (7-B; Transition metals) and features most oxidation numbers between 0 (elemental) and VII (permanganate), with manganese (II) being stable in aqueous solution over the entire range of acidity. Manganese is ubiquitous in rocks, soil, water and food, yet it seldom occurs as free metal other than embedded in iron-manganese nodules contained in cosmogenic iron meteorites. The metal is whitish-grey in colour, very hard but ordinarily too brittle to be of structural value itself; yet, it has proved over centuries to be an irreplaceable alloying material imparting strength and hardness to iron and steel. Manganese stands as the fourth most widely used metal in the world, 90% being employed to alloy iron and steel for strength and hardness. Commercially important ores include those containing pyrolusite (MnO_2), the main manganese ore, and the much less common rose-red to pink rhodochrosite ($MnCO_3$), from which the metal is obtained by thermal reduction. The main chemical forms of manganese of concern for occupational safety include: • *Manganese chloride* ($MnCl_2$): used in the manufacturing of dry cell batteries, as supplemental trace element in animal feed, as catalyst for chlorination of organic compounds, and precursor of other manganese compounds. • *Manganese dioxide* (MnO_2): used in the manufacturing of dry cell batteries, porcelain and glass-bonding materials, in amethyst glass production (manganese oxides and salts are used as pigments and decolourizing agents in the glass and ceramic industry), as flux in electric steel welding, incendiaries, fireworks, matches, and as the starting material for other manganese compounds. • *Manganese II sulphate* ($MnSO_4$): used in fertilizers, ceramics, glazes, varnishes, fungicides, and as livestock nutritional supplement. • *Potassium permanganate* ($KMnO_4$): produced by the electrolytic oxidation of MnO_2 in potassium hydroxide (KOH) is used as a disinfectant, anti-algal agent, water purifier; in metal cleaning, bleaching and tanning; and as a preservative for fruit and flowers. Manganese dioxide and potassium permanganate are strong oxidizing agents and are able to generate elemental halogens from the halogenides (especially toxic chlorine gas from chloride) and to oxidize organic compounds, with explosion hazard. Manganese specialty chemicals include manganese-ethylene-bis-dithio carbamate (Maneb) and ethylene-bis-dithio carbamate of manganese and zinc (Mancozeb): these are widely applied to edible crops as fungicides and are therefore potential sources of manganese in soil and in food crops (see item 1.1.36). Methylcyclopentadienyl manganese tricarbonyl (MMT) is used to improve combustion in boilers and motors and may be used as a substitute for lead as anti-knock additive in petrol/gasoline. Manganese dipyridoxyl diphosphate and other manganese compounds have been recommended to replace gadolinium complexes as tissue-specific contrast agents.

1.1.5 Diseases caused by manganese or its compounds	ICD Code T57.2 +Z57
Occupational exposures	Occupational exposure to manganese mainly occurs through the inhalation of dusts and fumes. Exposures occur in ore mining, in metallurgical processing, in steel alloy production and in the downstream machining of steel alloys (cutting, boring and welding). Other industrial uses of manganese that cause exposure are dry cell battery manufacture, glass and pottery production, and the industrial production of manganese-containing chemicals and their formulation into end-products. Laboratory uses of manganese compounds as reagents also cause occupational exposure: in particular, the carbonyls of manganese, such as MMT and dimanganese deca-carbonyl, which are appreciably volatile and strongly toxic. The main productive activities involving exposure to the metal are detailed below. *Mining and preliminary treatment of ore:* manganese ore must be mined, milled, separated from other minerals, dried, sometimes crushed or ground again, often packed and mixed with other minerals before it can be refined for commercial use. *Manganese refining and making of iron and steel:* the ore must be refined. Pure manganese, that is used for the production of non-ferrous alloys, is purified by hydrometallurgical and electrolytic processes. Blast or electric furnaces are used to process the much greater quantities of ore required in the manufacture of basic iron and in steelmaking. At the end of this process, the alloy ingots may be cut for easier handling and often crushed or milled for transport. This allows better control of formulation during steel manufacture, when specified quantities of such alloys are added to the furnace charge (to impart properties including hardness and wear resistance, stiffness and strength), which equip them for particular fabrication or manufacturing uses. No substitute for manganese has been found to provide these essential qualities in steel. Occupational exposures to manganese oxide compounds may occur at each and any of these stages in manufacture. The composition and structure of the aerosol particles in the emissions are complex and vary from process to process. *Fabrication and manufacture:* most steel welding consumables that are melted to form a joint contain less than 6% manganese. Those used to join high manganese steels – such as on railway crossing points or in the process of hard facing (used for toughening surfaces such as the 'biting edge' of bulldozer blades) – contain much higher concentrations. Selective distillation of the fume in the welding-arc can increase the proportion of manganese seven-fold, compared with concentrations in the consumable.
Toxicological profile, main health effects and diagnostic criteria	
Short toxicological profile	Manganese (as ultrafine metal particles) and its compounds may be absorbed into the body through both the respiratory and the gastrointestinal tracts. The respiratory route is usually much more important in occupational exposures than the oral one. The manganese pool of the human body is estimated at about 12 mg. It is mostly stored as metal-protein conjugate(s) in the liver and kidneys and in the bones in its divalent form. Exogenous manganese absorbed from non-nutritional sources, like occupational exposures, is mostly present as solid particles. The metal is more or less rapidly leached from these particles, since it is very soluble in acid conditions (such as those of lung surfactant) and cell lysosomes are extremely efficient in this process. High-valency absorbed manganese (e.g. MnO_2 particles), is rapidly reduced to its ionic manganese (II) form by a number of endogenous soluble molecules, such as sugars and amino acids, and as such is carried in the blood like other divalent cations (e.g. magnesium(II), calcium(II), zinc(II)). Manganese is rapidly cleared from the bloodstream by the liver, which retains a mobile manganese pool and from which the metal is distributed to the body. Approximately 98% of excess manganese is excreted in the bile for disposal in faeces, and only 2% in urine. Manganese secreted by the liver as metal-proteins, is actively absorbed by cells, and incorporated in the active catalytic centre of crucial enzymes, such as zinc/manganese superoxide dismutase (Zn, Mn SOD) and arginase. In the human brain, manganese is bound to proteins, the most abudant of which is glutamine synthetase in astrocytes. When homeostatic mechanisms controlling the free manganese pool are overwhelmed by excess exposure and absorption (through the lungs and the gastrointestinal tract) or by liver dysfunction, free diffusible manganese (II) can exert toxic effects in cells: the metal ion is an active catalyst of the hydroxyl-generating dismutation of hydrogen peroxide through the Fenton-Haber-Weiss cycle. This phenomenon can be particularly destructive in specific areas of the brain, such as the basal nuclei, and in particular the globus pallidus and substantia nigra. This brain area is vulnerable to the effects of oxidative stress and the destruction of its cells by manganese and toxic organic compounds such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). These cause a clinical syndrome similar to idiopathic Parkinson's disease. Due to the generalized reduction of exposure levels, at least in the developed world, attention nowadays focuses on prolonged and lifetime exposure of the general population to low levels of manganese.

1.1.5 Diseases caused by manganese or its compounds ICD Code T57.2 +Z57

Name of the diseases and ICD code: **Acute diseases caused by manganese or its compounds**
(Specific disease code) **+T57.2 +Z57**

Mucous membrane irritation (J68), Bronchitis and pneumonitis (J68.0), Burns and corrosion of respiratory tract (T27), Burns and corrosions of external body surface (T20-T25), Burns and corrosions of mouth, pharynx and oesophagus (T28.0-T28.1, T28.5-T28.6), Burns and corrosions of eye and adnexa (T26.0-T26.1, T26.5-T26.6), Acute toxic encephalopathy (G92)

Short description of the disease

Acute manganese effects are rare and seldom described. Inhalation of fumes and vapours of manganese as well as particulate manganese compounds affects the mucous membranes. Potassium permanganate can cause considerable corrosive damage to the mucous membranes, skin and eyes. Solutions of potassium permanganate > 1:5000 are corrosive, and ingestion (uncommon at the workplace) carries the risk of local and possibly life-threatening burns of the upper gastrointestinal tract. The central nervous system may be affected, with an acute encephalopathy.

Diagnostic criteria

Clinical manifestations

Irritation and inflammation of the eyes and of the airways, with cough, bronchitis, pneumonitis, and impaired respiratory functions, can all occur. The first phases of encephalopathy due to acute manganese intoxication are characterized by mood alteration, emotional frailty, hallucinations, and aggressiveness. After some months, this stage, sometimes known as “manganese madness”, can further evolve into a chronic toxic encephalopathy (see below).

Exposure assessment

- History of occupational exposure: confirmed acute exposure to manganese fumes and dusts at the workplace and, when available, workplace air monitoring.
- Minimum duration of exposure: a few minutes.
- Maximum latent period: 48 hours.

Metal fume fever (T56.8)

Short description of the disease

Symptoms are not specific and the diagnosis can be difficult, as metal fume fever presents as a flu-like syndrome. Symptoms generally appear a few hours after exposure, and are reversible 1-4 days after cessation of exposure.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: fever, chills, nausea, headache, fatigue, malaise, muscle aches, and joint pains appearing some hours after exposure. A sweet or metallic taste in the mouth, which alters the taste of food and cigarettes, is usually reported, along with a dry or irritated throat which may lead to hoarseness. Symptoms may include a burning sensation in the body, shortness of breath, chest pain, cough, dyspnoea, rash, vomiting, watery or bloody diarrhoea and low blood pressure.
- Examinations: pulmonary function is commonly unaffected, but tests may show reduced lung volumes. Chest X-ray findings are generally unremarkable. There is an increase of white blood cell count (leucocytosis), but not in all cases. High levels of urine, blood and serum manganese can be detected.

Exposure assessment

- History of occupational exposure: confirmed acute exposure to manganese or its compounds and, when available, workplace air monitoring.
- Minimum duration of exposure: few minutes.
- Maximum latent period: few hours.

Irritant contact dermatitis (L24)

Skin lesions have been observed in manganese mineworkers. For further details on diagnostic and exposure assessment criteria, refer to item 2.2.2.

Allergic contact dermatitis (L23)

Manganese may be absorbed through damaged skin and has been implicated in the development of allergic contact dermatitis. For further details on diagnostic and exposure assessment criteria, refer to item 2.2.1.

1.1.5 Diseases caused by manganese or its compounds — ICD Code T57.2 +Z57

Name of the diseases and ICD code: **Chronic diseases caused by manganese or its compounds**
(Specific disease code) **+T57.2 +Z57**

Manganism (T57.2), Chronic toxic encephalopathy (G92)

Short description of the disease

Manganese can cause a slowly progressive and disabling Parkinsonian syndrome called "Manganism". This disease is characterized by neuropsychiatric and extrapyramidal dysfunction, with changes in neuropsychological function, motor slowing, and memory deficits attributed to deposition of manganese in the brain. The brain areas affected are those dedicated to the control of movement (principally the basal ganglia). Symptoms include gait disorders, postural instability, a mask-like expressionless face, tremor and psychiatric symptoms. The disease may be reversible, but when advanced, it can be permanent.

Manganism typically evolves in a four-stage process:

- *Stage 1:* only very mild clinical performance deficits and mood changes can be observed, and they might not be detected unless they are actively sought. Note that disease detection at this stage would allow preventive interventions and avoid the progression of the disease.
- *Stage 2:* the symptoms observed in this phase are not specific and may include weakness, irritability, anxiety, anorexia, headache, alterations of sleeping cycles and confusion. In some cases, loss of libido and impotence are reported, together with sphincter dysfunction. In general, these symptoms are initially very mild and may not be detected without active enquiry. More striking symptoms are uncontrollable laughter or tears, and impulsive/compulsive behaviour. Since this phase is not present in idiopathic Parkinson's disease, emotional symptoms may be the first indication of manganese toxicity. Neuropsychological testing can be useful in detecting abnormalities at an early stage.
- *Stage 3:* this is an intermediate stage characterized by signs and symptoms typical of basal ganglia impairment, such as slow speech and a mask-like face. This is followed by the onset of tremor, which differs from Parkinson's disease as it typically occurs on movement and is symmetrical. In this phase, the affected subject is mainly dystonic and bradykinetic, showing a typical waving movement of the arms. The patient is unable to run and can walk backwards only with difficulty. Assessment with specifically designed computer tests (e.g. the CATSYS® system) can document degree of tremor and postural sway.
- *Stage 4:* this is the most severe and final stage of the disease. The patient's condition deteriorates noticeably and various disorders, especially those affecting the gait, grow steadily more pronounced. A significant decline in memory function can be evident. Postural tremor may be observed, walking and turning around become more difficult, and walking backwards impossible. There may be a postural tremor, frequently in the lower limbs, but even generalized. Handwriting becomes irregular, with micrographia: writing may become illegible with tremor observed in cursive writing. Similar to Parkinson's disease, in advanced stages of manganism the patient has difficulty in maintaining balance, and may fall when attempting to walk backwards. As a result of increasing muscular rigidity, there may be development of the characteristic 'cock gait': slow, spasmodic, unsteady walking or strutting on extended feet and toes, putting weight on the metatarsals, with elbow flexion and a straight spine. Tendon reflexes become exaggerated. At this stage, the disease is usually irreversible.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: impaired memory and judgement, anxiety and, sometimes, psychotic manifestations, parkinsonian-like signs with progressive bradykinesia, dysarthria, axial and extremity dystonia, paresis, gait disturbances, muscle-rigidity, intention tremor, postural instability, impaired coordination and a mask-like face. For more details on the temporal evolution of signs and symptoms, see the above four-stage classification.
- Examinations:
  - Neuropsychological tests can detect abnormalities at an early stage.
  - Magnetic resonance imaging (MRI) shows bilateral hyper-intense lesions typical of manganese deposition, mainly in the *globus pallidus*.
  - Magnetic resonance spectroscopy (MRS) shows abnormal brain metabolites such as N-acetylaspartate (NAA), myoinositol, or gamma-aminobutyric acid (GABA).
  - Diffusion tensor imaging (DTI) reveals altered microstructural integrity of white matter in the *corpus callosum* and frontal areas.
  - Functional MRI shows increased activation of sensorimotor or working memory networks of the cortex due to neural compensation.
  - Fluorodopa positron emission tomography (PET) shows a typical reduction of dopaminergic transmission.

1.1.5 Diseases caused by manganese or its compounds ICD Code T57.2 +Z57

- Differential diagnosis: classical manganism can be differentiated from idiopathic Parkinson's disease (PD) and other forms of parkinsonism, in particular:
  - Early symptoms of manganism are psychiatric, differing from Parkinson's disease.
  - Symmetrical impairment is another important criterion: a non-symmetrical distribution of effects is not indicative of manganism.
  - Postural or kinetic tremor (*vs*. resting tremor in PD), early onset of gait dysfunction with peculiar high-stepped gait, tendency to fall backwards, pronounced dystonia, facial grimacing.
  - Earlier age of onset (Parkinson's disease typically occurs after the age of 60 years) and usually a poor response to levodopa.
  - On MRI neuronal damage is mainly in the *globus pallidus*, and not the *substantia nigra*.

Exposure assessment

- History of occupational exposure: confirmed prolonged exposure to manganese compounds and, when available, workplace air monitoring.
- Minimum duration of exposure: few months.
- Maximum latent period: 10 years (but latencies up to few decades have been reported).

Irritant-induced occupational asthma (J68.3)

Long-lasting observed effects of prolonged or repeated exposure to manganese include asthma and impaired lung function. For more details on clinical features and exposure assessment criteria, see item 2.1.7.

Key actions for prevention	The prevention of manganese poisoning is primarily a question of suppression of manganese dusts and fumes. In mines, dry drilling should always be replaced by wet drilling. Shot-firing should be carried out after the shift so that the heading can be well ventilated before the next shift starts up. Good general ventilation at source is essential. Airline respiratory protection equipment as well as independent respirators have to be used in specific situations to avoid excessive short-term exposures. A high standard of personal hygiene is essential, and adequate sanitary facilities, clothing, and time must be provided so that compulsory showering after work, a change of clothes, and a ban on eating at the workplace can be effected. Smoking at work should be prohibited as well. Periodic measurements of exposure levels should be performed, and attention should be given to the size distribution of airborne manganese particles. Contamination of drinking water and food as well as workers' dietary habits ought to be considered as a potential additional source of exposure. With the introduction of methylcyclopentadienyl manganese tricarbonyl (MMT) as a gasoline additive, there is concern for the toxic potential of environmental manganese exposure. Some workers may have increased susceptibility to the effects of exposure such as those with psychological or neurological disorders. Nutritional deficiency states may predispose to anaemia: mechanisms of iron absorption are similar to those of other divalent metals, and a diet deficient in iron can lead to excess absorption of and increase susceptibility to manganese. Therefore, workers suffering from such deficiencies have to be kept under strict surveillance. During the anaemic state, subjects should avoid exposure to manganese. The same relates to those suffering from lesions of the excretory organs, or from chronic obstructive lung disease. Threshold limit values (TLV) are recommended for occupational exposure to manganese and its compounds, with values intended to minimize the potential for pre-clinical adverse effects in the lungs and central nervous system (CNS). Nonetheless, the lowest exposure concentration of manganese at which early effects on the CNS and the lungs may occur is still unknown. The group of experts considered that the following limits of exposure of workplace atmospheric concentrations have been observed to provide a reasonable level of protection for workers' health and have been used in a number of countries. • Manganese and most inorganic compounds: 0.02 mg/m^3 (respirable fraction), 0.1 mg/m^3 (inhalable fraction) as 8 hours' time-weighted average (8hr TWA). • Potassium permanganate: 0.2 mg/m^3 as 8hr TWA. • Methylcyclopentadienyl manganese tricarbonyl: 0.2 mg/m^3 as 8hr TWA.

1.1.5 Diseases caused by manganese or its compounds ICD Code T57.2 +Z57

Further reading

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For the chemical entities listed below an entry exists in the collection of International Chemical Safety Cards (ICSC) hosted in the ILO website

Name	Synonyms	ICSC
Maneb	Manganese, ethylenebis(dithiocarbamate); ((1,2-Ethanediylbis(carbamodithioato))(2-)) manganese; Manganese ethylene-1,2-dithiocarbamate	0173
Manganese		0174
Manganese dioxide	Manganese(IV)oxide; Manganese peroxide	0175
Manganese sulphate monohydrate	Manganous sulphate monohydrate	0290
Potassium permanganate	Permanganic acid potassium salt	0672
Mancozeb	Manganese ethylenebis(dithiocarbamate)(polymeric)complex with zinc salt; Manzeb; Manganese-zinc ethylenebis (dithiocarbamate)	0754
Manganese, cyclopentadienyltricarbonyl	Cyclopentadienyl manganese tricarbonyl; MCT	0977
Methylcyclopentadienyl manganese tricarbonyl	MMT	1169
Manganese oxide	Trimanganese tetraoxide; Manganomanganic oxide	1398

▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
1.1.5	Acute and chronic diseases caused by manganese or its compounds	T57.2	NE61 & XM3FY4
1.1.5	Mucous membrane irritation	J68	CA81.Z
1.1.5	Bronchitis and pneumonitis	J68.0	CA81.0
1.1.5	Burns and corrosion of respiratory tract	T27	NE01
1.1.5	Burns and corrosion of external body surface	T20-T25	ND9Z, ND9Y,NE2Z, NE10, NE11
1.1.5	Burns and corrosion of mouth, pharynx and esophagus	T28.0-T28.1, T28.5-T28.6	NE02, NE01, NE0Z, ND90.Z
1.1.5	Burns and corrosion of eye and adnexa	T26.0-T26.1, T26.5-T26.6	NE00
1.1.5	Toxic encephalopathy (acute/chronic)	G92	8D43.0,
1.1.5	Metal fume fever	T57.2	NE61
1.1.5	Irritant contact dermatitis	L24	EK02
1.1.5	Allergic contact dermatitis	L23	EK00
1.1.5	Manganism	T57.2	NE61 & XM3FY4& 8A00.2Y
1.1.5	Irritant-induced occupational asthma	J68.3	CA23.0
	Occupational exposure to risk factors	Z57	QD84.Y

1.1.6 Diseases caused by arsenic or its compounds	ICD Code T57.0 +Z57
General characteristics of the causal agent	Arsenic (As), CAS number 7440-38-2, the chemical element with atomic number 33 in the periodic table of elements, has one stable isotope (^{75}As), and a mean atomic mass of 74.9 Da. Arsenic is classified in Group 15 (3-B, semi-metals) and features four different oxidation (valence) conditions: -3, 0, +3 (or III), and +5 (or V), the most important of which are: 1. Inorganic arsenic (III) *'arsenite'* and arsenic (V) *'arsenate'* compounds. 2. Organic arsenic compounds [both arsenic (V) and arsenic (III) oxidation states]. 3. Arsine gas and substituted arsines (-3 oxidation state: arsenic hydrides, arsenic alkyls). Elemental arsenic is an abundant, silver-grey, semi-metallic element, which sublimes into a vapour above 615°C rather than melting. Typical soil levels of arsenic are 1-10 ppm, while seawater has concentrations around 1.6 ppb. In nature, arsenopyrite (FeAsS) contained in sulphide ores is the most abundant form of arsenic. Other important minerals are the sulphides, orpiment and realgar. Due to the natural presence of arsenic organic compounds in several organisms, there is a natural bio-geochemical arsenic cycle. Organic arsenic compounds are abundant in marine organisms and are usually characterized by very low toxicity and low biological conversion rates to toxic forms. Arsenic commonly occurs in the atmosphere, mainly in particulate matter (ash) released from the combustion of carbon reservoirs, such as coal and oil, of which it is a natural constituent at levels up to some tens of grams per ton (parts-per-million). Arsenic fumes [mainly comprising arsenic (V) oxides] are released from the processing of mixed sulphides and arsenides in primary metallurgy. Arsine gas and alkyl-arsines (trimethyl-arsine, *Gosio gas*) are generated by moulds, which can naturally grow on arsenic-containing organic materials. Some benthonic seawater organisms are also able to incorporate arsenic into alkyl-arsenic fatty acids.
Occupational exposures	Humans have used arsenic since antiquity, as testified by manufactured bronze articles recovered at archaeological sites. Due to its toxicological hazards (see below), low-technology production and dispersion into the environment are decreasing, and the industrial use of arsenic has been restricted or banned in many countries. Nonetheless, current industrial uses and possible occupational exposures occur in several processes, which include: smelting of sulphide-arsenide ores (primary metallurgy), the preparation and manufacturing of alloys with other metals (e.g. with lead, copper, zinc), and the residual manufacture and use of arsenic-containing compounds. The latter include insecticides, herbicides, fungicides and wood preservatives (monosodium methyl arsenate, mainly in the past), and arsenic containing pigments (e.g. Paris green - cupric acetoarsenite; and Scheele's green - cupric arsenite). Applications include impregnating construction timber with copper arsenate as a biocide to prevent rotting and insect infestation. Arsenic-containing pesticides are banned in many countries, but in others, their use is still authorized. Some arsenic compounds are used in microelectronics (gallium arsenide) and in the glass-making and optical industry, where manufacturing is performed under strict conditions of isolation: occupational exposure in these contexts is thus usually very limited. The presence of both natural and non-occupational exposures to arsenic should be considered when high concentrations of arsenic are found in biological samples. Arsenic found in trace-amounts in coal, and released on burning is one of the main sources of environmental contamination from anthropogenic sources. The presence of arsenic in natural ground-water in some areas, such as coastal Bengal and Bangladesh, some regions in China and the USA, in Andean South America, as well as in central Italy, can cause environmental exposure of the general population. This may be a consequence of ingesting contaminated water, as well as arsenic incorporated in grain crops. Arsenic incorporated in combustible biomass and in treated timber, can leach into the ground, or be released in the atmosphere when these materials are burned.
Toxicological profile, main health effects and diagnostic criteria	
Short toxicological profile	Most inorganic arsenic compounds are readily absorbed after oral exposure (about 80-90% for soluble compounds, lower for less soluble compounds) and less well absorbed after inhalation although better for small particulates and soluble arsenicals. But large airborne arsenic-containing particulates that are deposited in the upper airways may be absorbed in the intestine if they are swallowed.

1.1.6 Diseases caused by arsenic or its compounds — ICD Code T57.0 +Z57

Short toxicological profile

In the human body, inorganic arsenic compounds are converted to arsenic (III) and arsenic (V); arsenic (V) is in turn rapidly converted to arsenic (III) by cellular glutathione. Arsenic (III) species are more toxic and bioactive than arsenic (V) species, both because arsenic (III) is more chemically reactive, and because it enters the cell more easily.

Arsenic can exert its toxic effects at low doses by disrupting several biological systems due to its chemical similarity to the essential element phosphorus, and its ability to bind biological thiols.

The main chemical forms of arsenic of concern for occupational health include: elemental arsenic, the inorganic compounds arsenic trioxide (As_2O_3), copper arsenite ($Cu(AsO_2)_2$), sodium arsenite ($NaAsO_2$), lead arsenate ($Pb_3(AsO_4)_2$), arsenic pentoxide (As_2O_5), and arsine gas (AsH_3). Soluble trivalent compounds are the most toxic for humans.

The toxicological targets of acute arsenic poisoning are the gastrointestinal tract and the nervous system. At cellular level, arsenic hampers energy utilization by inhibiting the key enzyme pyruvate dehydrogenase, uncoupling oxidative phosphorylation and, downstream, inhibiting energy-linked reduction of NAD+, mitochondrial respiration, and adenosine triphosphate (ATP) synthesis. Next, the excessive production of hydrogen peroxide (H_2O_2) triggers oxidative stress. The global effect of these metabolic disturbances is necrotic cell death, which can lead to death from multi-system organ failure. In cases of acute poisoning, a post-mortem examination reveals brick-red coloured mucosae, due to severe haemorrhage.

At lower doses, which are relevant to occupational exposure and to higher levels of environmental contamination, arsenic is a growth promoter initiating cell hyperplasia. For example hyperkeratosis, changes in skin pigmentation, and other adverse effects are observed in the general population of the Indian sub-continent (Bangladesh, India) and of other countries in the world where the content of inorganic arsenic in drinking water is unusually high.

Arsine gas (AsH_3) forms through electrolytic or metallic reduction of arsenic and is peculiar in its toxicity, in that it is a strong, rapidly acting haemolytic agent. Trimethyl-arsine ($As(CH_3)_3$) is a volatile arsenic compound which can be naturally generated by microorganisms and fungi, when they grow on organic media which contains arsenic. One typical source is rotting old or vintage wallpapers usually printed in green colours.

Arsenic can be measured in blood, urine, hair, and fingernails. In blood, it has a half-life of about 60 hours. In subjects with a normal renal function, its biological half-life reflected in urine excretion is between 1 to 2 days. Measurement of arsenic in urine, preferably in a 24-hour sample and corrected for creatinine excretion, is a more reliable method of monitoring absorption of inorganic arsenic by exposed workers, when compared to its measurement in blood, and in long-term compartments such as hair or nails.

Most organic arsenic compounds, which are mainly present in the diet, are eliminated in the urine in their unchanged form, while about 75% of absorbed inorganic arsenic is converted to methylated arsenic compounds in the body prior to urinary excretion; therefore, in vivo methylation represents a true detoxification process.

Exposure to arsenic both in the environment and at workplaces has been classified as a cause of cancer by the IARC (see item 3.1.15).

Name of the diseases and ICD code: **Acute diseases caused by arsenic or its compounds**
(Specific disease code) **+T57.0 +Z57**

Irritation of mucous and respiratory membranes (J68), Chemical bronchitis and pneumonia (J68.0), Chemical pulmonary oedema (J68.1), Upper respiratory inflammation (J68.2), Systemic acute poisoning (T57.0)

Short description of the disease

At high levels of exposure, arsenic and its compounds cause irritation of the nasal mucosae, larynx and bronchi. Acute intake of to large doses of inorganic arsenic (70-180 mg by ingestion) has been proved to be fatal, while absorption of sub-lethal doses can cause a plethora of systemic effects as detailed below.

1.1.6 Diseases caused by arsenic or its compounds ICD Code T57.0 +Z57

Diagnostic criteria

Clinical manifestations

- Inhaled arsenic is irritating to the respiratory mucosae and the lungs, thus inducing rhinitis, laryngitis, and bronchitis progressing to pneumonia. Pulmonary oedema can occasionally be observed.
- Sub-lethal doses of arsenic, most likely through ingestion, may cause abdominal pain, nausea, vomiting, diarrhoea; possible skin rash, hair loss, haematological alterations (anaemia, leucopaenia, neutropenia), neurological manifestations (convulsions, cramping muscles), and pulmonary dysfunction can be observed. In the most severe cases, the syndrome evolves into severe gastroenteritis, loss of fluid and electrolytes, cardiac disorders, kidney impairment, convulsions, and shock. In detail:
  - *Cardiovascular effects:* acute and chronic arsenic exposure can cause myocardial depolarization, cardiac arrhythmias, and ischaemic heart disease. Arsenic causes dilatation of capillaries, with increased permeability and consequent oedema after acute exposures, this mechanism is likely responsible for the peripheral vascular disease following chronic exposure to arsenic.
  - *Gastrointestinal effects:* acute or sub-acute exposure to high doses of arsenic by ingestion is associated with gastrointestinal symptoms, which range from mild cramping, diarrhoea, and vomiting to gastrointestinal haemorrhage and death. At higher doses there is inflammation and necrosis of the sub-mucosa and rupture of the intestinal wall.
  - *Renal effects:* the action of arsenic on renal capillaries, tubules, and glomeruli can cause severe kidney damage.
- Inhalation of arsine (AsH_3) can be lethal due to fulminant haemolysis. A few hours after exposure, patients can develop headache, anorexia, vomiting, paraesthesia, abdominal pain, chills, haemoglobinuria, bilirubinaemia, and anuria. Jaundice appears after 24 hours. Arsine induces renal toxicity that can progress to kidney failure both by itself and as a consequence of haemolysis. Approximately 25% of cases of arsine exposure result in death but this gas is seldom the cause of occupational poisonings.

Exposure assessment

- History of occupational exposure: confirmed occupational exposure to arsenic dusts, fumes or vapour and measurements of arsenic and its compounds in urine, whenever biological specimens can be obtained within 24–48 hours of exposure. A level of urinary arsenic excretion >25 µg over 24 hours might indicate poisoning. In laboratory assays, toxic inorganic arsenic must be distinguished from non-toxic organic arsenic originating from seafood by chemical speciation.
- Minimum duration of exposure: few minutes.
- Maximum latent period: few hours.

Acute toxic encephalopathy (G92)

Short description of the disease

In rare cases, high-dose acute arsenic exposure (e.g. after massive ingestion, most likely for suicidal or homicidal aims) may cause haemorrhagic encephalopathy.

Diagnostic criteria

Clinical manifestations

Neurological symptoms can progress through headache, lethargy, mental confusion, delirium, hallucination, seizures, loss of consciousness and coma. Cognitive and behavioural alterations may appear as sequelae of the acute poisoning. Typical symptoms and signs occur from few days to some weeks after the recovery from an acute poisoning.

Exposure assessment

- History of occupational exposure: confirmed previous acute arsenic poisoning occurring at the workplace.
- Minimum duration of exposure: a previous acute poisoning is necessary.
- Maximum latent period: 40 days from the onset of the acute poisoning symptoms.

1.1.6 Diseases caused by arsenic or its compounds ICD Code T57.0 +Z57

Name of the diseases and ICD code: **Chronic diseases caused by arsenic or its compounds**
(Specific disease code) **+T57.0 +Z57**

Nasal septum ulceration (J34.0)

Short description of the disease

Erosion, ulceration or perforation of the mucosal membrane of the nasal septum have been observed in cases of repeated or continuous contact of the mucous membranes of the nasal septum with elevated concentrations of arsenic fumes or dusts.

Diagnostic criteria

Clinical manifestations

Evidence of ulceration preceded by irritation, possibly progressing to septal perforation.

Exposure assessment

- History of occupational exposure: confirmed occupational exposure to arsenic dusts, fumes or vapour and measurements of arsenic and its compounds in urine, whenever biological specimens can be obtained within 24–48 hours from last exposure. A level of urinary arsenic excretion >25 µg over 24 hours might indicate poisoning. In laboratory assays, toxic inorganic arsenic must be distinguished from non-toxic organic arsenic originating from seafood. For exposures in the more distant past, arsenic (or its organic derivatives) can be measured in blood, hair (levels between 0.1 and 0.5 mg/kg on a hair sample may indicate chronic poisoning), and fingernails.
- Minimum duration of exposure: few months.
- Maximum latent period: six months.

Arsenical keratosis (warts) (L85.8), Palmar and plantar hyperkeratosis (L85.1, L85.9)

Short description of the disease

Arsenic has been shown to alter differentiation of epidermal keratinocytes, affect cell cycle and apoptosis, induce over-expression of growth factors, and enhance proliferation of keratinocytes. Among the most significant diagnostic criteria of chronic arsenic poisoning are diffuse hyperkeratotic lesions of the palms and soles. Hyperkeratotic lesions of the skin can progress to squamous cell carcinoma.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: epidermal thickening usually occurs at sites of friction and trauma, especially on both palms of the hands and soles of the feet, together with transverse white bands in the nail beds (Mee's lines). Keratoses may develop on the dorsum of the hands, the arms, and the legs. They manifest as small, punctate, non-tender, hard, horny, yellowish, often symmetric, corn-like papules.
- Examinations: biopsy of skin lesions can document hyperkeratosis.

Exposure assessment

- History of occupational exposure: confirmed chronic occupational exposure to arsenic dusts, fumes or vapour; measurements of arsenic and its compounds in blood, hair, and fingernails can document exposures occurred in the past 6-12 months.
- Minimum duration of exposure: a few months.
- Maximum latent period: three years.

Skin hyperpigmentation or depigmentation (L81.8)

Short description of the disease

Chronic arsenic exposure can cause hyperpigmentation of skin, interspersed with spots of hypopigmentation.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: melanosis (hyperpigmentation) of the face, eyelids, neck, areolae, trunk, axillary folds and genitalia. Spotted depigmentation of pigmented areas. Spotty rain-drop pigmentation of the skin distributed bilaterally and symmetrically over trunks and limbs is the best diagnostic feature of arsenical hyperpigmentation.

1.1.6 Diseases caused by arsenic or its compounds ICD Code T57.0 +Z57

Exposure assessment

- History of occupational exposure: confirmed chronic occupational exposure to arsenic dusts, fumes or vapour; measurements of arsenic and its compounds in blood, hair, and fingernails can document exposures occurred in the past 6-12 months.
- Minimum duration of exposure: a few months.
- Maximum latent period: three years.

Sensorimotor polyneuropathy (G62.2)

Short description of the disease

A common neurological effect of repeated exposure to arsenic is a peripheral neuropathy characterized by the loss of sensation in the hands and feet (a so-called "stocking and glove" distribution), followed by muscle weakness. Neuropathy occurs several days after exposure to arsenic and can be reversible following cessation of exposure, although a prolonged gradual but usually incomplete recovery may occur. Motor and sensory dysfunction is a frequent sequel of an acute poisoning; dysfunction can be observed in mild cases only in subclinical forms.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: decreased sensation (e.g. touch, pain, vibration, or proprioception), diminished reflexes (ankle, commonly), muscle atrophy, muscle twitching (fasciculation), muscle weakness, paralysis of the hands and lower limbs. Other accompanying manifestations include gastrointestinal symptoms, skin discolouration and anaemia.
- Examinations: electrophysiological features suggest a distal sensorimotor axonopathy, but proximal demyelination may be conspicuous at an early stage. Pathological examination confirms axonal loss.

Exposure assessment

- History of occupational exposure: confirmed chronic occupational exposure to arsenic dusts, fumes or vapour and, when available, measurements of arsenic and its compounds in blood, hair, and fingernails.
- Minimum duration of exposure: six months.
- Maximum latent period: three years.

Vasospasm/Raynaud's syndrome (I73.0)

Short description of the disease

Arsenic dilates capillaries and increases their permeability. Chronic exposure to arsenic causes peripheral vascular disease. The most typical example of chronic exposure to arsenic is *"black foot disease"*, a condition with a vasospastic tendency that leads to acrocyanosis and recurrent Raynaud's phenomenon. This progresses to severe venous obstruction and gangrene of the lower legs. It is worth mentioning that black foot disease is endemic in regions of Taiwan, with arsenic levels in drinking water up to 800 µg/L.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: the clinical picture typically progresses from numbness or coldness of one or more extremities to intermittent claudication, and finally to gangrene and spontaneous amputation.
- Examinations: measurement of digital artery pressure may show a decrease of about 15 mmHg after hands/feet have been cooled. Doppler ultrasound may show peripheral vascular disease. Infrared thermographic imaging of hand/feet and fingers/toes is a useful diagnostic tool. Full blood count may show anaemia.
- Maximum latent period: one year.

1.1.6 Diseases caused by arsenic or its compounds ICD Code T57.0 +Z57

Liver impairment (K71.9)

Short description of the disease

Arsenic compounds may cause necrosis of hepatocytes, injure sinusoidal and endothelial cells, and eventually cause thrombosis of intrahepatic portal vein radicals. Liver injury, including steatosis, cirrhosis, non-cirrhotic portal hypertension, angiosarcoma and primary liver cancer, can occur. Liver impairment is very often characterized by mild changes in serum hepatic enzyme concentrations and liver enlargement.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: the clinical onset of non-cirrhotic portal hypertension is often insidious with weight loss, fatigue and abdominal swelling and minor, nonspecific elevation of serum enzymes, followed by the appearance of variceal haemorrhage or ascites. Features of portal hypertension (ascites, variceal haemorrhage) rather than hepatic failure (jaundice, encephalopathy or coagulopathy) are predominant. Chronic exposure to arsenic has been linked to cirrhosis and liver cancer, although the contribution of alcohol and other chronic liver diseases in reported cases could not be excluded.
- Examinations: liver ultrasound, liver biopsy, as well as computed tomography (CT), magnetic resonance imaging (MRI), endoscopic retrograde cholangiopancreatography (ERCP), and magnetic resonance cholangiopancreatography (MRCP) can support the diagnosis and indicate the severity of liver dysfunction. Note that in liver damage due to chronic arsenic poisoning, liver function tests are often normal.

Exposure assessment

- History of occupational exposure: confirmed prolonged or repeated occupational exposure to arsenic dusts, fumes or vapour; measurements of arsenic and its compounds in blood, hair, and fingernails can document exposures that occurred in the past 6-12 months.
- Minimum duration of exposure: few months.
- Maximum latent period: few months.

Haematological alterations (D61.2)

Short description of the disease

Arsenic is likely to cause both direct cytotoxic effects on blood cells and suppression of erythropoiesis through bone marrow toxicity. Arsenic may also inhibit the synthesis of haeme.

Diagnostic criteria

Clinical manifestations

Anaemia, thrombocytopaenia, and leucopaenia can be documented through routine examinations such as full blood count. Bone marrow examination can show signs of suppressed erythropoiesis through direct bone marrow toxicity.

Exposure assessment

- History of occupational exposure: confirmed acute and chronic exposure to arsenic dusts, fumes or vapour and measurements of arsenic and its compounds in urine, whenever biological specimens can be obtained within 24–48 hours from last exposure. For exposures in the more distant past, arsenic (or its organic derivatives can be measured in blood, hair (levels between 0.1 and 0.5 mg/kg on a hair sample may indicate chronic poisoning), and fingernails, as measurement in these biological matrices can document exposures occurred in the last 6-12 months.
- Minimum duration of exposure: few months.
- Maximum latent period: one year.

1.1.6 Diseases caused by arsenic or its compounds — ICD Code T57.0 +Z57

Name of the diseases and ICD code: **Carcinogenic effects of exposure to arsenic or its compounds**
(Specific disease code) **+T57.0 +Z57**

Lung cancer (C34), Skin cancer (C44), Bladder cancer (C67)

There is sufficient evidence in humans for the carcinogenicity of mixed exposures to inorganic arsenic compounds. Inorganic arsenic compounds cause cancer of the lung, urinary bladder, and skin. In addition, a positive association has been observed between exposure to arsenic and inorganic arsenic compounds and cancer of the kidney, liver, and prostate. IARC classified arsenic and inorganic arsenic compounds as Group 1 carcinogens. For more details, refer to item 3.1.15.

Key actions for prevention	Most applications once involving arsenic have been superseded. In those where the use of the element, of its compounds and of arsenic-containing materials is required, strict isolation of the workers from the potential source of exposure should be enforced and specific personal protective equipment should be provided. This is usually the case in high technology production, such as semiconductors (gallium arsenide), where the production conditions themselves are in enclosed systems. Where this is not the case, such as in energy generation from fossil fuels, tiered protection of workers through measures such as isolation of sources followed by personal protection of workers should be employed. In addition to inhalation exposure, oral exposure via contaminated clothes, hands, tobacco and so on should be monitored, and biological monitoring of inorganic arsenic in urine may be useful for evaluation of absorbed doses. Workers should be supplied with suitable protective clothing, protective boots and, when there is a risk that the exposure limit for airborne arsenic will be exceeded, respiratory protective equipment. Lockers should be provided with separate compartments for work and personal clothes, and adjacent sanitary facilities of a high standard should be made available. Smoking, eating and drinking at the workplace should not be allowed. Pre-placement medical examinations should be carried out. Persons with pre-existing diabetes, cardiovascular diseases, anaemia, allergic or other skin diseases, neurologic, hepatic or renal lesions, should be thoroughly assessed for appropriate job placement in arsenic-related work. Periodic medical examinations of all arsenic-exposed workers should be performed with special attention to possible arsenic-related symptoms. Determination of the level of inorganic arsenic and its metabolites in urine allows estimation of the total dose of inorganic arsenic taken up by various exposure routes. This methodology is only useful when inorganic arsenic and its metabolites can be measured specifically. Total arsenic in urine may often give erroneous information about industrial exposure, since even a single meal of fish or other marine organisms (containing considerable amounts of non-toxic organic arsenic compounds) may cause greatly elevated urinary arsenic concentrations for several days. The group of experts considered that the following limits of exposure of workplace atmospheric concentrations have been observed to provide a reasonable level of protection for workers' health and have been used in a number of countries as 8hr threshold limit value time-weighted average (TLV-TWA): • 0.01 mg/m^3 for arsenic and its inorganic compounds. • 0.005 ppm for arsine.

1.1.6 Diseases caused by arsenic or its compounds ICD Code T57.0 +Z57

Further reading

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For the chemical entities listed below an entry exists in the collection of International Chemical Safety Cards (ICSC) hosted in the ILO website

Name	Synonyms	ICSC
Arsenic	Grey arsenic	0013
Arsenic trichloride	Arsenic (III) chloride; Arsenous chloride	0221
Arsine	Arsenic trihydride; Hydrogen arsenide; Arsenic hydride	0222
Disodium arsenate heptahydrate	Arsenic acid, disodium salt, heptahydrate; Sodium arsenate heptahydrate; Sodium arsenate, dibasic, heptahydrate	0326
Arsenic pentoxide	Arsenic (V) oxide; Arsenic acid anhydride; Arsenic anhydride	0377
Arsenic trioxide	Arsenic (III) oxide; Arsenous oxide anhydride; White arsenic; Arsenous acid anhydride	0378
Copper (II) orthoarsenate	Arsenic acid, copper salt; Copper arsenate	0648
Calcium arsenate	Tricalcium arsenate; Calcium ortho-arsenate; Arsenic acid, calcium salt	0765
Lead arsenate	Arsenic acid, lead salt; Acid lead arsenate; Dibasic lead arsenate	0911
Diammonium hydrogen arsenate	Arsenic acid, diammonium salt; Ammonium arsenate	1207
Sodium arsenate dibasic	Arsenic acid disodium salt; Disodium arsenate; Disodium hydrogen arsenate	1208
Magnesium arsenate	Arsenic acid, magnesium salt; Magnesium o-arsenate	1209
Potassium arsenate	Potassium dihydrogen arsenate; Potassium arsenate, monobasic; Potassium acid arsenate	1210
Copper (II) arsenite	Copper orthoarsenite; Acid copper arsenite; Arsenious acid, copper (II) salt; Cupric arsenite	1211
Lead (II) arsenite	Lead arsenite; Lead metaarsenite	1212
Potassium arsenite	Potassium metaarsenite; Arsenious acid, potassium salt; Potassium arsonate	1213
Iron (III)-o-arsenite, pentahydrate	Ferric arsenite	1241
Chlorodiphenylarsine	Diphenyl arsinous chloride; Diphenyl chloroarsine	1526
Sodium arsenite	Arsenious acid, sodium salt; Sodium meta-arsenite; Sodium dioxoarsenate	1603
Arsenic acid (80% in water)	Arsenic acid hemihydrate; ortho-Arsenic acid solution	1625

▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
1.1.6	Acute/chronic diseases caused by arsenic and its compounds	T57.0	NE61 & XM2KQ2
1.1.6	Irritation of mucous and respiratory membranes	J68	CA81.Z
1.1.6	Chemical bronchitis and pneumonitis	J68.0	CA81.0
1.1.6	Chemical pulmonary oedema	J68.1	CA81.1
1.1.6	Upper respiratory inflammation	J68.2	CA81.2
1.1.6	Acute toxic encephalopathy	G92	8D43.0Y
1.1.6	Nasal septum ulceration	J34.0	CA0K.Y
1.1.6	Palmar and plantar hyperkeratosis	L85.1	ED55.0
1.1.6	Skin hyperpigmentation or depigmentation	L81.8	ED6Y
1.1.6	Arsenical keratosis (warts)	L85.8	EK90.Y
1.1.6	Sensorimotor polyneuropathy	G62.2	8C01.Y
1.1.6	Vasospasm/Raynaud's syndrome	I73.0	BD42.1
1.1.6	Liver impairment	K71.9	DB97.Y
1.1.6	Haematological alterations	D61.2	3A70.11
1.1.6	Lung cancer	C34	2C25.Z
1.1.6	Skin cancer	C44	2C3Z
1.1.6	Bladder cancer	C67	2C94.Z
	Occupational exposure to risk factors	Z57	QD84.Y

1.1.7 Diseases caused by mercury or its compounds	ICD Code T56.1 +Z57
General characteristics of the causal agent	Mercury (Hg), CAS number 7439-97-6, is the chemical element with atomic number 80 in the periodic table of elements and is classified in Group 17 (II-B; Transition metals). Mercury is poly-isotopic with natural isotopes between ^{196}Hg and ^{204}Hg (the most abundant, at 30%, is ^{202}Hg), and its mean atomic mass is 200.56 Da. Under ambient temperature and pressure conditions, mercury is the only metallic element in liquid form with a high specific gravity (13.59 at 20°C); in addition, it vaporises slowly even at ambient temperature and boils at 356.73°C. Liquid mercury is silver-grey, shiny and mobile, has a high surface tension (which leads to the formation of tiny droplets) and a high expansion coefficient with temperature. In the elemental state, mercury is sparingly soluble in water and oily solvents, and forms inter-metallic alloys (*amalgams*) with other pure elements, among which several are of technological importance. Mercury has a positive electrochemical reduction potential in water and features oxidation numbers I (only as Hg_2^{2+}) and II, which is stable in aqueous solution over the entire range of acidity. Mercury (II) has a specific strong chemical affinity with sulphur, selenium and tellurium (*chalcogen*), a property that has important biological and environmental consequences. Mercury occurs in the natural environment in the form of the free liquid metal in cinnabar sands, although it also occurs as inorganic salts and as organic compounds of biogenic origin. The main industrial source of mercury is cinnabar ore (HgS), which is localized in exploitable quantity and concentration only in some regions, e.g. Spain, central Italy, some areas of China and of Andean South America. Recycled mercury is recovered from heating scrapped mercury-containing products and wastes. Inorganic compounds of mercury of practical relevance are mainly those of mercury (II) and include oxide, sulphate and nitrate. Of the two chlorides, that of mercury (I) (Hg_2Cl_2) is also known as calomel, is poorly soluble in water and historically was used as a bactericidal and purgative. Mercury (II) chloride ($HgCl_2$) is an easily sublimating white solid (corrosive sublimate) with a high solubility in water, where it forms very stable tetrahedral coordination complexes with chloride (e.g. $HgCl_4^{2-}$, which is one of the main chemical forms of mercury in extracellular biological fluids). Some organic compounds of mercury are found in the natural environment and are important in the bio-geochemical cycling of the element: these are the volatile di-methyl mercury, which is produced by some micro-organisms, and the water and lipid-soluble mono-methyl mercury, which is an important mercury species for its toxicological role. Biotransformation of inorganic mercury compounds to methyl mercury when in contact with water and soil explains why high concentrations of organic mercury can be found in fish and other sea organisms. Aryl-mercury compounds, such as phenyl-mercury, are of human synthetic origin.
Occupational exposures	Prehistoric man used mercury compounds as evidenced by the cinnabar red pigments present in cave paintings and in burials. Since ancient historical times, mercury has been extensively employed in the extraction of metallic gold from low-grade ores, in the process of amalgamation. The extensive use of this highly polluting technology in Andean South America, starting in the 16th century, has caused extensive pollution. An even larger release of mercury into the atmosphere started in the 19th century, with the use of mined coal, not only for combustion but increasingly as a starting material in the chemical industry. This is still the largest individual source of environmental mercury. Due to the health hazards presented by mercury, in recent years, many countries have banned the industrial and consumer uses of mercury, and the Minamata international convention was signed in 2013 to this effect. Historical industrial uses of mercury were in the felt-hat industry and in the treatment of animal furs. Organo-mercurials were previously used as fungicides, algicides, insecticides, antibacterial and disinfectant drugs. Mercury amalgams are still widely used in dentistry, although composite resins have superseded them in several countries. Occupational exposure to elemental mercury is still possible in the chemical industry, especially with old or outdated production methods. It is employed in the production of sodium hydroxide using the chloralkali (amalgam) process, as a catalyst in the production of vinyl acetate from acetylene, and in small amounts as a laboratory reagent. Other uses which are steadily decreasing are the residual manufacture, maintenance, repair and disposal of medical instruments (e.g. sphygmomanometers and thermometers), fluorescent lamps, and electric batteries for small devices. The artisan mining industry still uses mercury to amalgamate gold and silver in their extraction from very low-grade ores: this activity entails the exposure of informal workers and of their communities to health-threatening levels of mercury.
Toxicological profile, main health effects and diagnostic criteria	

1.1.7 Diseases caused by mercury or its compounds — ICD Code T56.1 +Z57

Short toxicological profile

Elemental mercury is rapidly absorbed by inhalation, moderately absorbed through the skin. There is no significant absorption via the gastrointestinal tract. From the blood, it rapidly distributes to the central nervous system (grey matter especially) and other organs, such as kidneys, liver, intestinal mucosa, myocardium, skin, and respiratory system, all representing the main targets of mercury deposition.

Inorganic mercury compounds vary in their absorption characteristics. They tend to be absorbed less rapidly through inhalation, probably because they usually occur in the form of dust particles that deposit in the higher respiratory tract and are eliminated through mucociliary clearance. Some are absorbed rapidly via the gastrointestinal tract and skin, depending on their specific chemical characteristics. Since inorganic compounds are less liposoluble, they mainly distribute in plasma, deposit in the kidneys and the liver, and are less likely to pass the blood-brain barrier.

Alkyl (i.e., organic) mercury compounds pass through the blood-brain barrier and the placenta very rapidly. Methyl mercury is one of the most hazardous of the alkyl compounds because of its prolonged elimination (the half-life is 40 to 105 days), and because other forms of mercury in the environment are bio-transformed to methyl mercury. Methyl mercury in the blood is found mainly in red blood cells. From the blood, it distributes to the central nervous system, kidneys and liver, reaching a blood-tissue steady-state in about four days.

Elemental mercury and its organic compounds are excreted mainly in urine and faeces, with small amounts in exhaled air, sweat and saliva. Organic compounds are mainly excreted through the bile, and 90% is eliminated with the faeces.

Name of the diseases and ICD code: **Acute diseases caused by mercury or its compounds**
(Specific disease code) **+T56.1 + Z57**

Acute conjunctivitis (H10.2), Burn of mouth and pharynx (T28), Irritant contact dermatitis (L24), Allergic contact dermatitis (L23), Acrodynia (T56.1), Upper respiratory inflammation (J68.2), Acute chemical bronchitis and pneumonitis (J68.0), Acute chemical bronchiolitis (J68.4), Chemical pulmonary oedema (J68.1), Acute gastrointestinal toxicity (K52.1), Acute toxic nephropathy (N14.3), Acute toxic encephalopathy (G92)

Short description of the disease

Exposure to mercury via inhalation, skin contact, or ingestion may lead to respiratory damage, renal dysfunction, involvement of the eyes, skin and mucosae, nervous system and gastrointestinal tract effects. Many inorganic and aryl compounds, including bichloride, nitrate, phenyl and butyl salts, are corrosive when swallowed. The compounds high solubility in acidic chloride-containing gastric juice show the highest levels of toxicity. However, inhalation rather than ingestion represents the most common route of exposure in occupational settings.

Diagnostic criteria

Clinical manifestations

- Inhalation of high mercury vapour concentrations for relatively short periods can cause weakness, chills, bronchitis, bronchiolitis, pneumonitis, chest pain, dyspnoea, cough, and general malaise: basal, late-inspiratory crackles on physical examination and patchy shadowing on chest radiograph may be present, in the most severe cases, pulmonary oedema, respiratory failure, and eventually death can occur.
- Effects following the direct contact of metal vapours with the skin or the ocular and gastrointestinal mucosae include irritant contact dermatitis, conjunctivitis, stomatitis, gingivitis, sialorrhoea, metallic taste, nausea, vomiting, abdominal pain, and diarrhoea.
- Soluble and insoluble inorganic and organic mercury compounds are absorbed through the skin, and allergic contact dermatitis may develop as a consequence of exposure to elemental mercury and its divalent inorganic compounds. For further details on clinical features of allergic and irritant contact dermatoses, refer to items 2.2.1 and 2.2.2, respectively.
- A particular form of mercury-related skin disease can develop, called acrodynia, also known as “pink disease” being characterized by erythema of the palms and soles with oedema of the hands and feet. This may be an idiosyncratic hypersensitivity response.
- Inorganic mercury has been associated with an immunologically mediated, rapidly presenting glomerulonephritis or nephrotic syndrome. Acute exposure to elemental mercury and inorganic compounds can cause transient proteinuria and oliguria, renal tubular dysfunction, whilst acute papillary necrosis and renal failure can also occur. Since occupational mercury exposure leads to a small reversible increase in urinary enzymes (such as urinary N-acetylglucosaminidase and gamma glutamyl-transpeptidase), these indicators are used in epidemiological studies as markers of exposure that might lead to toxicity.

1.1.7 Diseases caused by mercury or its compounds — ICD Code T56.1 +Z57

- Inhalation of elemental mercury vapours can cause acute intoxication in the central nervous system which manifests as headache, tremor, myoclonus and fasciculations, hallucinations, irritability, hyperactivity, emotional frailty, violent behaviour and suicidal tendency. Symptoms of methyl mercury intoxication include visual disturbances, ataxia, paraesthesia, fatigue, hearing loss, slurring of speech, cognitive deficits, muscle tremor, movement disorders, paralysis, shock, oedema and death following severe exposure.
- Increases in blood pressure and heart rate have been reported.

Exposure assessment

- History of occupational exposure: confirmed occupational exposure to high levels of mercury (or related compounds) vapours and, when available, workplace air monitoring and measurements of mercury and its compounds in blood and urine (assessment of blood mercury levels should be preferred when investigating acute exposures).
- Minimum duration of exposure: a single contact may be sufficient to cause disorders of the skin and ocular mucosae; few seconds for respiratory and gastrointestinal outcomes; a few hours for renal and nervous system disorders.
- Maximum latent period: 48 hours for skin, ocular, gastrointestinal and respiratory outcomes; seven days for renal and nervous system disorders.

Name of the diseases and ICD code: **Chronic diseases caused by mercury or its compounds**
(Specific disease code) **+T56.1 +Z57**

Chronic gastrointestinal toxicity (K52.1), Mercury pigmentation (L81.8), Chronic gingivitis (K05.1), Disturbances of taste and smell (R43.8), Chronic toxic encephalopathy (G92), Toxic polyneuropathy (G62.2), Chronic toxic nephropathy (N14.3), Chronic progressive renal failure (N14.3), Chronic kidney dysfunction (N18.9)

Short description of the disease

Sub-acute or chronic exposure to mercury or its compounds can cause a plethora of clinically manifest disorders whose manifestations are reported below. Recall that:

- the main targets of elemental mercury vapours are the kidneys and the nervous system,
- inorganic mercury compounds mostly affect the gastrointestinal tract and the kidneys,
- alkylmercury (di-methyl mercury) mainly causes nervous system toxicity.

Note also that maternal exposure to alkyl, especially methyl, mercury compounds, in particular during the first trimester of pregnancy, may cause adverse effects on the unborn child (such as cognitive deficits and motor retardation), also at doses below those able to cause maternal toxicity.

Diagnostic criteria

Clinical manifestations of disorders involving the nasal and oral cavities and the gastrointestinal tract

The earliest findings are usually non-purulent gingivitis, sialorrhoea and an unpleasant, metallic taste. A dark mercurial (bluish) line on the dental margin of the gums, similar to that seen in lead workers, and a slate-grey or reddish, punctate pigmentation of the buccal mucosa, the vestibular side of the gums (usually those of the lower jaw), the palate, and even the inside of the cheeks have been occasionally observed. Recurrent gingivitis (affecting in particular subjects with poor oral hygiene) may cause loosening or loss of teeth, alveolar destruction, and digestive disturbances, accompanied by anorexia and weight loss. The nose can be affected with irritation, epistaxis, and olfactory disturbances.

1.1.7 Diseases caused by mercury or its compounds ICD Code T56.1 +Z57

Clinical manifestations of disorders involving the central and peripheral nervous systems

- Signs and symptoms:
  - Tremor is the first neurological indication of chronic mercury poisoning. It affects eyelids, face, fingers and hands, accompanied by mild motor retardation (mercurial micro-parkinsonism). The tremor may impair the worker's ability to carry out fine and complex movements (such as handwriting), and in the most severe cases, it can be postural. When methyl mercury is involved (or alkyl-mercury), cerebellar ataxia and dysarthria predominate, sometimes with constriction of the visual fields due to damage to the visual cortex. Other symptoms of methyl mercury exposure include paraesthesia, fatigue, hearing loss, slurring of speech, cognitive deficits, muscle tremor, movement disorders, up to paralysis and death, in case of severe exposures.
  - Neuropsychiatric manifestations can occur. Mercurial erethism is characterized by emotional frailty, excessive timidity, morbid irritability, mental hyperactivity and outbursts of temper, anxiety, and depression. In milder cases, erethism and tremors slowly regress after removal from exposure.
  - The affected subjects show cognitive dysfunctions, including difficulty with concentration, somnolence, depression, memory deficits, and reduced psychomotor speed and precision.
  - When organic mercury is involved, the predominant dysfunctions affect the peripheral nervous system and include sensory loss, paraesthesiae of the extremities and around the mouth. Binocular vision dysfunction and blindness have been observed. In fatal cases, axonal degeneration of the dorsal and ventral roots of the spinal cord can be observed.
  - All the above can parallel more generic symptoms, such as insomnia, fatigue and headache, that may intensify and become irreversible with increasing duration and level of exposure.
- Examinations:
  - Symptoms of central nervous system dysfunction often overshadow the neuropathy. Clinical and electrophysiological evaluations show features of axonal sensorimotor polyneuropathy.
  - When organic mercury is involved, magnetic resonance imaging (MRI) can reveal atrophic changes in the occipital lobe, cerebellum and post-Rolandic region in the cerebrum. Axonal degeneration and degeneration of dorsal root ganglia the primary site of neuromuscular pathology, calcarine, and cerebellar cortex are also seen.
  - Electroneuromyography shows decreased sensory and motor velocities. In some cases, very mild and early changes have been reported in asymptomatic subjects.

Clinical manifestations of disorders involving the kidneys

Mercury can cause increased excretion of proteins and enzymes, indicative of subclinical toxicity and reversible proteinuria is the first sign of adverse renal effects due to mercury. Inorganic mercury is particularly toxic to the glomerulus. The main sign of nephrotoxicity is albuminuria. Membranous nephropathy and minimal change nephropathy may be observed; renal disease mediated by anti-glomerular basement membrane anti-body may develop. In the most severe cases, a nephrotic syndrome may occur. Mercury poisoning may cause renal tubular damage. An early sign of tubular effects is increased urinary excretion of enzymes, such as N-acetylglucosaminidase (NAG) and gamma-glutamyltransferase (GGT).

Exposure assessment

- History of occupational exposure: confirmed prolonged or repeated occupational exposure to high levels of mercury (and related compounds) vapours and, when available, workplace air monitoring and measurements of mercury and its compounds in blood and urine (assessment of mercury levels in the urine should be preferred when investigating stable chronic exposures).
- Minimum duration of exposure: a few months.
- Maximum latent period: one year for disorders involving the oral cavities, four years for disorders involving the peripheral nervous system, not applicable for disorders involving the central nervous system or the kidneys.

1.1.7 Diseases caused by mercury or its compounds	ICD Code T56.1 +Z57
Key actions for prevention	Mercury poisoning can be prevented by reducing or eliminating exposure to mercury and its compounds. Discontinuation of occupational exposure is the most effective measure to prevent further health damage. On October 10, 2013, the "Minamata Convention for Mercury" was signed to protect human health and the environment from anthropogenic emissions and releases of mercury and mercury compounds. The Convention includes a ban on new mercury mines, the phasing-out of existing ones, control measures for air emissions, and the international regulation of the informal sector for artisanal and small-scale gold mining. The extraction and use of mercury have been already prohibited in many countries, and its use in devices such as medical thermometers and blood pressure measuring devices has been discontinued. In exceptional cases, where it is impossible to find alternatives, such as in laboratory analyses of mercury, it might become necessary (based on risk assessment) to provide closed-cycle equipment with full-time environmental control and warning systems. In industry, mercury should be handled in hermetically sealed systems, and extremely strict hygiene rules should be applied at the workplace. When mercury is spilled, it very easily infiltrates crevices, gaps in floors and workbenches. Due to its vapour pressure, a high atmospheric concentration may occur even following seemingly negligible contamination. It is therefore important to avoid the slightest soiling of work surfaces; these should be smooth, non-absorbent and slightly tilted towards a collector or, failing this, have a metal grill over a gutter filled with water to collect any drops of spilt mercury which fall through the grill. Working surfaces should be cleaned regularly, and, in the event of accidental contamination, any drops of mercury collected in a water trap should be drawn off as rapidly as possible. Where there is a danger of mercury volatilizing, local exhaust ventilation systems should be installed. Work arrangements should be planned in such a way as to minimize the number of persons exposed to mercury. Most exposure to organic mercury compounds involves mixed exposure to mercury vapour and the organic compound, as the organic mercury compounds decompose and release mercury vapour. Contamination of clothes and parts of the body should be avoided, as these may be dangerous sources of mercury vapour close to the breathing zone. Special protective work clothes should be used and changed after the work shift. Individuals planning to have children should keep their exposure to mercury as low as possible by using engineering controls, personal protective equipment for the skin and respiratory tract and good personal hygiene. Pregnant workers should avoid any exposure to the metal. Workers exposed to mercury should be cautious when breast-feeding, since breast-milk may contain significant amounts of inorganic as well organic mercury. The group of experts considered that the following limits of exposure of workplace atmospheric concentrations (estimated as 8hr TWA) have been observed to provide a reasonable level of protection for workers' health and have been used in a number of countries: • 0.1 mg/m^3 for aryl mercury compounds. • 0.025 mg/m^3 for elemental and inorganic mercury. • 0.01 mg/m^3 for organometallic alkyl mercury compounds.

1.1.7 Diseases caused by mercury or its compounds ICD Code T56.1 +Z57

Further reading

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3. International Programme on Chemical Safety - Environmental Health Criteria 118: Inorganic mercury (1991) at: http://www.inchem.org/documents/ehc/ehc/ehc118.htm. Last accessed: 26.01.2022.
4. International Agency for the Research on Cancer (IARC). Beryllium, Cadmium, Mercury, and Exposures in the Glass Manufacturing Industry, IARC Monographs Volume 58 (1993) at: http://monographs.iarc.fr/ENG/Monographs/vol58/mono58.pdf. Last accessed: 26.01.2022.
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7. U.S. Dept. of Health and Human Services - Public Health Service. Agency for Toxic Substances and Disease Registry: Toxicological Profile for Mercury (1999) at: http://www.atsdr.cdc.gov/ToxProfiles/tp.asp?id=115&tid=24. Last accessed: 26.01.2022.
8. Agency for Toxic Substances and Disease Registry - Division of Toxicology and Human Health Sciences: Addendum to the Toxicological Profile for Mercury (Alskyl and Dialkyl Compounds) (2013) at: http://www.atsdr.cdc.gov/ToxProfiles/tp.asp?id=115&tid=24. Last accessed: 26.01.2022.
9. Hunter's Diseases of Occupations. Editors Baxter PJ, Aw T-C, Cockcroft A, Durrington P, Harrington JM. Tenth Edition, London: Hodder Arnold, 2010.
10. European Commission: Information notices on occupational diseases: A guide to diagnosis (2009). Office for official publication for the European communities, Luxemburg. Annex I 107. Mercury or compounds thereof. P 39- 42. Annex I 135. Encephalopathies due to organic solvents which do not come under other headings. P 150-2.
11. Harrison's Principles of Internal Medicine. 18th Edition. Chapter 384. Peripheral Neuropathy. Mercury.
12. Michael C. Byrns; Trevor M. Penning. Environmental Toxicology: Carcinogens and Heavy Metals. Chapter 67, in Goodman & Gilman's The Pharmacological Basis of Therapeutics, 12e.
13. CRC Handbook of Chemistry and Physics, 84th ed.; CRC Press: Boca Raton, FL., 2003.

For the chemical entities listed below an entry exists in the collection of International Chemical Safety Cards (ICSC) hosted in the ILO website

Name	Synonyms	ICSC
Mercury	Quicksilver; Liquid silver	0056
Phenyl mercuric acetate	Phenylmercury (II) acetate; Phenylmercury acetate; Acetoxyphenylmercury; PMA	0540
Mercuriphenyl nitrate	Mercuriphenyl nitrate; Merphenyl nitrate; Mercury, Nitratophenyl	0541
Mercuric acetate	Acetic acid, mercury (2+) salt; Mercury di(acetate)	0978
Mercuric chloride	Mercury dichloride; Mercury (II) chloride	0979
Mercuric nitrate	Mercury (II) nitrate; Mercury dinitrate	0980
Mercuric oxide	Mercury (II) oxide	0981
Mercuric sulfate	Mercury (II) sulphate; Mercuric bisulfate	0982
Mercurous chloride	Dimercury dichloride; Calomel	0984
Dimethyl mercury	Mercury, dimethyl	1304

▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
1.1.7	Acute/chronic diseases caused by mercury or its compounds	T56.1	NE61 & XM1FG4
1.1.7	Gastrointestinal toxicity	K52.1	1A40.0
1.1.7	Toxic nephropathy	N14.3	GB55.1
1.1.7	Toxic encephalopathy	G92	8D43.0Z
1.1.7	Upper respiratory inflammation	J68.2	CA81.2
1.1.7	Acute chemical bronchitis and pneumonitis	J68.0	CA81.0
1.1.7	Acute chemical bronchiolitis	J68.4	CA81.Y
1.1.7	Chemical pulmonary oedema	J68.1	CA81.1
1.1.7	Irritant contact dermatitis	L24	EK02
1.1.7	Acute conjunctivitis	H10.2	9A60.Z
1.1.7	Allergic contact dermatitis	L23	EK00
1.1.7	Acrodynia	T56.1	NE61
1.1.7	Mercury pigmentation	L81.8	ED6Y
1.1.7	Chronic gingivitis	K05.1	DA0B.Y
1.1.7	Disturbances of taste and smell	R43.8	MB41.Z
1.1.7	Toxic polyneuropathy	G62.2	8D43.2Y
1.1.7	Chronic progressive renal failure	N14.3	GB61.Z
1.1.7	Chronic kidney dysfunction	N18.9	GB61.Z
	Exposure to occupational risk factors	Z57	QD84.Y

1.1.8 Diseases caused by lead or its compounds	ICD Code T56.0 +Z57
General characteristics of the causal agent	Lead (Pb, *Plumbum*), CAS number 7439-92-1, is a metal with the atomic number 82 in the periodic table of elements, and is sited in Group VII (7-B; Transition metals). It has two oxidation numbers (II and IV). Lead is the stable terminal nuclide of the radioactive decay of the naturally occurring actinide elements thorium and uranium. Lead is poly-isotopic, the isotopic composition changes with the source of lead minerals, and their measurement can be employed to trace the mineral source. ^{206}Pb, ^{207}Pb and ^{208}Pb are the most abundant isotopes in the proportion 1:1:2 (approximately). The mean atomic mass of lead is 207.2 Da. It has a high density (10.66 g/cm^3), but is malleable. It has a low melting point (327.4°C), and is appreciably volatile at temperatures greater than 500°C. The metal is silvery-grey in colour with a dull-bluish shine. Lead II is stable in water solutions, while lead IV is a mild oxidizer. Lead is resistant to corrosion by some acids (such as carbon dioxide and sulphuric acid), due to the formation of protective insoluble oxide and salt layers. Nonetheless, its negative oxido-reductive potential in water makes it react with strong inorganic acids (e.g. hydrochloric and nitric), with some organic acids (especially acetic acid), and with oxidants. Elemental metallic lead is not found in nature, and lead minerals consist of a variety of inorganic and organic compounds, the latter combined primarily with carbon and hydrogen. Industrially exploitable lead ores include galena (lead sulphide), which is the richest primary commercial source of lead), cerussite (carbonate), anglesite (sulphate), corcoite (chromate), wulfenite (molybdate), pyromorphite (phosphate), mutlockite (chloride) and vanadinite (vanadate). Lead has been employed in technology since prehistoric times. Inorganic compounds of industrial importance include acetate, carbonate, chloride and nitrate salts (which are readily soluble in water); chromates and stearates (moderately soluble), and sulphide and oxides (poorly soluble). Lead oxide is still widely used as an anti-corrosive primer paint for iron structures, since iron oxides and elemental iron combine with lead (II, IV) oxide to yield insoluble iron (II) and iron (III) plumbates. Organic compounds include tetraethyl lead (TEL) and tetramethyl lead (TML). These are water-insoluble liquids that very easily dissolve in organic solvents and therefore in biological fats and lipids. In some countries, TEL is still used as anti-knock additive in gasoline.
Occupational exposures	Occupational exposure can occur in all phases of the metal's life cycle: mining, refining, production and use of metallic lead, alloys (e.g. with antimony and copper) and of lead compounds, followed by recycling and disposal of lead material and products. In primary production of lead, exposure occurs in lead mining, smelting and refining, and the chemical industry. Workers are exposed in secondary use in the chemical industry, the plastics industry, the rubber industry, shipbuilding, and the construction industry including installation and maintenance of structures painted with lead, lead pipes and plumbing fittings and lead linings in tanks. Lead is employed in manufacturing electric accumulators (batteries), small-calibre ordnance for civil, security and military purposes, high-refractive leaded or stained glass and crystals, fillers especially for PVC plastic items, pigments, ceramics and pottery, and gasoline additives. Foundry workers can experience high exposures, scrap metals smelted to produce steel typically contain lead paint or fittings. Other occupations at risk of exposure include plumbers, pipe fitters, welders, industrial soldering of lead products and of non-ferrous metals (e.g. copper electric wires), pottery workers, radiation protection, radiator repair, firing-range instructors, gasoline-station attendants, printers, jewellers, and even the wholesale trade. Demolition workers may handle lead fittings, and can experience particularly exposures when flame cutting metal structures coated in lead paint. Exposure occurs during solid-waste transportation and disposal, and land-remediation. Exposure at health-threatening levels often occurs in small-scale, informal, or recreational activities. For example in scrap lead foundries, on-site repair soldering (e.g. of radiators and pipes), grinding, welding and cutting of materials painted with lead-containing paints and enamels, soldering of jewellery, casting works of art, enamelling, manufacture of highly refractive glass (e.g. Bohemia crystal), and pottery.
Toxicological profile, main health effects and diagnostic criteria	
Short toxicological profile	Inorganic lead is absorbed mainly by inhalation of airborne fumes, and by ingestion of dusts. In particular, 'red' lead oxide Pb_3O_4 (red minium), which is soluble in gastric juice. Absorbed inorganic lead is distributed throughout the body, with most carried bound to thiol-rich proteins (e.g. serum albumin, thiol amino acids and peptides), and with organic oxy-acids.

1.1.8 Diseases caused by lead or its compounds — ICD Code T56.0 +Z57

Short toxicological profile

Due to its strong binding to red blood cells, the half-life of the circulating metal is approximately 30 days. Skeletal bones account for the long-term storage of most absorbed inorganic lead (because of lead ion's similarity to calcium), where its elimination half-life is approximately 30 years. From the bones, inorganic lead can be released back into the circulation and the soft tissues: this occurs when bones face extensive remodelling, e.g. during pregnancy, breast-feeding, old age and in calcium homeostasis imbalances caused by chronic kidney disease. The way in which inorganic lead is absorbed, distributed, stored and excreted in the body (i.e., the toxicokinetics) has important implications for exposure assessment and prevention of toxicity (see below).

Lead toxicity affects multiple organs: the nervous, gastrointestinal, renal, haematopoietic, cardiovascular, endocrine and reproductive systems. High occupational exposures typically cause anaemia, central nervous system effects, peripheral neuropathy, chronic kidney disease leading to secondary hypertension and cardio-vascular disease.

The molecular basis of its biological effects include interference with calcium signalling and haeme biosynthesis, as well as the generation of oxidative stress. Lead binds to the active catalytic site and to the regulatory sites of key enzymes of the haeme biosynthetic pathway, the most sensitive being amino-levulinic acid dehydratase (ALAD). Some enzyme iso-forms are more sensitive than others to inhibition by lead, and subjects carrying the gene polymorphism allele ALAD2 are more prone to lead toxicity. Dose-response relationships between lead exposure and haeme biosynthesis have been measured *in vivo* in lead-exposed workers: and on this basis, biological exposure indices and threshold limit values may be derived.

Exposure to organic lead mostly occurs by inhalation and dermal exposure to 'leaded' gasoline, but is declining with the decreasing use of this fuel. Absorbed organic lead compounds are very soluble in body lipids. They readily cross the blood-brain barrier and accumulate in the brain and other lipid-rich tissues such as bone-marrow. In neurons the neutral alkyl-lead compounds are partially de-alkylated to more water-soluble forms and the clearance of the metal from the nervous system is very slow. Organic lead compounds such as tetramethyl lead (TML) and tetraethyl lead (TEL) predominantly cause nervous system toxicity, as well as irritation of skin and mucous membranes.

Name of the diseases and ICD code: **Diseases caused by inorganic lead** *(Specific disease code)* **+T56.0 +Z57**

Mucous membrane irritation (J68), Chemical bronchitis and pneumonitis (J68.0), Burn of mouth, pharynx and oesophagus (T28.0-T28.1, T28.5-T28.6), Burn of eye and adnexa (T26.0-T26.1, T26.5-T26.6), Upper respiratory tract inflammation (J68.2), Burn and corrosion of respiratory tract (T27), Chemical pulmonary oedema (J68.1), Reactive airways dysfunction syndrome (RADS) (J68.3), Irritant-induced occupational asthma (J68.3), Gastrointestinal toxicity (K52.1), Hypertension (I15.8), Acute lead nephropathy (N14.3), Chronic lead nephropathy (N14.3), Fanconi-like syndrome (E72.0), Acute and chronic toxic encephalopathy (G92), Cerebral oedema (G93.6), Ulnar nerve palsy (G56.2), Infertility male (N46) Infertility female (N97.0)

Short description of the disease

Inorganic lead usually causes occupational toxicity following inhalation of dust/fume, and to a lesser extent following ingestion and gastrointestinal absorption. Airborne exposure causes irritation and inflammation of the eyes. Inhalation causes irritation and inflammation of the airways with cough, bronchitis, pneumonitis, and impaired respiratory function. Acute inorganic lead toxicity affects the gastrointestinal, hematopoietic, nervous, cardiovascular systems and the kidneys. It usually occurs in the hours or days after very high exposure. Recall that, after absorption, the metal is stored in body tissues, particularly in bones where is toxicologically silent unless it is released. Therefore, acute toxicity can occur after release of lead from bone storage into the circulatory system, e.g. in conditions causing a massive release of mineral substance from the bone, such as pregnancy, and metabolic conditions leading to bone demineralization. Additionally lead chelating therapy carried out at excessively high doses. With regard to reproductive toxicity, past high levels of chronic lead exposure have been associated with adverse pregnancy outcomes. Testicular effects, such as reduced sperm counts and motility, may result from chronic exposure to lead. However, the literature is not entirely consistent.

Diagnostic criteria

Clinical manifestations

- *General symptoms and signs*

  Lead toxicity is often insidious at onset, and difficult to detect without pathology investigations. Pallor (caused by vasoconstriction), malaise and unexplained sense of fatigue, headache, dizziness, loss of memory, anxiety, depression, irritability, sleep disturbances, mildly progressive cognitive impairment, generalized weakness, muscle and joint pain. A blue or *Burtonian* line may be present in the dental margin of the gums, it is caused by bacterial deposition of lead sulphide, and is usually associated with poor dental hygiene.

1.1.8 Diseases caused by lead or its compounds ICD Code T56.0 +Z57

- *Haematopoietic system*

  Lead inhibits δ-aminolevulinic acid dehydratase (ALAD), coproporphyrinogen oxidase, and ferrochelatase, and thus impairs haeme biosynthesis. The result is a mild microcytic or normochromic anaemia, and (non-immune) haemolytic anaemia. The latter may be normocytic or slightly macrocytic, depending on the degree of reticulocytosis. The activity of the rate-limiting enzyme of the pathway, δ-aminolevulinic synthetase (ALAS), which is feedback inhibited by haeme, is increased. The consequences of these changes in enzymatic activity are increased urinary coproporphyrin, and δ-aminolevulinic acid (ALA). In the blood, increased blood and plasma ALA, and abnormally high blood levels of free erythrocyte protoporphyrin. A measurable parameter of the latter is zinc protoporphyrin (ZPP). The lag period for the increase of blood ALA is only 2 weeks from beginning of exposure.

- *Gastrointestinal system*

  Abdominal symptoms are a well-known and consistent early symptom of acute lead poisoning. They are caused by autonomic dysfunction of intestinal motility. Symptoms include abdominal pain and cramps (colic), constipation, nausea, vomiting, anorexia, and weight loss.

- *Nervous system*

  In acute poisoning, typical neurological symptoms are pain, muscle weakness, paraesthesia, and, rarely, symptoms associated with encephalitis. Severe lead poisoning typically causes progressive ulnar nerve paralysis with symptoms of tingling and burning and loss of sensation in the fingers, manual pain and weakness. A typical sign is "wrist drop" and loss of extension of the fingers caused by weakness of the extensor muscles of the forearm. Severe poisoning increases capillary endothelium permeability in the central nervous system, with perivascular haemorrhagic exudates and cerebral oedema. Symptoms include disorientation, and confusion. Signs include impaired consciousness which may progress to stupor and even coma. There may be repeated seizures, hemiparesis and a positive unilateral Babinski sign. Chronic neurological effects can be documented by a decrease of cognitive performance.

- *Urinary system*

  Inorganic lead exposure sometimes causes acute kidney toxicity probably from accumulation of lead-protein complex in proximal tubular cells. This results in Fanconi syndrome with proximal tubular nephropathy, aminoaciduria, glycosuria and loss of phosphate.

  Chronic lead toxicity causes glomerular sclerosis, progressive tubular atrophy, and interstitial fibrosis. This can lead to elevated blood pressure, hyperuricaemia (causing saturnine gout), and chronic kidney disease. Proteinuria is typically minimal, but proximal tubular damage gives increased urine levels of low-molecular weight proteins and enzymes.

- *Cardiovascular system*

  Secondary hypertension and cardiovascular disease are important consequences of chronic lead toxicity. Changes in cardiac conduction and rhythm may be associated with increasing lead body burden.

Exposure assessment

- History of occupational exposure: confirmed occupational exposure to inorganic lead compounds (fume and dust).
- Minimum duration of exposure: a few hours for acute effects, a few months for chronic effects.
- Maximum latent period: Uncertain for most acute effects. For chronic neurological effects, four years. For chronic nephropathy, eight years.
- Ingestion is an important route of lead toxicity, and inhalation exposure is influenced by the particle size of lead compounds in the air. As a consequence, environmental air levels are usually poorly correlated with levels of toxicity. Nevertheless, they provide a general estimate of exposure control measures. Biological monitoring and biological exposure monitoring for lead are the mainstays of assessing exposure. No one method provides a comprehensive estimate of toxicity, and the paragraphs below describe the raft of monitoring methods that are usually employed. Periodic monitoring is recommended, e.g. at yearly intervals for low levels of exposure, but more frequently in higher exposures.
- Full blood counts are a simple way of monitoring for lead toxicity. Anaemia can occur with blood lead levels above 50 µg/dL. however, it is more commonly caused by other medical conditions. Basophillic stippling (punctate basophilia) may be observed in blood films, and is proof of lead exposure (as opposed to toxicity).

1.1.8 Diseases caused by lead or its compounds — ICD Code T56.0 +Z57

- Lead concentration in whole blood is the principal method of monitoring for lead toxicity. Levels above 50 µg/dL are associated with anaemia, and levels over 100 µg/dL are associated with neurological and renal toxicity. The concentration at a specific point in time is the result of several inter-related factors: 1) the principal one is exposure to lead in the preceding weeks and months, 2) with relative low levels of recent exposure, the whole blood lead will reflect the balance between release of lead from bone stores, and excretion by the kidney, 3) high bone levels of lead result from high exposures over decades, and 4) in addition, any chronic kidney disease will impair excretion of lead by the kidney, and increase its blood levels. Whole blood lead is a good measure of recent exposure, but usually a poor measure long-term body burden which is the principal factor in end-organ disease. To overcome this weakness, serial measurements of whole blood lead have been employed to derive a cumulative blood lead index.
- Blood zinc protoporphyrin (ZPP) levels provide an estimate of exposure in the preceding two weeks. In unexposed workers, levels are normally less than 2 µg/g haemoglobin and start to rise with blood lead levels between 30 µg/dL and 60 µg/dL.
- In cases of severe toxicity, when chelation treatment is being considered, ethylenediamine tetraacetic acid (EDTA) lead mobilisation studies can be used to estimate body burden.
- K-line X-ray fluorescence studies of bone, usually of cortical bone in the tibia, have been used extensively in epidemiological studies to estimate total body burdens of lead. In production plants with large stable work-populations, this can identify trends and hot-spots of exposure. However, occupational exposure standards do not appear to have been developed.

Name of the diseases and ICD code: **Diseases caused by organic lead** *(Specific disease code)* **+T56.0 +Z57**

Acute organic lead poisoning (T56.0), Gastrointestinal toxicity (K52.1), Eye irritation (T26.0-T26.1), Upper respiratory tract inflammation (J68.2), Irritant contact dermatitis (L24), Acute toxic encephalopathy (G92)

Short description of the disease

Occupational acute organic lead poisoning is usually caused by exposure to tetraethyl lead (TEL), either pure or present in "leaded" or "ethyl" gasoline. Toxicity is characterized by acute encephalopathy accompanied by neurobehavioral disorders. Symptoms may include abdominal discomfort, anorexia, vomiting and diarrhoea. Exposures to very high environmental concentrations causes irritation of skin, mucous and ocular membranes.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms:
  - Inhalation can induce sneezing and irritation of the upper respiratory tract; eye and skin contact can provoke itching, burning and redness.
  - Encephalopathy may appear several hours to weeks after the exposure. Symptoms include malaise, fatigue, headache, anorexia, sialorrhoea, nausea, vomiting, insomnia or lethargy, depression, irritability, and decreased libido. Aggressive behaviour, tremor and ataxia are often seen. In the most severe cases, acute mania, psychosis, hallucinations, convulsions, delirium, tremor, choreiform movements, gait disturbances, coma and death can be observed.
- Examinations: neurobehavioral tests usually show decreased scores. Laboratory analyses show increased urinary tetraethyl lead levels. Changes in the blood count or in the metabolites of haeme synthesis are absent.

Exposure assessment

- History of occupational exposure: confirmed working conditions supporting the evidence of acute (often accidental) exposure to organic lead. If available, elevated TEL concentrations in urine. Blood lead levels are usually normal.
- Minimum duration of exposure: few hours.
- Maximum latent period: 20 days.

1.1.8 Diseases caused by lead or its compounds — ICD Code T56.0 +Z57

Chronic toxic encephalopathy (G92)

Short description of the disease

Chronic intoxication due to organic lead compounds is similar to the acute intoxication, but with a slower onset of the symptoms, and a milder clinical picture.

Diagnostic criteria

Clinical manifestations

Irritability, insomnia, disturbing dreams, hallucinations, psychosis, anorexia, nausea, vomiting, tremulousness and ataxia.

Exposure assessment

- History of occupational exposure: confirmed working conditions supporting the evidence of exposure to organic lead. If available, elevated TEL concentrations in urine. Blood lead levels are usually normal.
- Minimum duration of exposure: few months.
- Maximum latent period: years.

Key actions for prevention	Lead poisoning in occupational settings can be prevented using the hierarchy of controls; e.g. the elimination of the use of lead and its compounds, and control of lead dusts, vapours and fumes in environmental air. Wherever possible, lead compounds are replaced by less-hazardous substitutes. In particular, much less toxic zinc and titanium-based anti-corrosive paints, as substitutes for yellow lead chromate and 'red' lead oxide (Pb_3O_4, red minium). It should be noted that copper (cuprous) oxide and not Pb_3O_4 is normally used to protect the under-water hulls of ships. In many countries the use of tetra-ethyl lead as anti-knock agent for the formulation of gasoline has been banned. Local and general exhaust ventilation can effectively reduce workers' exposure. Although skin absorption of inorganic lead is usually negligible, the use of protective coveralls and the application of standard personal hygiene of workers is very effective in reducing lead ingestion and transport out of the workplace. Cloakroom accommodation should be provided for protective coveralls, with separate accommodation for non-work clothing. Personal washing facilities, including soap and warm water, should be provided and used. Time should be allowed for washing before eating. Arrangements should be made to prohibit eating and smoking in the vicinity of lead processes and suitable eating facilities should be provided. The possibility of contaminating the homes of workers, and exposing family members to lead dust from the working clothes should be considered. Lead is especially hazardous to young children and pregnant workers, and should be prevented. As described above, the measurement of blood lead levels and biological effects in workers at regular intervals, are fundamental tools for occupational physicians to estimate whether excessive exposure has taken place. Workers' health surveillance programs should be organized taking into account the level of exposure at workplaces, the duration of exposure, the results of biological monitoring and clinical manifestations, if present. Occupational exposure limits are available for lead and its compounds, and vary in different countries. The group of experts considered that the following limits of exposure of workplace atmospheric concentrations (as 8hr TLV-TWA) provide a reasonable level of protection for workers' health: • Lead and most inorganic compounds: 0.05 mg/m^3. • Tetraethyl lead: 0.1 mg/m^3. • Tetramethyl lead: 0.15 mg/m^3.

1.1.8 Diseases caused by lead or its compounds ICD Code T56.0 +Z57

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For the chemical entities listed below an entry exists in the collection of International Chemical Safety Cards (ICSC) hosted in the ILO website

Name	Synonyms	ICSC
Lead	Lead metal; Plumbum	0052
Lead chromate	Plumbous chromate; Chromic acid, lead (II) salt (1:1)	0003
Lead (II) oxide	Lead monoxide; plumbous oxide; Lead protoxide; Litharge	0288
Lead naphthenate	Naphthenic acid, lead salt	0304
Lead acetate	Lead diacetate; Lead dibasic acetate	0910
Lead arsenate	Arsenic acid, lead salt; Acid lead arsenate; Dibasic lead arsenate	0911
Lead carbonate	Carbonic acid, lead (2+) salt; Lead (2+) carbonate; Cerussite	0999
Lead nitrate	Lead (II) nitrate; Lead dinitrate; Plumbous nitrate	1000
Lead dioxide	Lead peroxide; Lead (IV) oxide	1001
Lead tetroxide	Lead orthoplumbate; Red lead; Minium; C.I. Pigment red 105	1002
Lead(II) arsenite	Lead arsenite; Lead metaarsenite	1212
Lead bis (dimethyldithiocarbamate)	Lead dimethyldithiocarbamate; Bis(dimethylcarbamodithioato-S,S') lead; Ledate; Methyl ledate	1545
Tetraethyl lead	Tetraethyl plumbane; Lead tetraethyl; TEL	0008
Tetramethyl lead	Tetramethyl plumbane	0200

▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
1.1.8.	Acute and chronic diseases caused by lead or its compounds	T56.0	NE61 & XM0ZH6
1.1.8	Mucous membrane irritation	J68	CA81.Z
1.1.8	Chemical bronchitis and pneumonitis	J68.0	CA81.0
1.1.8	Chemical pulmonary oedema	J68.1	CA81.1
1.1.8	Burn of mouth, pharynx and oesophagus	T28.0-T28.1, T28.5-T28.6	NE02
1.1.8	Burn of eye and adnexa	T26.0-T26.1, T26.5-T26.6	NE00
1.1.8	Upper respiratory tract inflammation	J68.2	CA81.2
1.1.8	Burns and corrosion of respiratory tract	T27	NE01
1.1.8	Reactive airways dysfunction syndrome (RADS)	J68.3	CA81.Y
1.1.8	Irritant-induced occupational asthma	J68.3	CA81.Y
1.1.8	Gastrointestinal toxicity (organic and inorganic, acute and chronic)	K52.1	DA42.82
1.1.8	Hypertension (secondary)	I15.8	BA04.Z
1.1.8	Acute lead nephropathy	N14.3	GB55.1
1.1.8	Fanconi-like syndrome	E72.0	5C60.Z
1.1.8	Acute toxic encephalopathy (organic and inorganic)	G92	8D43.0Y
1.1.8	Cerebral oedema	G93.6	8D60.1
1.1.8	Polyneuropathy (organic and inorganic)	G62.2	8D43.2Y
1.1.8	Chronic toxic encephalophaty (organic and inorganic)	G92	8D43.0Y
1.1.8	Burton line on the gums	K05	DA0B.Y
1.1.8	Chronic progressive renal failure	N14.3	GB55.1
1.1.8	Infertility male	N46	GB04.Z
1.1.8	Infertility female	N97.8	GA31.Z
1.1.8	Irritant contact dermatitis	L24	EK02
	Occupational exposure to risk factors	Z57	QD84.Y

1.1.9 Diseases caused by fluorine or its compounds	ICD Code T59.5 +Z57
General characteristics of the causal agent	Fluorine (F), CAS number 7782-41-4, is the chemical element with atomic number 9 of the periodic table of elements, is mono-isotopic and has an atomic mass of 18.99 Da. Fluorine is classified in Group 17 (VII-A; Main group) and mostly features the oxidation number 1 (fluoride). A short-lived radioactive isotope, ^{18}F (half-life approximately 2 hours, decays by emitting positrons), is artificially produced by several irradiation methods in a cyclotron (such as from the minor isotope ^{18}O of enriched water) and is incorporated into drugs such as [^{18}F]-6-fluorodesoxy-glucose and [^{18}F]-fluoro-DOPA, which are used for medical diagnostics in the technique of Positron-Emission Tomography (PET). Molecular fluorine, seldom present in its elemental state in nature, is a diatomic yellow gas with a typical pungent odour, is heavier than air and reacts violently with water, producing toxic and corrosive vapours, such as ozone and hydrogen fluoride; the latter as an aqueous solution is called hydrofluoric acid. Fluorine is highly reactive and combines with nearly all other organic and inorganic substances, reacting violently with ammonia, metals, oxidants and many other materials giving fire and explosion hazards. Fluoride is the most common form of fluorine in naturally occurring minerals and inorganic compounds. A few natural fluorine-containing organic compounds are known and are used by producing organisms, usually plants, as chemical deterrents against predators. Fluorine atoms are incorporated into the chemical structure of different manufactured products to impart specific properties. Several classes of fluorine compounds are of relevance for occupational hygiene and toxicology. Among the most important are those employed in the industrial preparation of fluorinated chemicals, and the fluorinated chemicals themselves: tetrafluoroethylene and its polymer whose best-known brand name is Teflon®, chloro-fluoro-hydrocarbons, perfluoro-acids and alcohols, some pharmaceutically important compounds such as the anticancer drug 5-fluorouracil, and the volatile anaesthetic drugs Halothane, Isoflurane, Sevoflurane and Desflurane.
Occupational exposures	Fluorine is widely distributed in the environment since it is present, although at low concentrations, in virtually all rocks, in normal soils, in surface and seawater, and in the air. Some minerals are present in nature as industrially exploitable ores and are the staple of fluorine industrial chemistry. *Fluorspar* (CaF_2) is used as a flux in high temperature smelting and in refining processes of the production of metals and alloys. It can react with sulphuric acid with the production of hydrogen fluoride. *Cryolite* (Na_3AlF_6) is mainly used in the manufacture of aluminium by electrochemical reduction of bauxite. *Fluorapatite* ($CaF_{2-3}Ca_3(PO_4)_3$) is used in the production of phosphate fertilizers, phosphoric acid and phosphorus. Over 50% by weight of mammalian skeleton is constituted of hydroxylapatite, which is more soluble. Substitution of the hydroxyl groups with fluorine makes bone and teeth enamel more mechanically resistant. This is the rationale underlying the supplementation of drinking water with low concentrations of fluoride (about 1 ppm) and of toothpaste with sodium fluoride or sodium mono-fluoro-phosphate to prevent dental caries. *Elemental fluorine* and *hydrofluoric acid* (HF) are used as starting materials in the synthesis of organic and inorganic fluorine compounds. Industrial activities at risk of exposure include production of phosphate fertilizers, aluminium production, brick manufacture, tiles, pottery and cement products; production of glass enamel and glass fibre; steel and non-ferrous metal casting and arc welding, carried out with the use of calcium fluoride and other inorganic fluorides; petroleum refining; coal combustion. A minor but hazardous activity is uranium processing, where isotopes of uranium are separated with the use of uranium hexafluoride. Hydrofluoric acid is a highly volatile, colourless gas or liquid which is very soluble in water and has a bitter smell. This corrosive liquid boils at 19.4°C and reacts in moist air to form an acid mist. Hydrofluoric acid is used in the production of organic and inorganic fluorine compounds, in fluorination processes and as an acid catalyst particularly in paraffin alkylation in the petroleum industry; in non-chemical technological processes, such as removing of sand from metallic castings, polishing, frosting and etching of glass and enamel processing. Sodium fluoride, prepared by neutralizing hydrofluoric acid, is an inhibitor of glycolysis and is thus used as an insecticide and to stop fermentation in brewing. Industrial exposure to fluoride may arise in mining and use of fluoride-containing materials. Several hazardous industrial fluorine compounds hydrolyse to hydrofluoric acid. Hydrofluoric acid is widely used as a de-rusting agent in household products and by plumbers, who most often operate in the informal sector.

1.1.9 Diseases caused by fluorine or its compounds	ICD Code T59.5 +Z57
Occupational exposures	*Boron trifluoride* (BF_3) is a non-flammable colourless gas with a sharp odour, which is used as a general "Lewis acid" catalyst and forms a mist of hydrogen fluoride and boric acid in moist air. *Nitrogen trifluoride* (NF_3) is a gas used in rocket fuel production and in fluorination reactions. *Carbonyl fluoride* (COF_3) is a gas produced during the thermal decomposition of polytetrafluoroethylene (PTFE) and of other fluorinated hydrocarbons; it is used as a chemical intermediate in the synthesis of organic compounds (e.g. fluorinated alkyl isocyanates). *Oxygen difluoride* (OF_2) is a gas characterized by a foul smell and very strong oxidizing properties. It is a very toxic compound, used as an oxidizer in rocket fuel systems. *Perchloryl fluoride* (ClO_3F) is a colourless, stable, non-flammable, sweet-smelling gas, used in organic chemistry as a mild fluorinating agent. *Phosphorus trifluoride* (PF_3) is a colourless gas able to cause toxic effects at concentrations well below its odour threshold, mainly used as a ligand in metal complexes. *Phosphorus pentafluoride* (PF_5) is a colourless gas with a sharp odour, which produces hydrogen fluoride and phosphorus oxy-fluorides in contact with moist air; it is used as a polymerization catalyst. *Silicon tetrafluoride* (SiF_4) is a colourless non-flammable gas with an overwhelming odour. It is naturally present in volcanic emissions and produces a dense white mist of hexafluorosilicic acid in air. Industrially, silicon tetrafluoride is produced when hydrofluoric acid is used to etch glass. In water, this toxic gas hydrolyses to yield fluosilicic acid (H_2SiF_6) which is the agent most commonly used to fluoridate water. *Sulphur tetrafluoride* (SF_4) is rapidly hydrolysed to hydrogen fluoride and thionyl fluoride, which in turn is slowly hydrolysed with the production of hydrogen fluoride and sulphur dioxide; it is used as a fluorinating agent and in making water and oil repellent materials, as well as pesticides. *Sulphur hexafluoride* (SF_6) is an inert, colourless and odourless gas whose very high dielectric constant makes it useful as an electric insulator of high-voltage devices. It brings about some health risks only in confined spaces because it can displace air and cause asphyxia. Electric sparking in the presence of oxygen will produce sulphur oxyfluoride, sulphur dioxide and sulphuryl fluoride. *Sulphuryl difluoride* (SO_2F_2) is used as a fumigant and chemical sterilant for grains and timber and as a non-greenhouse alternative to methyl iodide and methyl bromide. It is very toxic and can be hazardous because it has no odour. *Tetrafluorohydrazine* (N_2F_3) is a colourless gas with a musty odour, which slowly hydrolyses to hydrazine and hydrogen fluoride; it is used in some chemical syntheses, as a precursor or a catalyst, and as a high-energy liquid oxidizer in some rocket fuel formulas. *Tetrafluoroethylene* (C_2F_4, TFE) is the monomer for the preparation of poly-tetrafluoroethylene (PTFE). It is a colourless gas, which is industrially prepared from chloroform and hydrogen fluoride. Its highly exothermic polymerization can be triggered by trace metals such as iron, and by oxygen and peroxides such as persulphate. PTFE is a thermoplastic, non-stick, water repellent and chemically highly inert material, which has widespread applications in consumer products and in industrial applications. About 50% of PTFE production is used for cable insulation in computer and microwave applications; other applications are as very low-friction material for pipes in fluid mechanic actuators, as non-stick material for covers and gaskets, and as a water-repellent component of textiles. *Hexafluoropropylene* (C_3F_6) is a colourless gas, which shares most chemical properties and applications with TFE. Its main use is as co-monomer in PTFE (6-9%). *Chloro-Fluoro Hydrocarbons* (CFCs) are heavy, colourless and usually non-flammable gases or volatile liquids. They do not have any biological activity. CFCs had several uses as fire extinguishers, as expanding gases in the manufacture of foam polymers, and as refrigerant gases. Later, they were found to be strong greenhouse gases and ozone-depleting in the stratosphere. To mitigate anthropogenic climate changes, these compounds are being gradually banned since 1990 from production and use under a system of international agreements (e.g. the "Vienna Convention for the Protection of the Ozone Layer" and the "Montreal Protocol on Substances that Deplete the Ozone Layer").

1.1.9 Diseases caused by fluorine or its compounds — ICD Code T59.5 +Z57

Toxicological profile, main health effects and diagnostic criteria

Short toxicological profile	Fluorine is a highly reactive element that is widely present in the environment and in the industrial settings. Acute exposure may result in skin and mucous membrane irritation, as well as in respiratory effects. Low-level chronic exposure may result in skeletal, dental, and respiratory disorders. Fluorine and hydrofluoric acid are toxicological hazards with severe and potentially life-threatening effects when they are swallowed or come into contact with the skin. Hydrofluoric acid is the weakest and most lipophilic of all halogen acids and can easily penetrate biological barriers. After systemic absorption of hydrofluoric acid, uptake by the cells is usually fast and the fluoride anion stays trapped inside the cells and interacts with intracellular calcium ions, generating insoluble calcium difluoride. Depletion of intracellular calcium in turn triggers several effects due to its physiological role in multiple signalling pathways. Tetrafluoroethylene (TFE) shares the chemical alkylating characteristics of other halogenated olefins. It directly binds cellular glutathione through the action of glutathione S-transferase (GST) enzymes, and the conjugate is bio-transformed into the cytotoxic 1,1,2,2-tetrafluoro-etanethiol. Although evidence for the carcinogenicity of TFE in humans is currently inadequate, it has been considered sufficient in experimental animals. Hence, in 2017 IARC reconsidered the classification of this substance and evaluated it as probably carcinogenic to humans (Group 2A).

Name of the diseases and ICD code: **Acute diseases caused by fluorine or its compound**
(Specific disease code) **+T59.5 +Z57**

Mucous membrane irritation (J68), Upper respiratory inflammation (J68.2), Acute chemical pneumonitis (J68.0), Acute chemical pulmonary oedema (J68.1), Reactive airways dysfunction syndrome (RADS) (J68.3), Acute irritant contact dermatitis (L24), Burns and corrosions of external body surface (T20-T25), Burns and corrosion of eye and adnexa (T26.0-T26.1, T26.5-T26.6), Burns and corrosion of respiratory tract (T27), Burns and corrosion of internal organs (T28.0-T28.2, T28.5-T28.7), Conjunctivitis (H10.2), Corneal ulcer (H16.0)

Short description of the disease

Fluorine and hydrofluoric acid act as strong irritants for the skin, eyes and respiratory tract. Gaseous fluoride is capable of reacting with the skin to induce severe thermal or chemical burns. Skin contact with hydrofluoric acid may cause severe skin burns with tissue destruction. In the most severe cases, toxic hypocalcaemia due to the binding of fluoride ions to calcium ions can be observed. Electrolytic imbalance can bring to cardiac arrhythmias and tetanic crises. Fluoride poisoning can cause enzyme inhibition and impairment of nerve transmission.

In industrial exposures to gaseous and particulate fluoride, the main route of absorption is through the respiratory tract. Acute systemic toxicity consequent to ingestion or absorption from skin burns is very uncommon in occupational scenarios, although absorption through skin exposure following splashes of hydrofluoric acid is very dangerous and should always be considered as a possibility.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms:
  - Exposure causes the immediate onset of symptoms of respiratory irritation such as coughing, chest tightness, shortness of breath, choking, and chills. Symptoms may last 12 hours after exposure. Inhalation may cause tachypnoea and a reactive airways dysfunction syndrome (RADS).
  - In very high exposure scenarios, bronchospasm, laryngospasm, and acute pneumonitis can be observed, up to rapid death from gross haemorrhagic pulmonary oedema.
  - For lower doses, delayed effects are possible. In these cases, pulmonary oedema may develop after an asymptomatic period lasting between some hours and two days.
  - Burns from hydrogen fluoride have a characteristic whitish aspect and are intensely painful. The acid can penetrate deeply into soft tissues, reaching in some cases the bone, especially in areas such as the hands. The geometric size of burns is not predictive of the extent of a systemic uptake of hydrofluoric acid.
- Examinations:
  - Evidence of various degrees of irritation and burns of skin and mucous membranes at physical examination.
  - Pulmonary auscultation should document signs of respiratory impairment (e.g. crepitations or crackles).
  - Determination of electrolyte serum concentration might show hypocalcaemia, hypermagnesaemia and hyperkalaemia.

1.1.9 Diseases caused by fluorine or its compounds ICD Code T59.5 +Z57

Exposure assessment

- History of occupational exposure: confirmed occupational exposure to high concentrations of fluorine or its compounds (via either inhalation or absorption through skin lesions).
- Minimum duration of exposure: a single short exposure may be sufficient to cause the onset of the disease.
- Maximum latent period: few hours.

Polymer fume fever (T59.8)

Short description of the disease

Acute exposure to polytetrafluoroethylene (PTFE) fumes can cause polymer fume fever also known as fluoro polymer fever, Teflon flu or Teflon fume fever. When PTFE is heated above 450°C, inhalation of thermolysis products can cause acute lung injury or a flu-like syndrome. Onset usually occurs about four to eight hours after exposure to the pyrolysis products of PTFE.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: fever, chills, headache and backache with mild cough and tightness of the chest.
- Examinations: normal chest X-ray and leukocytosis can be observed. Pulmonary auscultation can document typical signs of bronchial irritation (e.g. wheezes and crackles).

Exposure assessment

- History of occupational exposure: confirmed occupational exposure to thermolysis products of PTFE.
- Minimum duration of exposure: even a very short exposure can cause the disease.
- Maximum latent period: 12 hours.

Name of the diseases and ICD code: **Chronic diseases caused by fluorine or its compound**
(Specific disease code) **+T59.5 +Z57**

Skeletal fluorosis (M85.1)

Short description of the disease

Skeletal fluorosis or "osteofluorosis" is a systemic disease due to prolonged overexposure to inorganic fluoride. It is due to the accumulation of fluoride in the skeletal tissues associated with pathological bone formation: this brings about an increased bone density secondary to both elevated osteoblastic activity and the replacement of hydroxyapatite by the denser fluoroapatite. First signs appear in the lumbar spine and pelvis, in some cases accompanied by ossification of ligaments.

This occupational disease was first reported in workers engaged in aluminium production, magnesium foundries, fluorspar processing and superphosphate manufacture. A similar disease is observed in subjects environmentally exposed to drinking water containing fluoride exceeding the concentration of 5-10 ppm.

Diagnostic criteria

Clinical manifestations

The onset is usually asymptomatic, even when radiological changes are present, such as increased density of vertebral and pelvic bones on X-rays. Early symptoms may include sporadic pain, back stiffness, burning-like sensation, pricking and tingling in the limbs, muscle weakness, and chronic fatigue. In the clinically manifest form, also the bones of the extremities are affected, showing irregular periosteal thickening with calcification of ligaments and muscular attachments, together with exostoses and osteophytes in the most severe cases. The vertebrae may fuse together, and the subject may eventually be unable to walk with pronounced kyphosis or lordosis).

Exposure assessment

- History of occupational exposure: confirmed prolonged or repeated occupational exposure to high concentrations of fluoride and, when available, workplace air monitoring and measurements of fluoride in urine (for a proper interpretation, non-occupational sources of fluoride intake should be assessed).
- Minimum duration of exposure: one year.
- Maximum latent period: 10 years.

1.1.9 Diseases caused by fluorine or its compounds — ICD Code T59.5 +Z57

Dental fluorosis (mottled teeth) (K00.3)

Short description of the disease

Elevated fluoride levels during enamel maturation can result in dental fluorosis, which is characterized by hypomineralization of subsurface enamel layers. Mottled enamel results from a partial failure of the enamel-forming ameloblasts to elaborate and lay down enamel itself.

It is important to recall that exposure to fluoride in subjects older than about 14 years does not bring about a risk of dental fluorosis because permanent teeth can no longer be mottled, independently from fluoride intake. Therefore, the disease can be observed as occupational only in circumstances of child labour. Cases of dental fluorosis have been reported in children exposed to fluoride through the intake of contaminated mother's breast milk.

Diagnostic criteria

Clinical manifestations

The mildest form of fluorosis is characterized by small, opaque, white areas irregularly scattered over the tooth. In more serious forms, the mottled patches can involve from half up to all of the teeth surface area. In the latter case, brown stains are frequently present. Severe fluorosis is characterized by brown discolouration and pitting, both giving the teeth a corroded-looking appearance.

Exposure assessment

- History of occupational exposure: confirmed occupational exposure to high concentrations of fluoride during childhood.
- Minimum duration of exposure: few years.
- Maximum latent period: three years.

Potroom asthma (J68.9), Chronic obstructive pulmonary disease (COPD) (J68.4)

Short description of the disease

The term potroom arises from the use of metal pots for the preparation of aluminium by electrolysis of a high-temperature molten mixture of alumina (purified bauxite), cryolite and sodium fluoride (the Hall-Héroult process). This process is accompanied by emissions of dust and gases, which are able to cause an asthma-like syndrome known as "potroom asthma", a very relevant health issue among potroom workers, smelters and casters. The most likely causative agents are irritant airborne particulates and fumes containing gaseous hydrogen fluoride, cryolite, and other elements that may be adsorbed onto aluminium. Elicitation of the disease can be observed for low dose exposures.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: wheezes on auscultation, chest tightness, tachypnoea, dyspnoea, tachycardia, non-productive cough, occurring during working hours but more typically some hours after leaving work (delayed onset). Symptoms become more frequent with repeated exposure and tend to improve when exposure ceases. Increased bronchial reactivity, once induced, has a tendency to persist.
- Examinations:
  - Reduced forced expiratory volume in the first second (FEV_1) at pulmonary function test, usually reversible by bronchodilators; bronchial challenge test (e.g. with methacholine) is often abnormal in this condition, as increased nonspecific airway reactivity is common.
  - If the disease evolves into COPD, bullae on the chest X-ray or CT scan can be seen, together with altered blood gas analyses, showing mild to moderate hypoxaemia without hypercapnia (in the mild forms) or more evident hypoxaemia with development of hypercapnia (in the most serious forms).

Exposure assessment

- History of occupational exposure: confirmed prolonged or repeated exposure to high levels of fluoride and, if available, biological monitoring of fluoride urinary levels (recall that raised urinary fluoride levels can be observed even years after heavy industrial exposures).
- Minimum duration of exposure: few weeks.
- Maximum latent period: 3 years.

1.1.9 Diseases caused by fluorine or its compounds	ICD Code T59.5 +Z57
Key actions for prevention	Fluorine and hydrofluoric acid should be manipulated in the chemical industry under very strict conditions of source segregation during all operations: from bulk production of the commodities, their transport, storage and use in closed reactors, to purification of reaction products and recovery of hydrofluoric acid and fluorides from the reaction mixtures. Speciality fluorinating reagents are usually expensive, and reaction conditions are intrinsically violent and hazardous: thus, appropriate safety measures (such as the availability of personal protective equipment) should be implemented in all production facilities. The inert nature of several fluorinated organic compounds – such as chlorofluorocarbons (CFCs) (residual use) and hydrochlorofluorocarbons (HCFCs) – often makes asphyxia the most relevant risk. Nonetheless, if fire extinguishing systems are equipped with alarms, the hazard posed by the extinguishing gas should be marginal with respect to the others generated by fires. Other fluorine compounds that may be used in open environments, such as fumigants, need the implementation of full safety measures, including on-site monitoring with portable devices and full personal protection (respirators). Only trained workers should be allowed to do the applications. Hydrofluoric acid is a very hazardous chemical due to the life-threatening delayed consequences of absorption through skin exposure following splashes of acid. This accident is reported especially in low-technology or informal sector activities, such as the manufacture and repair of bath tubs and kitchen sinks with vitreous enamel coatings, derusting of water pipes, or rust stain removal from textiles in laundries. To avoid contact with hydrofluoric acid, a hydrofluoric acid-resistant protective garment is necessary for the hands, the body and the eyes, and a facemask should be worn. The group of experts considered that the following limits of exposure of workplace atmospheric concentrations have been observed to provide a reasonable level of protection for workers' health and have been used in a number of countries: • Fluorides (as F): 2.5 mg/m^3 as 8hr TWA. • Fluorine: 1 ppm as 8hr TWA. • Hydrogen fluoride: 0.5 ppm as 8hr TWA.

1.1.9 Diseases caused by fluorine or its compounds ICD Code T59.5 +Z57

Further reading

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For the chemical entities listed below an entry exists in the collection of International Chemical Safety Cards (ICSC) hosted in the ILO website

Name	Synonyms	ICSC
Fluorine		0046
Trichlorofluoromethane	Trichloromonofluoromethane; Fluorotrichloromethane; CFC 11; R 11	0047
Dichlorodifluoromethane	Difluorodichloromethane; R 12; CFC 12	0048
Chlorodifluoromethane	Monochlorodifluoromethane; Methane, chlorodifluoro; HCFC 22; R 22	0049
1,1,2-Trichloro-1,2,2-Trifluoroethane	Trichlorotrifluoroethane; CFC 113; R 113	0050
Trifluralin	alpha, alpha, alpha-Trifluoro-2,6-dinitro-N,N-dipropyl-p-toluidine; 2,6-Dinitro-N,N-dipropyl-4-(trifluoromethyl)benzenamine	0205
Antimony pentafluoride	Antimony(V) fluoride	0220
Boron trifluoride	Trifluoroborane	0231
Fluoroacetic acid	alpha-Fluoroacetic acid; Monofluoroacetic acid; FAA	0274
Halothane	2-Bromo-2-chloro-1,1,1-trifluoroethane; 1-Bromo-1-chloro-2,2,2-trifluoroethane	0277
Hydrogen fluoride	Hydrofluoric acid, anhydrous	0283
Chlorotrifluoromethane	CFC 13; Monochlorotrifluoromethane; Trifluoromethyl chloride	0420
Sodium fluoroacetate	Sodium fluoroacetic acid; Fluoroacetic acid, sodium salt	0484
Sulphur hexafluoride	Sulfur fluoride	0571
Tetrafluoromethane	Carbon tetrafluoride; Freon 14; Halon 14	0575
Tetrafluorosilane	Silicon tetrafluoride; Silicon fluoride; Perfluorosilane	0576
Trifluoromethane	Carbon trifluoride; Fluoroform; R 23; Methyl trifluoride (cylinder)	0577
Vinyl fluoride	Fluoroethene; Fluoroethylene	0598
Carbonyl fluoride	Carbon oxyfluoride; Carbon difluoride oxide; Difluoroformaldehyde; Fluorophosgene	0633
Bromochlorodifluoromethane	Freon 12 B 1; R 12 B 1; Halon 1211	0635
Chlorodifluoroethane	1-Chloro-1,1-difluoroethane; HCFC 142 b	0643
Dichlorotetrafluoroethane	1,2-Dichloro-1,1,2,2-tetrafluoroethane; CFC114	0649
Chlorine trifluoride	Chlorine fluoride; Chlorotrifluoride	0656
Trifluorochloroethylene	Chlorotrifluoroethylene; Trifluorovinyl chloride	0685
Vinylidene fluoride	1,1-Difluoroethylene; 1,1-Difluoroethene; R1132a; Vinylidene difluoride	0687
Oxygen difluoride	Oxygen fluoride; Fluorine monoxide; Difluoride monoxide	0818
Bromotrifluoromethane	Trifluorobromomethane; Fluorocarbon-1301; Bromofluoroform; (cylinder)	0837
Chloropentafluoroethane	1-Chloro-1,1,2,2,2-pentafluoroethane; Fluorocarbon 115; CFC 115; (cylinder)	0848
Cyhalothrin	(RS)-alpha-Cyano-3-phenoxybenzyl (Z)-(1RS,3RS)-(2-chloro-3,3,3-trifluoropropenyl)-2,2-dimethylcyclopropanecarboxylate; Cyclopropanecarboxylic acid, 3-(2-chloro-3,3,3-trifluoro-1-propenyl)-2,2-dimethyl-, cyano(3-phenoxyphenyl)methyl ester	0858
Lambda-cyhalothrin	alpha-Cyano-3-phenoxybenzyl 3-(2-chloro-3,3,3-trifluoropropenyl)-2,2-dimethylcyclopropanecarboxylate; a 1:1 reaction mixture of the (Z)-(1R,3R), (S) ester and (Z)-(1S,3S), (R) ester	0859
Tin(II) fluoride	Stannous fluoride; Tin bifluoride; Tin difluoride	0860
Enflurane	2-Chloro-1,1,2-trifluoroethyl difluoromethyl ether; 2-Chloro-1-(difluoromethoxy)-1,1,2-trifluoroethane; Ethrane; Ether, 2-chloro-1,1,2-trifluoroethyl difluoromethyl	0887
Selenium hexafluoride	Selenium fluoride	0947
Sodium fluoride	Natrium fluoride; Sodium monofluoride	0951
Bromine pentafluoride	Bromine fluoride	0974

Name	Synonyms	ICSC
Fluorosulfonic acid	Fluorosulfuric acid; Fluorosulphuric acid	0996
Fluoroboric acid	Borofluoric acid; Fluoboric acid; Hydrogen tetrafluoroborate, Hydrofluoboric acid	1040
Hexafluoroacetone	1,1,1,3,3,3-Hexafluoro-2-propanone; Perfluoroacetone	1057
Dichloromonofluoromethane	Fluorodichloromethane; HCFC 21; Fluorocarbon 21	1106
Perchloryl fluoride	Chlorine oxyfluoride; Chlorine fluoride oxide; Trioxychlorofluoride	1114
Perfluoroisobutylene	Octafluoroisobutylene; 1,1,3,3,3-Pentafluoro-2-trifluoromethyl-1-propene; Octafluoro-sec-butene	1216
Ammonium fluoride	Neutral ammonium fluoride	1223
Fluorosilicic acid	Hexafluorosilicic acid; Dihydrogen hexafluorosilicate; Fluosilicic acid; Hydrosilicofluoric acid	1233
Nitrogen trifluoride	Nitrogen fluoride; Trifluoroamine; Trifluoroammonia; Perfluoroammonia	1234
Dipotassium hexafluorosilicate	Potassium fluorosilicate; Potassium silicofluoride; Dipotassium hexafluorosilicate	1242
Sodium hexafluorosilicate	Sodium fluorosilicate; Sodium silicofluoride; Disodium hexafluorosilicate	1243
Uranium hexafluoride	Uranium fluoride	1250
Triflumizole	(E)-4-Chloro-alpha,alpha,alpha-trifluoro-N-(1-imidazol-1-yl)-2-propoxyethylidene-o-toluidine; 1-(1((4-Chloro-2-(trifluoromethyl) phenyl)imino)-2-propoxyethyl)-1H-imidazole	1252
Flutolanil	alpha,alpha,alpha-Trifluoro-3'-isopropoxy-o-toluanilide; N-(3-(1-Methylethoxy)phenyl)-2-(trifluoromethyl)benzamide	1265
Hexaflumuron	1-(3,5-Dichloro-4-(1,1,2,2-tetrafluoroethoxy)phenyl)-3-(2,6-difluorobenzoyl)urea	1266
Flocoumafen	4-Hydroxy-3-(1,2,3,4-tetrahydro-3-(4-(4-trifluoromethylbenzyloxy) phenyl)-1-naphthyl)coumarin; 4-Hydroxy-3-(1,2,3,4-tetrahydro-3-(4-((4-(trifluoromethyl)phenyl)methoxy)phenyl)- 1-naphthalenyl)-2H-1-benzopyran-2-one	1267
1,1,1,2-Tetrafluoroethane	HFC 134°	1281
Chlorotrifluoroethane	2-Chloro-1,1,1-trifluoroethane; 1-Chloro-2,2,2-trifluoroethane; CFC 133;(cylinder)	1299
Calcium fluoride	Calcium difluoride	1323
Aluminium fluoride (Anhydrous)	Aluminium trifluoride	1324
2,2-Dichloro-1,1,1-trifluoroethane	HCFC 123	1343
Beryllium fluoride	Beryllium difluoride	1355
Sulfuryl fluoride	Sulfuryl difluoride; Sulfuric oxyfluoride	1402
Dibromodifluoromethane	Difluorodibromomethane; Fluorocarbon 12-B2	1419
1,1,1,2-Tetrachloro-2,2-difluoroethane	1,1-Difluoro-1,2,2,2-tetrachloroethane; CFC-112a	1420
1,1,2,2-Tetrachloro-1,2-difluoroethane	1,2-Difluoro-1,1,2,2-tetrachloroethane; CFC-112; Fluorocarbon 112	1421
Fluoroacetamide	2-Fluoroacetamide; Monofluoroacetamide; Fluoroacetic acid amide	1434
Isoflurane	Ether, 1-chloro-2,2,2-trifluoroethyl difluoromethyl; 2-Chloro-2-(difluoromethoxy)-1,1,1-trifluoroethane	1435
Sevoflurane	1,1,1,3,3,3-Hexafluoro-2-(fluoromethoxy)propane; Ether, fluoromethyl 2,2,2-trifluoro-1-(trifluoromethyl)ethyl-	1436
Desflurane	1,2,2,2-tetrafluoroethyl difluoromethyl ether	1437
Sulfur tetrafluoride	Tetrafluorosulfurane	1456
Fipronil	5-Amino-3-cyano-1-(2,6-dichloro-4-trifluoro-methylphenyl)-4-trifluoromethylsulfinylpyrazole	1503

Name	Synonyms	ICSC
Cryolite	Aluminium trisodium fluoride; Sodium fluoaluminate; Sodium aluminium fluoride; Sodium hexafluoroaluminate	1565
Perfluorooctanoic acid	Pentadecafluorooctanoic acid; Pentadecafluoro-n-octanoic acid; Perfluorocaprylic acid	1613
Methoxyflurane	2,2-Dichloro-1,1-difluoroethyl methyl ether; 2,2-Dichloro-1,1-difluoro-1-methoxyethane; Methoflurane; Penthrane	1636
Trifluoroacetic acid	Perfluoroacetic acid; Trifluoroethanoic acid	1673
Hydrofluoric acid		1777

▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
1.1.9	Acute/chronic diseases caused by fluorine or its compounds	T59.5	NE61& XM9SB2
1.1.9	Mucous membrane irritation	J68	CA81.0
1.1.9	Upper respiratory inflammation	J68.2	CA81.2
1.1.9	Acute chemical pneumonitis	J68.0	CA81.0
1.1.9	Acute chemical pulmonary oedema	J68.1	CA81.1
1.1.9	Reactive airways dysfunction syndrome (RADS)	J68.3	CA81.Y
1.1.9	Polymer fume fever	T59.8	NE61
1.1.9	Acute irritant contact dermatitis	L24	EK02
1.1.9	Burns and corrosions of external body surface	T20-T25	ND9Z, ND9Y, NE10
1.1.9	Burns and corrosions of eye and adnexa	T26.0-T26.1, T26.5-T26.6	NE00
1.1.9	Burns and corrosions of the respiratory tract	T27	NE01
1.1.9	Burns and corrosions of internal organs	T28.0-T28.2, T28.5-T28.7	NE0Z, NE10
1.1.9	Conjunctivitis	H10.2	9A60.Z
1.1.9	Corneal ulcer	H16.0	9A76
1.1.9	Skeletal fluorosis	M85.1	FB80.1
1.1.9	Dental fluorosis (Mottled teeth)	K00.3	DA07.0
1.1.9	Occupational asthma by fluorides (Potroom asthma)	J68.9	CA81.Y
1.1.9	Chronic obstructive pulmonary disease (COPD)	J68.4	CA22.Z
	Exposure to occupational risk factors	Z57	QD84.Y

1.1.10 Diseases caused by carbon disulfide	ICD Code T65.4 +Z57
General characteristics of the causal agent	Carbon disulfide (CS_2, carbon bisulfide, carbon sulphide), CAS number 75-15-0, is a colourless or pale-yellow liquid, with a characteristic sweet, pleasing and ether-like odour when the compound is pure; the technical-grade product usually has an offensive odour due to the presence of minor manufacturing impurities such as mercaptans (thiols). It has a molecular mass of 76.1 and is volatile, with a boiling point of 47°C. The vapour is heavier than air and may migrate along the ground. Vapour can ignite spontaneously on contact with heated surfaces. The critical temperature is above 102°C. Distant ignition and explosion are thus possible, also triggered by shock, friction, or concussion. Moreover, due to the relatively high dielectric constant of the liquid, flow, agitation, and other physical phenomena of technological occurrence can generate a substantial build-up of electrostatic charges, which carry along with fire and explosion hazards. Carbon disulfide reacts violently with air and with other chemical oxidants, causing fire and explosion hazards and producing toxic fumes of sulphur dioxide. Carbon disulfide is heavier than air and soluble in water. It is an excellent solvent, especially for certain polymers, such as natural rubber latex, and reacts with some natural polymers, such as cellulose in a strong alkaline solution, dissolving the material. Carbon disulfide can polymerize into a hard semiconducting material. Industrial-grade carbon disulfide used to be manufactured by reacting hot sulphur-containing gases (hydrogen sulphide, sulphur vapours or sulphur oxides deriving from the desulphurization of coal and oil) on red-hot coal and quickly condensing the gaseous stream. Currently, production is accomplished by direct reaction of sulphur with methane, with yearly production in the order of a million tons. Due to its hazardous properties, including human toxicity, its use has been largely downsized in most industrialized countries.
Occupational exposures	The excellent solubilizing properties of carbon disulfide on fatty substances, on natural rubber latex and on cellulose (in a strongly alkaline solution and in the presence of soluble copper salts; see item 1.1.28) gained this relatively cheap synthetic solvent several applications in manufacturing, and its chemical reactivity gave it a role in the synthesis of sulphur-containing fine chemicals. Among the historical industrial applications, most of which are now residual and generally abandoned in industrialized countries, are: • The production of viscose rayon fibre for textiles and of cellulose film for packaging. • The curing ("*cold vulcanization*") of natural rubber and the impregnation of textiles for waterproofing. • The extraction of industrial fats from slaughterhouse carcasses and from fish flour, of wax resins from wood pulp and of oils from natural sources. • The solubilisation of reagents such as sulphur mono-chloride and white phosphorus. • Some historical chemical syntheses of fine chemicals such as pesticides, dyes, and drugs, and intermediates for their manufacture. Among the best-known products manufactured with carbon disulfide as starting material are dithiocarbamate pesticides (mancozeb, zineb, see item 1.1.36). Another industrial product derived from carbon disulfide is carbon tetrachloride (see item 1.1.11). Carbon disulfide still finds some use for the fumigation of containers and goods, such as in airtight storage warehouses, railroad boxcars, grain elevators, and cereal mills. One traditional application of carbon disulfide in analytical laboratories is the desorption of volatile organic compounds adsorbed on carbon black. Although this operation involves a very small number of well trained operators in usually well equipped chemical laboratories, it represents an occasion of transient but intense respiratory exposure and the chance of skin exposure.

1.1.10 Diseases caused by carbon disulfide — ICD Code T65.4 +Z57

Toxicological profile, main health effects and diagnostic criteria

Short toxicological profile

Due to its low boiling point and excellent lipid solubility, carbon disulfide is absorbed rapidly and efficiently both by the airways and by the skin. The gastrointestinal route is of negligible importance due to the awful taste of the product which may discourage a suicidal use. Most toxic effects that follow acute exposures are thus in part common to other volatile organic vapours (irritation of the respiratory tract, of the skin and of the mucosae; neurotoxicity, systemic toxicity to the liver and to the kidney). Some specific effects of carbon disulfide are due to its behaviours towards biological structures, most of which are poorly characterised. Among the cellular targets of toxicity are:

- Chelation of "soft" essential trace metals by some addition compounds of carbon disulfide with endogenous soluble metabolites.
- Inhibition or inactivation of some enzymes by several mechanisms, including chelation of cofactor metal ions, inactivation of nucleophilic centres at the active site, structural disruption of enzyme architecture by reactive oxygen radicals; the liver toxicity may be partly explained by the inactivation of cytochrome P-450 via the oxidative desulfuration of carbon disulfide.
- Disturbance of the metabolism of vitamin B6 and nicotinic acid, catecholamines, and of lipids.

The extensive biotransformation of absorbed carbon disulfide yields carbon dioxide as end product, and entails the conversion of the sulphur component of the molecule into sulphate through a physiologically expensive biological oxidation. The electrophilic carbon disulfide molecule reacts with several nucleophilic molecules in the body in a complex sequence of reactions. Thiourea is a product of carbon disulfide excreted in urine and levels are well correlated to respiratory exposure to the solvent. Reaction with glutathione and cysteine yields specific metabolites, among which 2-thiothiazolidine-4-carboxylic acid (TTCA) is excreted in the urine and can be measured as exposure biomarker.

Name of the diseases and ICD code: **Acute diseases caused by carbon disulfide**
(Specific disease code) **+T65.4 +Z57**

Respiratory tract irritation (J68.4), Acute chemical pneumonitis (J68.0), Pulmonary oedema (J68.1), Upper respiratory inflammation (J68.2), Burns and corrosion of external body surface (T20-T25), Burns and corrosion of mouth, pharynx and oesophagus (T28.0-T28.1, T28.5-T28.6), Burns and corrosion of eye and adnexa (T26.0-T26.1, T26.5-T26.6), Conjunctivitis (H10.2), Corneal ulcer (H16.0), Irritant contact dermatitis (L24)

Short description of the disease

Carbon disulfide is soluble in water and can thus affect the lower respiratory tract with insidious onset. Contact with liquid or concentrated vapours of carbon disulfide causes irritation to the skin, eyes and mucous membranes.

Diagnostic criteria

Clinical manifestations

- The effects on the lower respiratory tract can be delayed (6 to 24 or even up to 72 hours), but are often although not always preceded by upper respiratory tract symptoms (runny nose, sore throat). Dyspnoea and respiratory failure may occur following exposure to high concentrations.
- Swallowing the liquid may cause aspiration into the lungs with the risk of chemical pneumonitis due to vaporization of the substance; pulmonary oedema may occur.
- In extreme exposure cases, direct contact may cause chemical burning of the skin, eyes, or mucous membranes. Direct contact may result in significant dermal absorption and contact with the liquid can result in second- and third-degree chemical burns and blistering in the skin. For further details on clinical features of irritant contact dermatitis, refer to item 2.2.2.
- Carbon disulfide is irritating to eyes and may cause corneal erosions.
- Ingestion of liquid can irritate the mouth, pharynx, and oesophagus.

Exposure assessment

- History of occupational exposure: confirmed occupational exposure to carbon disulfide via inhalation, ingestion, skin and eye contact and, when available, measurements of workplace airborne carbon disulfide concentrations. Presence of carbon disulfide in blood and urine, of 2-thiothiazolidine-4-carboxylic acid (TTCA) in urine and of carbon disulfide itself in the exhaled air can confirm exposure.
- Minimum duration of exposure: few minutes.
- Maximum latent period: 24 hours.

1.1.10 Diseases caused by carbon disulfide — ICD Code T65.4 +Z57

Acute toxic encephalopathy (G92)

Short description of the disease

Acute exposure (mostly accidental) to high levels of carbon disulfide from all routes of exposure (inhalation, ingestion and skin contact) can cause an acute toxic encephalopathy.

Diagnostic criteria

Clinical manifestations

Characteristic symptoms are dizziness, headache, nausea, vomiting, anorexia, memory disturbances, mood swings (with irritability, nervousness and euphoria), mania, depression, confusion, muscle weakness, sleeplessness, and fatigue. Main signs of high-dose intoxication are hyperexcitability, blind spots in vision, dilated pupils, mental confusion, delirium, and hallucinations. Extreme consequences can be represented by narcosis, convulsions, loss of consciousness, coma and, eventually, death. Neuropsychological tests can document intellectual, affective or motor changes (although minor).

Exposure assessment

- History of occupational exposure: confirmed occupational exposure to high levels of carbon disulfide via inhalation, ingestion, skin and eye contact and, when available, measurements of workplace airborne carbon disulfide concentrations. Presence of carbon disulfide in blood and urine, of 2-thiothiazolidine-4-carboxylic acid (TTCA) in urine, and of carbon disulfide itself in the exhaled air can confirm exposure.
- Minimum duration of exposure: few minutes.
- Maximum latent period: 24 hours.

Name of the diseases and ICD code: **Chronic diseases caused by carbon disulfide**
(Specific disease code) **+T65.4 + Z57**

Chronic toxic encephalopathy (G92), Toxic optic neuropathy (H46), Ototoxic hearing loss (H91.0), Peripheral polyneuropathy (G62.2), Atherosclerosis (I70.9), Chronic ischaemic heart disease (I25.8), Secondary hypertension (I15.9), Chronic kidney disease (N18.9), Intermittent claudication (I73.9)

Short description of the disease

Long-term exposure to carbon disulfide may induce a chronic toxic encephalopathy due to both its direct neurotoxicity and its ability to cause a cerebral vasculopathy, and may induce a mixed sensorimotor peripheral neuropathy. Carbon disulfide exposure can cause ocular and ear damage, and has been associated with increased risk of hypertension, angina pectoris, atherosclerosis, retinal vasculopathy, renal impairment and mortality from myocardial infarction. Gastrointestinal disturbances with anorexia and weight loss as well as liver damage have also been observed. Long-term exposure to high levels of carbon disulfide may induce, through endocrine disruption, reduced sperm count and changes in sperm morphology in males, as well as menstrual disorders in females: these alterations may lead to reduced fertility in both genders, but evidence remains unclear.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms:
  - Encephalopathy can be characterized by behavioural changes and both extrapyramidal and pyramidal lesions. Clinical picture of the encephalopathy may resemble parkinsonism with neuropsychological dysfunction. In some cases, a cerebellar syndrome can be observed. Effects may include emotional disturbances and psychosis.
  - The main target of the peripheral neuropathy are the legs, but it can also affect the cranial nerves; skin absorption may result in localized degeneration of peripheral nerves.
  - Cranial nerve effects may include retrobulbar optical neuritis with central scotoma and red-green colour blindness; noise-induced hearing loss may be potentiated by carbon disulfide exposure.
  - Retinopathy due to vascular damage has been documented, together with impairment of colour vision and retinal blind spots, narrowing of vision and decreased ability to see in the dark.
  - Atherosclerosis, coronary heart disease, and hypertension can also occur. The atherogenic effect of carbon disulfide can cause a peripheral artery disease of the extremities, possibly manifesting as intermittent claudication.

1.1.10 Diseases caused by carbon disulfide — ICD Code T65.4 +Z57

- Examinations:
  - Nuclear magnetic resonance images (MRI) show hyperintensity in the basal ganglia and the subcortical white matter.
  - Neurobehavioral tests show impaired performance: intellectual and cognitive impairment may be indicated by results in the lowest 5% of the distribution of scores from the normal population of similar age and intellect. Test performance should be abnormal in at least one test in each of two functional areas.
  - Cerebral atrophy detected through imaging techniques and electroencephalographic changes may be present in severe cases.
  - Electroneurography shows reduced nerve conduction velocities in the peripheral nerves.
  - Biopsies of peripheral nerves may show demyelination and infiltration of leukocytes with focal axonal swellings and accumulations of neurofilaments (histologically similar to the neuropathy produced by *n*-hexane, see item 1.1.21).
  - Pupillary and corneal reflexes can be reduced.
  - The fundoscopic examination shows a retinopathy with micro-aneurysms and punctate haemorrhages.
  - In cases of cardiovascular involvement, electrocardiographic evidence of ischaemic heart disease with different levels of severity can occur, together with increased blood levels of cholesterol and triglycerides, and altered blood pressure levels.
  - In cases of kidney impairment, haematuria, proteinuria, and reduced glomerular filtration rate can be observed.

Exposure assessment

- History of occupational exposure: confirmed prolonged or repeated exposure to carbon disulfide and, when available, measurements of workplace airborne carbon disulfide concentrations. Presence of carbon disulfide in blood and urine, of 2-thiothiazolidine-4-carboxylic acid (TTCA) in urine and of carbon disulfide itself in the exhaled air can confirm exposure.
- Minimum duration of exposure: one year (10 years for chronic encephalopathy).
- Maximum latent period: several years (from three years for effects on the central and peripheral nervous systems, up to eight years for cerebral vasculopathy).

Key actions for prevention	Due to its hazardous properties of flammability and toxicity, the industrial use of carbon disulfide has been largely limited and only few applications still exist, in which its chemical (rather than solvent) properties are exploited. Most of the current use of carbon disulfide is in the production of textile and stretchable polymeric cellulose (rayon yarn) from abundant cheap sources. Due to the enforcement of regulatory constraints for the protection of the environment and of human health, this process has been largely abandoned in several countries and areas of the world such as in the EU. Elsewhere, this process still supplies the raw material (regenerated cellulose) for the textile and clothing industry and for the very high-volume production of consumer goods such as diapers and other single-use personal hygiene commodities. The emission of carbon disulfide from the process varies according to the production. Only approximately half of the carbon disulfide used can be recovered and recycled at the end of the process, which generates hydrogen sulfide (see item 1.1.16) in the phase when xanthate cellulose is hydrolyzed to cellulose fibres (acid coagulation of viscose). To minimize exposure of workers, enclosure of production tanks and of spinning machines is the most efficient prevention, which also limits the possibility of potentially fatal accidents caused by falling into the tanks, containing highly concentrated alkaline and acidic solutions. The group of experts considered that a limit of exposure of workplace atmospheric concentrations of 1 ppm as an 8hr TWA has been observed to provide reasonable level of protection for workers' health, and to be used in a number of countries.

Further reading

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1.1.10 Diseases caused by carbon disulfide — ICD Code T65.4 +Z57

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For the chemical entities listed below an entry exists in the collection of International Chemical Safety Cards (ICSC) hosted in the ILO website

Name	Synonyms	ICSC
Carbon disulfide	Carbon disulphide, Carbon bisulfide, Carbon sulfide	0022

▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
1.1.10	Acute/chronic diseases caused by carbon disulfide	T65.4	NE61 & XM7S46
1.1.10	Respiratory tract irritation	J68	CA81
1.1.10	Acute chemical pneumonitis	J68.0	CA81.0
1.1.10	Pulmonary oedema	J68.1	CA81.1
1.1.10	Upper respiratory inflammation	J68.2	CA81.2
1.1.10	Burns and corrosion of external body surface	T20-T25	ND9Z, ND9Y
1.1.10	Burns and corrosion of mouth, pharynx and oesophagus	T28.0-T28.1, T28.5-T28.6	NE02
1.1.10	Burns and corrosion of eye and adnexa	T26.0-T26.1, T26.5-T26.6	NE00
1.1.10	Conjunctivitis	H10.2	9A60.Z
1.1.10	Corneal ulcer	H16.0	9A76
1.1.10	Irritant contact dermatitis	L24	EK02
1.1.10	Toxic encephalopathy	G92	8D43.0Z
1.1.10	Toxic optic neuropathy	H46	9C40.1Y
1.1.10	Ototoxic hearing loss	H91.0	AB53
1.1.10	Peripheral polyneuropathy	G62.2	8C0Z
1.1.10	Chronic ischaemic heart disease	I25.8	BA5Z
1.1.10	Secondary hypertension	I15.9	BA04.Z
1.1.10	Atherosclerosis	I70.9	BD40.Z
1.1.10	Chronic kidney disease	N18.9	GB61.Z
1.1.10	Intermittent claudication	I73.9	BD40.0
	Occupational exposure to risk factors	Z57	QD84.Y

1.1.11 Diseases caused by halogen derivatives of aliphatic or aromatic hydrocarbons
ICD Code T53 +Z57

General characteristics of the causal agent

Halogenated aliphatic and aromatic hydrocarbons are organic chemical compounds in which one or more hydrogen atoms directly linked to carbon atoms are replaced by a halogen atom (fluorine, chlorine, bromine, or iodine).

In *aliphatic halogenated compounds*, the halogen atom is linked to an aliphatic carbon atom and not to a benzene or higher aromatic ring system, although the molecule can contain such chemical groups in the structure. In *aromatic halogenated compounds*, the halogen atom is directly linked to the benzene or higher aromatic ring system of the molecule.

Lower aliphatic halogenated hydrocarbons are usually condensable gases or very volatile liquids under ambient conditions. Their volatility generally decreases with the increasing size of the hydrocarbon portion of their molecules and with the increasing number and an atomic number of attached halogen atoms (fluorine < chlorine < bromine < iodine).

Although lower aliphatic halogenated hydrocarbons are still flammable in air or in an oxygen-rich atmosphere, poly-halogenated compounds are not, and they are able to inhibit the chemical processes that sustain combustion.

Few lower aliphatic halogenated hydrocarbons are weakly soluble in water, while the majority of halogenated hydrocarbons are at most poorly, if at all, soluble in water (yet they can be dissolved in natural water at trace levels); in bulk, they are heavier than water and immiscible.

The halogen atom of aliphatic halogenated hydrocarbons can be chemically removed from the molecule by water, especially in alkaline conditions (a reaction named 'hydrolysis'), unless it is bound to a carbon-carbon double bond (in compounds named 'halogenated olefins'), a chemical structure which makes the halogen atom very unreactive. On the contrary, the proximity of a halogen atom to a carbonyl group makes it very easily displaceable even by atmospheric moisture, with a usually exothermic reaction and formation of corrosive and toxic gaseous hydrogen halogenide or halogenohydric acid mists.

Aromatic halogenated hydrocarbons are medium volatility liquids or crystalline solids, a few of which sublime under ambient conditions. They are usually not miscible with water, poorly flammable and their halogen atoms are chemically unreactive unless under very strong conditions or when some special arrangements of chemical groups and atoms are present in the molecule.

The chemical class of aromatic halogenated hydrocarbons includes, among the compounds of occupational concern, polychlorinated biphenyls (PCB), polybrominated biphenyls (PBB), and polyphenyls, polychlorinated dioxins, polychlorinated benzo- and dibenzo-furans, dichlorodiphenyltrichloroethane (DDT) and its derivatives, and hexachloronaphtalene.

The halogenated aromatic compounds of interest for occupational toxicology can be classified into three subgroups:

(i) derivatives of benzene in which one or more hydrogen atoms have been substituted by halogen atoms. Among the most important substances are: chlorinated benzene(s): mono-, di-, tri-, hexachloro-benzene; bromo-benzene; mono- and trichlorotoluene;

(ii) derivatives of biphenyls and of poly-phenyls in which one or more hydrogen atoms have been replaced by halogen atoms; the most important substances are polychlorinated biphenyls (PCB) and, to a lesser extent, polybrominated biphenyls (PBB);

(iii) polynuclear compounds composed of two or more fused benzene rings in which one or more hydrogen atoms have been replaced by halogen atoms. The substances of higher interest are the polychloro-naphthalenes (mainly hexachloro-naphthalene).

Following are the descriptions of a small number of individual compounds, mostly selected for their industrial relevance.

Methylene chloride (dichloromethane) is a volatile, colourless, liquid, heavier than water, and partially miscible, with a sweetish odour generally detectable above 200-300 ppm and intensely irritating for mucosa above 2,300 ppm. Methylene chloride is a bulk chemical, mostly used as solvent, while its use as chemical reagent is minor. Although it is not flammable, and it is often used to reduce flammability of petroleum-ether based solvent mixtures, in presence of fire methylene chloride generates hydrochloric acid and phosgene, a much more hazardous chemical (see item 1.1.32). Methylene chloride is in part eliminated with exhaled air and in part metabolized to carbon monoxide (see item 1.1.16), from which it derives, at least partially, its toxicity.

Trichloroethylene (trichloroethene, chlorylene, TRI) is a non-flammable liquid, heavier than water and immiscible, with a chloroform-like odour. It is mostly used as a degreasing solvent and in industrial dry-cleaning. Vapour/air mixtures are explosive and thermal decomposition generates dichloro-acetylene, hydrochloric acid fumes, carbon monoxide and phosgene. The main excreted metabolites of trichloroethylene are trichloroethanol and trichloroacetic acid.

1.1.11 Diseases caused by halogen derivatives of aliphatic or aromatic hydrocarbons ICD Code T53 +Z57	
	Tetrachloroethylene (tetrachlorethene, perchloroethylene) is a non-flammable liquid, heavier than water and immiscible, with an ether-like odour. It is mostly used as a degreasing solvent and in industrial dry-cleaning. Thermal decomposition produces carbon monoxide, phosgene and hydrochloric acid fumes. Although tetrachloroethylene has a very limited biotransformation (less than 3% undergoes biotransformation and excretion as trichloroacetic acid), and 80 to 90% of the absorbed dose is excreted unchanged with exhaled air, the remaining dose has a fairly long biological half-life due to accumulation in body lipids. *Vinyl chloride* (monochloroethylene) is the starting monomer for the synthesis of the important industrial polymer polyvinyl chloride (PVC) and is a condensable gas at ambient conditions. Due to its specific toxicological characteristics as a human carcinogen, refer to the dedicated item 3.1.7 for further details. *Allyl chloride* (1-chloro-propene) is a colourless liquid with an unpleasant odour, very reactive towards hydrolysis, strongly irritant and sensitizing. *Methyl bromide* (bromomethane) in ambient conditions is a colourless, odourless, and heavier-than-air gas.
Occupatinal exposures	Due to the very large number of compounds in this chemical class, occupational uses and sources of exposure are very diverse. Any situation in which exposure to the compounds in this chemical class is anticipated needs a separate and specific evaluation, addressed at defining the source(s) of exposure to specific compound(s) and the pertinent exposure levels. Most halogenated compounds, as pure chemicals or as more or less broadly defined mixtures, are produced as specialties or as chemical intermediates for the preparation of dyes, pharmaceuticals, pesticides and other higher-added value products. Aliphatic hydrocarbons are used as chemical feedstock, industrial process solvents, and formulating solvents for a variety of paints, inks, resins, varnishes, lacquers, surface coatings, paint removers, and automotive care products. Like other organic solvents, they are used in cleaning and degreasing. *Methylene chloride* can find use as paint and varnish remover; as propellant for aerosol sprays; as a solvent and a blowing agent for polymer foams. *Methyl bromide* is used as a fumigant insecticide and nematocide in greenhouses, grain silos etc., as a rodenticide, as a refrigerant, and as a methylation agent in the chemical industry. Some poly-halogenated alkyl compounds are of low toxicity but are asphyxiant in confined spaces; these compounds are often referred to as *Freons*, a proprietary name commonly used in a generic sense to indicate highly halogenated volatile or semi-volatile lower-aliphatic chemicals, often employed as refrigerating fluids and fire extinguishers. Poly-brominated aromatic compounds are used in the manufacture of flame-retardant fibres. Other poly-halogenated aromatic compounds, such as polychlorinated biphenyl and naphthalene mixtures were or still are employed as heat-exchange and insulating fluids, due to their very high chemical stability and dielectric constant (transformer oils). *Chloro- and bromo-benzenes, and chlorotoluene* find use mainly as solvents, but also as intermediates in the synthesis of different kinds of chemicals, in particular agrochemicals such as herbicides and fungicides. *Trichloroethylene* is mainly used as a solvent and as extracting agent and may also be present in the formulation of some stain removers. The main use of tetrachloroethylene is for dry cleaning, textile treatments and metal degreasing. *Vinyl chloride* is mainly used in the production of polyvinyl chloride. *Polychlorinated and polybrominated biphenyls* have been used in the past as dielectric fluids in condensers and transformers as lubricant and plasticizers, as well as in the production of synthetic rubber and fireproofing materials. *Chloronaphthalenes* do not find significant use nowadays but, in the past, they have been used as insulating fluids in the manufacture of electric condensers, for the insulation of electric cables, and as additives for extreme pressure lubricants. *Poly-halogenated dioxins and (di)-benzofurans* are generated as overheating by-products of these mixtures as well as trace pollutants of combustion. All these compounds are very lipid-soluble, are only poorly and slowly degraded by environmental and biological agents and accumulate in the food chain.

1.1.11 Diseases caused by halogen derivatives of aliphatic or aromatic hydrocarbons ICD Code T53 +Z57	
Occupational exposures	Some 'mobile-halogen' compounds, such as allyl bromide, chloroacetone, bromoacetone, *phenacyl chloride* (CN gas, tear gas, Mace), 2-chlorobenzalmalononitrile (CS gas) and other similar compounds (e.g. alpha-chlorotoluene) with a reactive halogen group are used as chemical reagents and as lachrymatory riot-control agents. *Hexafluoroacetone* (as the 'hydrate') is used for the production of hexafluoro-isopropanol and of polymers for textile coating. *Allyl chloride* is used to synthesize epichlorohydrin, which is employed mainly for the manufacture of epoxy resins. Epoxy-chlorinated compounds such as *glycidyl chloride* are used as intermediates for the synthesis of polymer resins. *2,4-dinitrochlorobenzene* is used in colour photography processing. From all the above, it is clear that occupational exposure is possible in several industrial activities: production of lacquers, inks, paints, varnishes, resins, surface coatings, paint removers, rubber, plastics, dye-stuff, textile, pharmaceutical, and dry-cleaning industries.
Toxicological profile, main health effects and diagnostic criteria	
Short toxicological profile	Halogenated aliphatic and aromatic hydrocarbons are absorbed rapidly by contact with the skin. Inhalation represents a significant source of exposure to the vapours of the most volatile compounds of the group. Distribution is often fast, and targets preferentially lipid-rich tissues and organs; the more volatile compounds can be rapidly eliminated through the exhaled air. Biodegradation, biochemical and toxicological interactions, and elimination of halogenated aliphatic and aromatic hydrocarbons strongly depend on their chemical structure, and mainly on the chemical nature and stability of the carbon-halogen bond. In principle, the more chemically reactive is the carbon-halogen bond the more likely the compound reacts with body water and the nucleophilic functional groups of the molecules constituting biological structures (i.e., proteins and DNA). These phenomena originate from chemical reactions classified as nucleophilic substitution. The consequence is often a more or less specific, permanent and physiologically impairing modification of the biological activity of those structures: enzymes can be permanently inactivated, DNA bases can be modified, and small organic molecules can add to carrier proteins and elicit an immunological response. Downstream in the physiological mechanisms, the impairment of the activity of inactivated enzymes can hamper the maintenance of homeostasis in sensitive areas of cell functioning. In the mitochondria, substantial damage can interfere with energy metabolism and trigger cellular apoptosis or necrosis. In the nucleus, a damage of DNA and an impairment of repair mechanisms can derange cells towards neoplastic transformation. Aromatic halogen derivatives and halogenated alkenes are bio-processed through P450-mediated oxidation, mainly occurring in the liver, and originate very reactive intermediates such as the arene oxides of halogenated benzenes and of (poly)chlorinated ethylene; the most relevant detoxification pathway of mammalian metabolism occurs through spontaneous or enzyme-catalysed reaction with glutathione, which generates glutathione thioethers. Further enzymatic processing of glutathione thioethers generates both the end-products for urinary excretion (the thioethers of N-acetyl-cysteine, or *mercapturic acids*) and some reactive intermediates which can cause somatic toxicity and possibly neoplastic transformation in the excretory organs, especially in the kidney. Poly-halogenated aromatic compounds, such as polychloro-biphenyls, -naphtalenes, -dibenzodioxins, -dibenzofurans, and polybromo-diphenylethers, strongly accumulate in the fatty tissues of the organism and are very resistant to biological degradation. Their toxicity mainly occurs through interference with natural signalling mechanisms exerted by natural steroid and by thyroid hormones (endocrine disruption). Since its metabolic pathway gives rise to the synthesis of carbon monoxide, exposure to methylene chloride might bring about an increase of the blood levels of carboxyhaemoglobin and therefore exacerbate a pre-existing ischaemic heart disease (see item 1.1.16). Cardiovascular sequelae (e.g. ischaemic heart disease) could be attributed to methylene chloride exposure only if occurring no later than one month following the acute exposure, which may be documented by high blood levels of carboxyhemoglobin (COHb) (note that the proportion of COHb over normal haemoglobin is usually around 1.5% among non-smokers and 5% among smokers).

1.1.11 Diseases caused by halogen derivatives of aliphatic or aromatic hydrocarbons ICD Code T53 +Z57

Name of the diseases and ICD code: **Acute diseases caused by halogen derivatives of aliphatic or aromatic hydrocarbons** *(Specific disease code)* **code +T53 +Z57**

Respiratory tract irritation (J68), Acute chemical pneumonitis and bronchitis (J68.0), Pulmonary oedema (J68.1), Upper respiratory inflammation (J68.2), Burns and corrosions of eye and adnexa (T26.0-T26.1, T26.5-T26.6), Conjunctivitis (H10.2), Keratoconjunctivitis (H16.2), Corneal ulcer (H16.0), Burns and corrosions of external body surface (T20-T25), Irritant contact dermatitis (L24)

Short description of the disease

Exposure and contact with some of these compounds may cause severe mucous membrane and skin irritation, as well as severe toxic burns in some cases. Contact with the respiratory tract may cause chemical pneumonitis and pulmonary oedema especially if chloroacetone, bromoacetone, hexafluoroacetone, alpha-chlorotoluene, allyl chloride, methylene chloride, and methyl bromide are involved. These substances can also be absorbed by inhalation, skin absorption and by ingestion. On evaporation, a harmful level of air contamination can be reached quickly at 20°C and much faster on spraying. The above effects can be caused by:

- Halogenated aliphatic hydrocarbons with poor chemical reactivity (e.g. halogenated olefins).
- Halogenated aliphatic hydrocarbons with strong hydrolytic chemical reactivity (e.g. methyl bromide, methyl iodide, chloroacetone, bromoacetone, hexafluoroacetone, benzyl bromide, phenacyl bromide).
- Halogenated activated benzene derivatives (e.g. chlorodinitrobenzene, picryl chloride).
- Halogenated derivatives of benzene and of simple olefins (e.g. chlorobenzene, alpha-chlorotoluene, dichlorobenzene isomers; mono and dichlorinated phenols; mono and dichlorinated naphtalenes, naphtols and chlorinated quinones; vinyl chloride; trichloroethylene and tetrachloroethylene; hexachlorobutadiene).
- Halogenated derivatives of biphenyls (e.g. polychlorinated biphenyls, dibenzofurans and dibenzodioxins).

Methyl bromide can cause pulmonary oedema, usually after a latency period of 2 - 48 hours. Methyl bromide gas can penetrate clothing and this, as well as its liquid phase, causes skin irritation, erythema, superficial burns, multiple vesicles, and bullae.

Short-term exposure to allyl chloride can cause delayed toxic effects on the eye, resulting in irreversible impairment of vision. Inhalation exposure to methylene chloride can result in pulmonary oedema and coma. Chloroacetone is a potent lacrimatory and irritant agent: a concentration of 0.018 mg/L is sufficient to produce lacrimation, and a concentration of 0.11 mg/L will normally not be tolerated for more than 1 min.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms:
  - Irritation of the skin: redness, erythema with blisters, up to severe burns. For further details on irritant contact dermatitis, refer to item 2.2.2.
  - Cough and dyspnoea related to respiratory tract irritation; pulmonary oedema can occur.
  - Profuse lacrimation, ocular burning and conjunctivitis, in case of contact with eyes and adnexa.
- Examinations:
  - Physical examination of the eyes and skin may reveal inflammation.
  - Chest X-rays may reveal signs of pneumonitis, bronchitis and pulmonary oedema.
  - Pulmonary function tests may reveal obstruction.

Exposure assessment

- History of occupational exposure: confirmed occupational exposure to halogen derivatives of aliphatic or aromatic hydrocarbons via inhalation, skin and eye contact and, when available, workplace air and biological monitoring.
- Minimum duration of exposure: few seconds for irritant effects; minutes for more severe burns and corrosions; several days for irritant contact dermatitis.
- Maximum latent period: 48 hours.

1.1.11 Diseases caused by halogen derivatives of aliphatic or aromatic hydrocarbons ICD Code T53 +Z57

Narcotic syndrome consequent to acute systemic poisoning by halogenated derivatives of aliphatic or alicyclic hydrocarbons: methylene chloride (T53.4), trichloroethylene (T53.2), tetrachloroethylene (T53.3), vinyl chloride monomer (T59.8, X46, X47, Y16) chloroacetone (T59.3, X47, Y17), bromoacetone (T59.3), hexafluoroacetone (T53.6), halogenated derivatives of benzene (T53.7)

Short description of the disease

Exposure to halogenated compounds can cause a narcotic syndrome. Severe narcotic syndromes may have cardiovascular and neurological sequelae. Anaesthetic effects can be observed in case of exposure to trichloromethane, trichloroethylene, 1-chloro-2,2,2-trifluoroethyl difluoromethyl ether (isoflurane). In case of severe acute exposure, there is always the danger of death from respiratory failure or cardiac arrest, due to the increased heart susceptibility to catecholamines, which is exerted by most halogenated aliphatic hydrocarbons.

Diagnostic criteria

Clinical manifestations

Headache, vertigo, nausea, weakness, drowsiness, confusion, loss of consciousness and, sometimes, coma can be observed. Usually, specific symptoms correspond to specific air concentrations of compounds, such as the following:

- Exposures exceeding 300 ppm of methylene chloride can usually cause dizziness in some minutes.
- For trichloroethanol, 20 ppm usually correspond to the odour perceptibility threshold, 110 ppm to an increase in reaction time, more than 1,200 ppm can cause pre-narcosis in few minutes, and about 2,500 ppm are able to cause rapid onset of narcosis.
- For tetrachloroethylene, exposure at concentrations in the order of 100 ppm tends to cause slight smell at first and, after some hours, dizziness and headache.

Exposure assessment

- History of occupational exposure: evidence of occupational exposure to halogen compounds such as methylene chloride, trichloroethylene, tetrachloroethylene, and vinyl chloride monomer. When available, workplace air monitoring and determination of the compounds or their metabolites in biological fluids (such as blood dichloromethane concentration and carboxyhaemoglobin for methylene chloride).
- Minimum duration of exposure: few minutes.
- Maximum latent period: 24 hours.

Acute neurological syndrome (T59.8, T60.8, X47, X48, Y17), Acute toxic encephalopathy (G92, T60.8), Toxic optic neuropathy (H46)

Short description of the disease

Intense acute exposure to some compounds of the group (e.g. methyl chloride, methyl bromide, and allyl chloride) can result in acute effects on the central nervous system, which can be mild to severe, and include memory loss, fatigue, depression, involuntary movements, difficulty in concentration, personality changes, increased irritability, impairment of vision, seizures, and unconsciousness.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: headache, vertigo, sleepiness, confusion, blurred vision, nausea and vomiting. For higher exposures, neuropsychiatric symptoms, seizures, convulsions, fever, and cyanosis may be observed, followed by fatality in the most severe cases.
- Examinations: neuropsychological assessment may show neurobehavioral impairment and should be conducted through the use of tests addressed at exploring verbal and visual memory, attention, psychomotor speed, visual analysis, construction and abstraction ability, and primary intellectual ability.

Exposure assessment

- History of occupational exposure: confirmed high occupational exposure to halogenated derivatives via inhalation or skin contact and, if available, biological monitoring and workplace air monitoring.
- Minimum duration of exposure: few minutes.
- Maximum latent period: 24 hours.

1.1.11 Diseases caused by halogen derivatives of aliphatic or aromatic hydrocarbons ICD Code T53 +Z57

Toxic liver disease (K71.9)

Short description of the disease

Acute inhalation of high concentrations of tetrachloroethylene, methyl bromide, methyl chloride, trichloroethylene, alpha-chlorotoluene, allyl chloride, or prolonged or repeated exposure to these compounds and other halogenated derivatives of the aromatic hydrocarbons (PCB, PBB, hexachloronaphthalene) can cause liver impairment and damage. Liver toxicity caused by these compounds includes acute toxic hepatitis, and acute hepatic failure. Mild to moderate hepatic parenchymal changes can occur such as fatty liver, liver fibrosis and centrilobular necrosis. Liver impairment caused by halogenated derivatives of naphthalene ranges from reversible and functional disorders to acute liver atrophy.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: pain in the liver/spleen area, hepatomegaly and splenomegaly.
- Examinations:
  - Serum direct-reacting bilirubin, transaminases and alkaline phosphatase may be elevated; low or moderate levels of ethylene dichloride can be associated with raised serum AST and ALT or GGT (current exposure).
  - Ultrasound scan shows mild to moderate hepatic parenchymal changes, including steatosis.
  - Liver biopsy: a variety of liver histological changes may be present, including steatosis (fatty liver), lobular inflammation, balloon degeneration of hepatocytes and Mallory bodies, with or without fibrosis.

Exposure assessment

- History of occupational exposure: confirmed occupational exposure to high concentrations of liquid, vapours or aerosols of halogen derivatives of aromatic (alpha-chlorotoluene), aliphatic or acyclic hydrocarbons or prolonged exposure to these compounds, PCB, PBB and hexachloronaphthalene by inhalation, skin and eyes contact and, when available, workplace air and biological monitoring.
- Minimum duration of exposure: six weeks for halogenated derivatives of biphenyls (e.g. PCB, PBB); a few months for halogenated derivatives of naphthalene (e.g. hexachloronaphthalene).
- Maximum latent period: six months for halogenated derivatives of biphenyls and of naphthalene.

Name of the diseases and ICD code: **Chronic diseases caused by halogen derivatives of aliphatic or aromatic hydrocarbons** *(Specific disease code)* **+T53 +Z57**

Chloracne (L70.8)

Short description of the disease

Acute, repeated or prolonged exposure to polychlorinated biphenyls, naphthalenes and dibenzodioxins (e.g. 2,3,7,8-tetrachlorodibenzo-p-dioxin [TCDD]) through skin contact may cause an acne-like eruption of pustules, blackheads and cysts known as chloracne. Chemicals that cause chloracne have two benzene rings in a planar orientation with halogen atoms laterally positioned; the induction of aryl hydrocarbon hydroxylase is associated with chloracnegenic activity. The disease is extremely persistent and in some cases may last for decades after cessation of exposure.

Diagnostic criteria

Clinical manifestations

- The appearances are of small straw-coloured cysts and closed comedones. In more severe cases, inflammatory lesions with larger cysts, abscesses and follicular hyperkeratosis can be observed.
- The lesions are distributed over the malar areas and posterior ears; typically, the nose is spared. The neck, shoulders, chest, back, gluteal region and scrotum may be involved. Hyperpigmentation of the face may also be a feature.
- The eye can often be affected with conjunctivitis and meibomian gland lesions.

Exposure assessment

- History of occupational exposure: evidence of occupational exposure to some halogenated compounds, such as polychlorinated biphenyls, naphthalenes and dibenzodioxins and, when available, workplace air monitoring and detection of compounds or their derivatives in biological fluids.
- Minimum duration of exposure: few weeks.
- Maximum latent period: four weeks.

1.1.11 Diseases caused by halogen derivatives of aliphatic or aromatic hydrocarbons ICD Code T53 +Z57

Effects on endocrine, immune, nervous, and reproductive systems following exposure to derivatives of biphenyls (T53.7, T65.8, X46, X49, Y16, Y19)

Short description of the disease

In addition to the abovementioned effects on the skin, exposure to halogenated derivatives of biphenyls may cause endocrinological alterations and immunosuppressive changes; reproductive and developmental effects and nonspecific neurological and psychological effects have been reported.

Diagnostic criteria

Clinical manifestations

- Endocrine system: thyroid function changes.
- Immune system: increased infection rates and alterations in circulating lymphocyte populations.
- Nervous system: fatigue, headache, depression, sleep disturbances, memory loss.
- Reproductive system: impaired sperm motility or foetal growth, and lower birthweight have been documented.

Exposure assessment

- History of occupational exposure: confirmed repeated or prolonged occupational exposure to polychlorinated biphenyls (PCB) or polybrominated biphenyls and, when available, workplace air monitoring and detection of compounds or their derivatives in biological fluids, such as plasma levels of PCB, especially congeners 28 (2,4,4′-Trichlorobiphenyl), 52 (2,2′,5,5′-Tetrachlorobiphenyl), 101 (2,2′,4,5,5′-Pentachlorobiphenyl), 138 (2,2′,3,4,4′,5′-Hexachlorobipheny), 153 (2,2′,4,4′,5,5′-Hexachlorobiphenyl), and 180 (2,2′,3,4,4′,5,5′-Heptachlorobiphenyl).
- Minimum duration of exposure: six weeks.
- Maximum latent period: data from environmental disasters suggest about two-three months for reversible effects; data on other potential long-term effects following low-level exposure to PCB still need further validation. Neurobehavioral and developmental deficits reported in newborns exposed to PCB in utero could be persistent, and maximum latent period could be not applicable.

Chronic toxic encephalopathy (G92), Toxic optic neuropathy (H47.0), Ototoxic hearing loss (H91.0)

Short description of the disease

Repeated or prolonged exposure to methylene chloride, trichloroethylene, tetrachloroethylene, methyl bromide, and allyl chloride can affect the central nervous system and cause a chronic toxic encephalopathy. In subjects exposed to high concentrations of tetrachloroethylene, impairments in visual reproduction and memory have been reported. Chronic exposure to methyl bromide in lower concentrations can result in nervous system involvement.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: visual disturbances (such as blurred vision and loss of colour vision), cortical deafness, motor impairment, mental confusion, psychiatric disturbances and tremor, which may be permanent effects.
- Examinations: neuropsychological assessment may show neurobehavioral impairment; pure tone audiometry may document sensorineural hearing loss; ophthalmoscopy may show visual loss.

Exposure assessment

- History of occupational exposure: evidence of prolonged or repeated occupational exposure to halogenated derivatives of the aliphatic or alicyclic hydrocarbons and, when available, workplace air monitoring and detection of compounds or their derivatives in biological fluids.
- Minimum duration of exposure: 10 years.
- Maximum latent period: not applicable.

Effects on the peripheral nervous system (G62.2)

Short description of the disease

Prolonged or repeated exposure to some halogen derivatives of aliphatic hydrocarbons (e.g. allyl chloride, methyl bromide) may have effects on the peripheral nervous system, resulting in numbness and sensorimotor polyneuropathy of arms and legs. Toxicity of allyl chloride to the liver and kidney generally overshadows any neurotoxicity, but outbreaks of polyneuropathy are reported in groups of subjects without liver and kidney dysfunction.

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Diagnostic criteria

Clinical manifestations

- Signs and symptoms: symptoms of sensorimotor polyneuropathy are commonly felt bilaterally, starting from the toes, and include numbness, pain, tingling, burning or abnormal feeling. Affected subjects experience weakness of the arms, face or legs. All these sensations can affect any part of the body.
- Examinations:
  - Neurological examination may show diminished reflexes.
  - Electroneurography may show variable levels of neuropathy.
  - Electromyography may show picture of second neuron syndrome.

Exposure assessment

- History of occupational exposure: evidence of prolonged or repeated occupational exposure to some halogen derivatives of aliphatic hydrocarbons (e.g. allyl chloride, methyl bromide) and, when available, workplace air monitoring and detection of compounds or their derivatives in biological fluids.
- Minimum duration of exposure: one month.
- Maximum latent period: six months.

Injury of trigeminal nerve (S04.3)

Short description of the disease

Prolonged or repeated exposure to trichloroethylene can cause damage to the 5th cranial nerve (trigeminal), which results in hypoaesthesia and paraesthesia of the corresponding innervated area.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: reduction or loss of facial sensations, jaw movements and corneal reflex.
- Examinations: alterations at sensory evoked potentials testing can be found.

Exposure assessment

- History of occupational exposure: evidence of prolonged or repeated exposure to trichloroethylene and, when available, workplace air monitoring and detection of the compound or its metabolites in biological fluids, such as blood trichloroethanol and urinary trichloroacetic acid.
- Minimum duration of exposure: several years.
- Maximum latent period: effects are usually observed during exposure.

Raynaud's phenomenon in the hands and feet (I73.0), Acro-osteolysis in the terminal phalanges of the hands and feet (M89.5), Distal skin disorders (scleroderma-like syndrome) (L94.8)

Short description of the disease

Repeated or prolonged exposure to high vinyl chloride concentrations can be associated with specific findings in the skin and bones, which include acro-osteolysis accompanied by scleroderma-like changes in the fingers and peripheral circulatory changes like Raynaud's disease. This set of symptoms is also known as "vinyl chloride disease". Some evidence suggests genetic susceptibility as a possible reason for the variability characterizing the clinical picture.

Diagnostic criteria

Clinical manifestations

- Raynaud's disease: features are identical to primary Raynaud's as well as to the Raynaud's disease caused by vibrations, thus including paroxysmal bilateral digital pallor and cyanosis followed by rubor (i.e., redness of the skin), usually precipitated by cold or emotional stress, and relieved by warmth. Cold testing may reveal Raynaud's phenomenon.
- Acro-osteolysis is associated with joint and muscle pain and may be accompanied by angioneurotic disorders. X-rays may show loss of structure from bones, caused by the decalcification of the terminal phalanges of the hands and feet, which may be reversible after cessation of exposure. Nailfold capillaroscopy is recommended to exclude angiopathic disorders.
- Scleroderma-like syndrome is characterized by smooth, shiny skin, in some cases accompanied by arthralgia and myalgia. Typical skin changes are thickening, decreased elasticity, and slight oedema. Skin biopsy can support the diagnosis.

1.1.11 Diseases caused by halogen derivatives of aliphatic or aromatic hydrocarbons ICD Code T53 +Z57

Exposure assessment

- History of occupational exposure: confirmed prolonged or repeated occupational exposure to vinyl chloride and, if available, workplace air monitoring.
- Minimum duration of exposure: one year.
- Maximum latent period: five years.

Liver fibrosis with portal hypertension (K74.0, +K76.6)

Short description of the disease

Chronic exposure to vinyl chloride monomer (VCM) can cause a typical liver impairment consisting in non-cirrhotic hepatic periportal fibrosis, hepatosplenomegaly, non-cirrhotic portal hypertension, peliosis hepatis (rarely), angiosarcoma (an extremely rare disease) and hepatocellular carcinoma. Both vinyl chloride and its metabolites produce hyperplasia of mesenchymal sinusoidal lining cells in the liver and spleen and hyperplasia of hepatocytes. Hepatic stellate cell activation results in fibrosis and the end result is splenomegaly and portal hypertension.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: hepatomegaly and splenomegaly. Non-cirrhotic portal hypertension usually presents with bleeding from gastric or oesophageal varices.
- Examinations: seldomly, hepatic function enzymes show changes; liver biopsy may show fibrosis.

Exposure assessment

- History of occupational exposure: confirmed occupational prolonged exposure to VCM by inhalation, or skin/eyes contact and, when available, workplace air and biological monitoring. Effects are unlikely at vinyl chloride air concentration below 130 mg/m^3 (50 ppm) and the risk of portal fibrosis is high for exposures at least as high as 200 ppm.
- Minimum duration of exposure: one year.
- Maximum latent period: 30 years.

Renal failure with tubular necrosis (N17.0), Chronic renal failure (N18.9)

Short description of the disease

Acute or prolonged exposure to trichloroethylene, tetrachloroethylene, allyl chloride, alpha-chlorotoluene, methyl chloride, or methyl bromide may cause renal failure.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms:
  - When present, symptoms are often due to uraemia, which can cause nausea, vomiting, malaise, and altered sensorium.
  - In chronic, more insidious onset, general symptoms of uraemia may include fatigue and weakness, anorexia, nausea, vomiting, and a metallic taste in the mouth are common. Other features may include irritability, memory impairment, insomnia, restless legs, paresthaesias. Twitching and generalized pruritus without rash may occur. Decreased libido and menstrual irregularities are common, as well as hypertension and altered fluid homeostasis.
- Examinations:
  - Serum creatine concentration is usually increased and creatinine clearance reduced.
  - At the beginning of the disease, presence in the urine of low molecular weight proteins such as beta-2-microglobulin and retinol binding proteins can be detected (tubular proteinuria), as well as N-acetylglucosaminidase (NAG) and gamma-glutamyl transpeptidase (GGT) (enzymuria).
  - When the disease progresses, red blood cells, white blood cells, tubular epithelial cells and albumin can be found in urine while high circulating anti-laminin antibodies are detected in serum; anaemia can also occur.
  - Ultrasound evaluation may show different levels of renal atrophy.
  - Renal biopsy may uncover a histopathological picture of glomerulonephritis.

1.1.11 Diseases caused by halogen derivatives of aliphatic or aromatic hydrocarbons ICD Code T53 +Z57

Exposure assessment

- History of occupational exposure: confirmed acute, prolonged or repeated occupational exposure to halogen derivatives of aromatic, aliphatic or alicyclic hydrocarbons and, when possible, biological and workplace air monitoring.
- Minimum duration of exposure: one year.
- Maximum latent period: two years.

Chemical porphyria (E80.1)

Hexachlorobenzene poisoning (mostly following accidental ingestion) can cause acquired porphyria cutanea tarda with disturbances in porphyrin metabolism, dermatological lesions, hyperpigmentation, hypertrichosis, enlarged liver, thyroid gland and lymph nodes, osteoporosis, and arthritis.

Name of the diseases and ICD code: **Carcinogenic effects of halogen derivatives of aliphatic and aromatic hydrocarbons** *(Specific disease code)* **+T53 +Z57**

Liver angiosarcoma (C22.3), Hepatocellular carcinoma (C22.0)

Exposure to vinyl chloride can cause liver angiosarcoma and hepatocellular carcinoma. IARC has classified vinyl chloride as carcinogenic to humans and allocated it in Group 1. For further details, refer to item 3.1.7.

Kidney cancer (C64)

There is sufficient evidence in humans for the carcinogenicity of trichloroethylene in causing cancer of the kidney. Trichloroethylene has been classified as carcinogenic to humans by the IARC (Group 1). Kidney, or renal cancer refers to any type of cancer that involves the kidney, and mainly originates in two parts of the kidney, the renal tubule and the renal pelvis.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: kidney cancer rarely shows signs or symptoms in its early stages. In the later stages nonspecific symptoms can appear: blood in urine, nonspecific back pain, loss of appetite, unexplained weight loss, tiredness, intermittent mild fever, lump or mass in the side or the abdomen.
- Examinations: currently there are no routine tests used to screen for kidney cancer in the absence of symptoms. Physical examination, urine tests, CT and magnetic resonance imaging (MRI) of kidney tissue, and ultrasound could be performed in case of suspected diagnosis and for staging.

Exposure assessment

- History of occupational exposure: confirmed acute, prolonged or repeated occupational exposure to trichloroethylene and, when possible, biological and workplace air monitoring.
- Minimum duration of exposure: kidney cancer can possibly develop in people with a short exposure duration.
- Maximum latent period: not applicable.

Melanoma (C43)

Exposure to polychlorinated biphenyls (PCB) can cause malignant melanoma. PCB have been thus classified as carcinogenic to humans (Group 1) by the IARC. This tumour originates in the pigment-producing melanocytes in the basal layer of the epidermis. The first signs can appear as one or more atypical moles.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: diagnostic suspect can arise from the evaluation of a new or pre-existing mole with the following characteristics: asymmetry, irregular borders, colour that tends to be very dark, and diameter usually ≥ 6 mm. Occasionally, bleeding, itching or crusting can be observed.
- Examinations: a complete excisional biopsy of a suggestive lesion or re-excision after biopsy permits histologic examination to confirm the diagnosis. Characteristic histologic findings include: cytologic atypia, numerous mitotic figures, upward growth of the melanocytes.

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Exposure assessment

- History of occupational exposure: confirmed acute, prolonged or repeated occupational exposure to PCB and, when possible, biological and workplace air monitoring.
- Minimum duration of exposure: melanoma has been observed in people with a short exposure duration.
- Maximum latent period: not applicable.

Key actions for prevention	The popularity of halogenated organic solvents in technological applications such as degreasing, dissolution of materials, and dispersion of resins and pigments, strongly depends on their good solvent power, their appreciable volatility and their poor flammability. However, due to their toxicity (and sometimes carcinogenicity), as well as their unfavourable environmental characteristics (poor degradation, ozone depletion, and greenhouse effect), there is a pressure to substitute them with non-halogenated solvents with poor flammability, substantially less toxicity, and environmental friendliness, such as with hydrocarbon ethers and glycol-ethers. When chlorinated hydrocarbons are used as process solvents in the chemical industry or in technological processes, source encapsulation is commonplace and, as such, this helps to mitigate workers' exposure. The use of personal protective devices helps to further reduce unnecessary exposure when production processes do not allow source encapsulation, such as in degreasing. Exposure limits for the most common industrial solvents should be enforced and analytical methods be established for routine measurement of exposure through workplace and biological monitoring. Waste management of spent chlorinated solvents is mandatory in most countries due to the high environmental toxicity and usually poor degradation of the mixtures. Solvent recycling by fractional distillation may be economically convenient when compared to the cost of disposal by thermal destruction, which needs to be carried out in dedicated facilities, due to the easy formation of persistent pollutants such as chlorinated dioxins when conditions are not appropriate. Pregnant workers should avoid occupational exposure to methylene chloride. The use of the most dangerous compounds among *halogenated aliphatic hydrocarbons* should be avoided entirely. Where it is technically feasible, they should be replaced by less harmful substances. For example, as far as practicable, less hazardous substances should be used instead of bromomethane in refrigeration and as fire extinguishers. In addition to the prudent safety and health measures applicable to volatile chemicals of similar toxicity, it should also be recalled that only some among the series of halogenated aliphatic hydrocarbons are not flammable and not explosive. Some of them do not support combustion and are used as fire extinguishers. In contrast other members of the series are flammable, in some instances even highly flammable (for example, 2-chloropropane), and form explosive mixtures with air. Besides, in the presence of oxygen, violently explosive peroxide compounds may arise from some unsaturated members (for example, dichloroethylene) even at very low temperatures. Toxicologically dangerous compounds may be formed by thermal decomposition of halogenated hydrocarbons. The effectiveness of engineering and hygiene measures for prevention should be confirmed by periodic health examinations and complementary laboratory tests aimed at the target organs, in particular the liver and kidneys. Safety and health measures for *halogenated aromatic hydrocarbons* are similar to those for solvents. In general, skin contact and vapour inhalation should be minimized. The manufacturing process should be enclosed as completely as possible. Effective ventilation should be provided together with local exhaust equipment at the main sources of exposure. Personal protective equipment should include appropriate respirators, eye and face protection as well as hand and arm protection. Work clothes should be frequently inspected and laundered. Good personal hygiene, including a daily shower, is important for workers handling chloronaphthalenes. For some of the agents, such as benzyl chloride, periodic medical examinations should be carried out. As regard PCB, their concentration in the work environment should be controlled periodically in order to check the efficacy of preventive measures in keeping these concentrations at recommended levels. The surveys should be repeated within 30 days of any change in the technological process likely to increase the occupational exposure to PCB.

1.1.11 Diseases caused by halogen derivatives of aliphatic or aromatic hydrocarbons ICD Code T53 +Z57	
Key actions for prevention	If PCB leak or are spilled, the personnel should be evacuated from the area immediately. Emergency exits should be clearly marked. Instructions with regard to emergency procedures appropriate to the specific features of the plant technology should be implemented. Only personnel trained in emergency procedures and adequately equipped should enter the area. The duties of the emergency personnel are to repair leaks, clean up spills (dry sand or earth should be spread on the leak or spill area) and fight fires. Workers should be informed of the adverse health effects caused by occupational exposure to PCB, as well as on their carcinogenicity and potential reproductive toxicity. Pregnant workers should be aware that PCB may endanger the health of worker and foetus, due to the placental transfer of PCB and their foetotoxicity and provided options for other work during pregnancy and lactation. It is also important to recall that high amounts of PCB are excreted with milk (the quantity of PCB transferred to the infant by milk is higher than that transferred by the placenta). Access to PCB work areas should be limited to authorized personnel. These workers should be provided with suitable protective clothing: long-sleeved overalls, boots, overshoes and bib-type aprons that cover the boot tops. Gloves are needed to reduce skin absorption during special tasks. The bare-handed handling of cold or heated PCB materials should be forbidden (the quantity of PCB absorbed through the intact skin may equal or exceed that absorbed by inhalation). Clean working clothes should be provided daily (they should be periodically inspected for defects). Safety glasses with side shields should be worn for eye protection. Respirators (meeting legal/technical requirements) should be used in areas with PCB vapours and during installation and repair of containers and emergency activities, when the air concentration of PCB is unknown or is likely to exceed occupational exposure limits (the respirators must be cleaned after use and properly stored). Ventilation will prevent accumulation of vapours. The workers should wash their hands before eating, drinking, smoking and so on, and refrain from such activities in the polluted rooms. Street clothes should be stored during the work shift in separate lockers. These clothes should be put on at the end of the working day only after a shower bath. Showers, eyewash fountains and washroom facilities should be readily accessible to the workers. Periodic clinical examination of workers (at least annually) with special emphasis upon skin disorders, liver function and reproductive history is recommended.

1.1.11 Diseases caused by halogen derivatives of aliphatic or aromatic hydrocarbons ICD Code T53 +Z57

Further reading

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3. European Commission: Information notices on occupational diseases: a guide to diagnosis (2009). Office for official publication for the European communities, Luxemburg. Annex 117, Halogenated derivates of the aliphatic or alicyclic hydrocarbons. P77-89. Annex I 127, Halogenated derivatives of the aromatic hydrocarbons. P121-4. Annex I 135, Encephalopathies due to organic solvents which do not come under other headings. P150-2. Annex I 121. Acetone, chloroacetone, bromoacetone, hexafluoroacetone, methyl ethyl ketone, methyl n-butyl ketone, methyl isobutyl ketone, diacetone alcohol, mesityl oxide, 2-methylcyclohexanone. P100.
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12. Maroni M, Mocci F, Visentin S, Preti G, Fanetti AC. Periportal fibrosis and other liver ultrasonography findings in vinyl chloride workers. Occup Environ Med. 2003 Jan;60(1):60-5.
13. U.S. Department of Health and Human Services - Public Health Service. Agency for Toxic Substances and Disease Registry, 2000. Toxicological profile for polychlorinated biphenyls (PCB). Available at: https://www.atsdr.cdc.gov/toxprofiles/tp17.pdf. Last accessed: October 2021.

For the chemical entities listed below an entry exists in the collection of International Chemical Safety Cards (ICSC) hosted in the ILO website

Name	Synonyms	ICSC
1,2-Dibromo-3-chloropropane	3-Chloro-1,2-dibromopropane; DBCP; 1-Chloro-2,3-dibromopropane	0002
Phosgene	Carbonyl chloride; Chloroformyl chloride	0007
Allyl chloride	3-Chloro-1-propene; 3-Chloropropylene; Chloroallylene	0010
Benzyl chloride	alpha-Chlorotoluene; (Chloromethyl)benzene; Tolyl chloride	0016
Carbon tetrachloride	Tetrachloromethane; Tetrachlorocarbon	0024
Chloroform	Trichloromethane; Methane trichloride Formyl trichloride	0027
2-Chloro-1-nitrobenzene	o-Chloronitrobenzene; o-Nitrochlorobenzene; 1-Chloro-2-nitrobenzene	0028
Epichlorohydrin	1-Chloro-2,3-epoxypropane; gamma-Chloropropylene oxide; 2-(Chloromethyl)oxirane	0043
Ethylene dibromide	1,2-Dibromoethane; EDB	0045
Trichlorofluoromethane	Trichloromonofluoromethane; Fluorotrichloromethane; CFC 11; R 11	0047
Dichlorodifluoromethane	Difluorodichloromethane; R 12; CFC 12	0048
Chlorodifluoromethane	Monochlorodifluoromethane; Methane, chlorodifluoro-; HCFC 22; R 22	0049
1,1,2-Trichloro-1,2,2-trifluoroethane	Trichlorotrifluoroethane; CFC 113; R 113	0050

Name	Synonyms	ICSC
Hexachloroethane	Perchloroethane; Carbon hexachloride	0051
Lindane	gamma-1,2,3,4,5,6-Hexachlorocyclohexane; gamma-BHC; gamma-HCH	0053
Dichloromethane	Methylene chloride; DCM	0058
1,1,1-Trichloroethane	Methyl chloroform; Methyltrichloromethane; alpha-Trichloroethane	0079
Trichloroethylene	1,1,2-Trichloroethylene; Trichloroethene; Ethylene trichloride; Acetylene trichloride	0081
Vinyl chloride	Chloroethene; Chloroethylene; VCM	0082
Vinylidene chloride	1,1-Dichloroethene; 1,1-Dichloroethylene; VDC	0083
Benzal chloride	Dichloromethyl benzene; Benzylidene chloride; alpha, alpha-Dichlorotoluene; Benzyl dichloride	0101
Bromoform	Tribromomethane; Methenyl tribromide	0108
Methyl bromide	Bromomethane; Monobromomethane	0109
2-Chloroacetophenone	2-Chloro-1-phenylethanone; alpha-Chloroacetophenone; Phenacyl chloride	0128
2-Chloroaniline	2-Chloroaminobenzene; 1-Amino-2-chlorobenzene; Fast yellow GC base; o-Chloroaniline	0129
1-Chloroethane	Ethyl chloride; Monochloroethane	0132
Chloroprene	2-Chloro-1,3-butadiene; 2-Chlorobutadiene; beta-Chloroprene	0133
Cyanogen bromide	Bromine cyanide; Cyanobromide; Bromocyan	0136
3,4-Dichloroaniline	1-Amino-3,4-dichlorobenzene; 3,4-Dichlorobenzenamine	0144
m-Chlorophenol	3-Chlorophenol; 3-Chloro-1-hydroxybenzene; 3-Hydroxychlorobenzene	0150
Hexachlorophene	2,2'-Methylenebis(3,4,6-trichlorophenol); HCP	0161
Acetyl chloride	Acetic chloride; Ethanoyl chloride; Acetic acid chloride	0210
Chloroacetic acid	Chloroethanoic acid; Monochloroacetic acid; MCA	0235
2-Chloroethanol	2-Chloroethyl alcohol; Ethylene chlorohydrin; Glycol chlorohydrin	0236
Bis(Chloromethyl) ether	BCME; sym-Dichloromethyl ether; 1,1'-Dichlorodimethyl ether; Oxybis(chloromethane); Chloro(chloromethoxy)methane	0237
Chloromethyl methyl ether	Dimethylchloro ether; Chloromethoxymethane	0238
1,1-Dichloroethane	Ethane, 1,1-dichloro-; Ethylidene chloride	0249
1,2-Dichloroethane	Ethylene dichloride; 1,2-Ethylene dichloride; Ethane dichloride	0250
2,3-Dichloro-1-nitrobenzene	2,3-Dichloronitrobenzene; 1,2-Dichloro-3-nitrobenzene	0251
1,3-Dichloro-4-nitrobenzene	2,4-Dichloro-1-nitrobenzene	0252
1,3-Dichloro-2-nitrobenzene	2,6-Dichloronitrobenzene	0253
1,2-Dichloro-4-nitrobenzene	3,4-Dichloronitrobenzene DCNB	0254
Fluoroacetic acid	alpha-Fluoroacetic acid; Monofluoroacetic acid; FAA	0274
Halothane	2-Bromo-2-chloro-1,1,1-trifluoroethane; 1-Bromo-1-chloro-2,2,2-trifluoroethane	0277
Isobutyl chloride	1-Chloro-2-methylpropane	0286
Isopropyl chloroformate	Isopropyl chlorocarbonate; Chloroformic acid, isopropyl ester Carbonochloridic acid; 1-methylethyl ester; Isopropyl chloromethanate	0287
Methyldichlorosilane	Dichloromethylsilane; Monomethyldichlorosilane	0297
Methyltrichlorosilane	Trichloromethylsilane	0301
1,1,2,2-Tetrachloroethane	Acetylene tetrachloride; sym-Tetrachloroethane 1,1-Dichloro-2-2,dichloroethane	0332
Dibromomethane	Methylene bromide; Methylene dibromide	0354
Acetyl bromide	Ethanoyl bromide	0365
Alachlor	2-Chloro-2',6'-diethyl-N-(methoxymethyl)acetanilide	0371

Name	Synonyms	ICSC
Bromochloromethane	Chlorobromomethane; Methylene chlorobromide	0392
Bromodichloromethane	Dichlorobromomethane; Methane, bromodichloro-	0393
2-Bromo-2-nitro-1,3-propanediol	&-Bromo-&-nitrotrimethyleneglycol	0415
1-Chloro-2,4-dinitrobenzene	1,3-Dinitro-4-chlorobenzene; 2,4-Dinitrophenyl chloride; DNCB	0416
Bis(2-chloroethyl) ether	Dichloroethyl ether 2,2'-Dichloroethyl ether; 1,1'-Oxybis(2-chloro) ethane; sym-Dichloroethyl; ether Diethylene glycol dichloride	0417
Sulfur mustard	HD; Mustard gas Bis(2-chloroethyl)sulphide; 1,1'-Thiobis(2-chloroethane)	0418
Methyl chloride	Chloromethane, Monochloromethane	0419
Chlorotrifluoromethane	CFC 13; Monochlorotrifluoromethane; Trifluoromethyl chloride	0420
1,1-Dichloro-1-nitroethane	Ethane, 1,1-dichloro-1-nitro-	0434
Dichloroisopropyl ether	Bis(2-chloro-1-methylethyl) ether; 2,2'-Oxybis(1-chloropropane); Dichlorodiisopropyl ether	0435
1,2-Dichloroethylene	1,2-Dichloroethene; Acetylene dichloride symmetrical; Dichloroethylene	0436
Sodium dichloroisocyanurate	Dichloro-s-triazine-2,4,6-trione; sodium salt	0437
1,2-Dichloropropane	Propylene dichloride	0441
Diethylthiophosphoryl chloride	Phosphorochloridothioic acid; O,O-diethylester; Diethyl chlorothiophosphate; Diethyl phosphochloridothionate	0448
Carbon tetrabromide	Tetrabromomethane	0474
Ethyl iodide	Iodoethane; Ethane iodide; Monoiodoethane	0479
Sodium fluoroacetate	Sodium fluoroacetic acid; Fluoroacetic acid, sodium salt	0484
Hexachlorocyclohexane (mixed isomers)	1,2,3,4,5,6-Hexachlorocyclohexane (mixed isomers); BHC/HCH (mixture of isomers); 1,2,3,4,5,6-Benzenehexachloride (mixed isomers)	0487
Methyl iodide	Iodomethane	0509
Tetrafluoromethane	Carbon tetrafluoride; Freon 14; Halon 14	0575
Trifluoromethane	Carbon trifluoride Fluoroform R 23 Methyl trifluoride	0577
2,3,5-Trichlorophenol	Phenol, 2,3,5-trichloro-; 1-Hydroxy-2,3,5-trichlorobenzene	0589
2,3,6-Trichlorophenol	Phenol, 2,3,6-trichloro-; 1-Hydroxy-2,3,6-trichlorobenzene	0590
Vinyl bromide	Bromoethene; Bromoethylene; Monobromoethylene	0597
Vinyl fluoride	Fluoroethene; Fluoroethylene	0598
2-Amino-5-chlorotoluene	4-Chloro-o-toluidine; 4-Chloro-2-methylaniline	0630
Carbonyl fluoride	Carbon oxyfluoride; Carbon difluoride oxide; Difluoroformaldehyde; Fluorophosgene	0633
Bromochlorodifluoromethane	Freon 12; B 1; R 12; B 1; Halon 1211	0635
2-Chloroacetamide	alpha-Chloroacetamide; Chloroacetamide; 2-Chloroethanamide	0640
Chlorobenzene	Benzene chloride; Chlorobenzol; Phenyl chloride	0642
Chlorodifluoroethane	1-Chloro-1,1-difluoroethane; HCFC 142 b	0643
2-Chloropropionic acid	Propanoic acid, 2-chloro-; 2-Chloropropanoic acid; alpha-Chloro-propionic acid	0644
Dichlorotetrafluoroethane	1,2-Dichloro-1,1,2,2-tetrafluoroethane; CFC114	0649
Chlorine trifluoride	Chlorine fluoride; Chlorotrifluoride	0656
1,2,4,5-Tetrachlorobenzene	Benzene tetrachloride; s-Tetrachlorobenzene	0676
1,2,3-Trichloropropane	Glycerol trichlorohydrin; Allyl trichloride	0683
Trifluorochloroethylene	Chlorotrifluoroethylene; Trifluorovinyl chloride	0685
Vinylidene fluoride	1,1-Difluoroethylene 1,1-Difluoroethene; R1132a; Vinylidene difluoride	0687
Cyclophosphamide	2-Bis(2-chloroethyl)amino; N,N-Bis(2-chloroethyl)tetrahydro-2H-1,3,2-oxazaphosphorin-2-amine 2-oxide	0689

Name	Synonyms	ICSC
1-Chlorobutane	n-Butyl chloride; n-Propylcarbinyl chloride	0703
Chloroacetaldehyde	2-Chloroacetaldehyde; 2-Chloro-1-ethanal; Monochloroacetaldehyde	0706
1-Chloro-3,4-dinitrobenzene	1,2-Dinitro-4-chlorobenzene	0722
1,1-Dichloropropane	Propylidene chloride	0723
1,3-Dichloropropane		0724
Chloroacetone	1-Chloro-2-propanone; Acetonyl chloride Monochloroacetone	0760
alpha-Hexachlorocyclohexan	alpha-1,2,3,4,5,6-Hexachlorocyclohexane; alpha-Benzenehexachloride (alpha-BHC); alpha-Hexachloran	0795
beta-Hexachlorocyclohexan	1-alpha,2-beta,3-alpha,4-beta,5-alpha,6-beta-Hexachlorocyclohexane; beta-1,2,3,4,5,6-Hexachlorocyclohexane; beta-Benzenehexachloride (beta-BHC)	0796
Bromotrifluoromethane	Trifluorobromomethane; Fluorocarbon-1301; Bromofluoroform	0837
Chloroacetonitrile	Chloroethanenitrile; Monochloroacetonitrile; Chloromethyl cyanide	0844
Chloroacetyl chloride	Chloroacetic acid chloride; Monochloroacetyl chloride	0845
Chloropentafluoroethane	1-Chloro-1,1,2,2,2-pentafluoroethane; Fluorocarbon 115	0848
o-Chlorophenol	2-Chlorophenol; 2-Chloro-1-hydroxybenzene, 2-Hydroxychlorobenzene	0849
p-Chlorophenol	4-Chlorophenol; 4-Chloro-1-hydroxybenzene, 4-Hydroxychlorobenzene	0850
Dichloroacetic acid	Bichloroacetic acid; Dichlorethanoic acid DCA 2,2;-Dichloroacetic acid	0868
2,2-Dichloroacetyl chloride	Dichloroacetyl chloride	0869
2,4,5-Trichlorophenol	2,4,5-TCP; 1-Hydroxy-2,4,5-trichlorobenzene	0879
Enflurane	2-Chloro-1,1,2-trifluoroethyl difluoromethyl ether; 2-Chloro-1-(difluoromethoxy)-1,1,2-trifluoroethane; Ethrane; Ether, 2-chloro-1,1,2-trifluoroethyl difluoromethyl	0887
Hexachlorobenzene	Perchlorobenzene; HCB; Pentachlorophenylchloride; Phenyl perchloryl	0895
Hexachlorobutadiene	1,1,2,3,4,4-Hexachloro-1,3-butadiene; Perchlorobutadiene	0896
Diisopropyl ether	Isopropyl ether; 2,2'-Oxybispropane; 2-Isopropoxypropane	0906
Benzyl chloroformate	Benzylcarbonyl chloride; Carbobenzoxy chloride; Formic acid, chlorobenzyl ester	0990
1,3-Dichloropropene	1,3-Dichloropropylene; Dichloropropene; 3-Chloroallyl chloride; DCP	0995
Fluorosulfonic acid	Fluorosulfuric acid; Fluorosulphuric acid	0996
Hexachloronaphthalene		0997
Benzoyl chloride	Benzenecarbonyl chloride; Benzoic acid chloride; alpha-Chlorobenzaldehyde	1015
Bromobenzene	Monobromobenzene; Phenyl bromide	1016
Ethyl chloroformate	Ethyl chlorocarbonate; Chloroformic acid ethyl ester; Carbonochloridic acid ethyl ester; Ethoxycarbonyl chloride	1025
O-Chlorobenzylidenemalononitrile	2-(Chlorophenyl)methylenemalononitrile; 2-Chlorobenzylidene malononitrile; (o-Chlorobenzal)malononitrile; beta,beta-Dicyano-o-chlorostyrene; (2-Chlorophenyl)methylenepropanedinitrile; CS (riot control agent)	1065
Bromoacetone	Bromo-2-propanone; Acetyl methyl bromide	1074
Chloronitroaniline	2-Chloro-4-nitroaniline; 1-Amino-2-chloro-4-nitrobenzene; o-Chloro-p-nitroaniline; Benzeneamine, 2-chloro-4-nitro-	1076
Ethyl chloroacetate	Chloroacetic acid, ethyl ester; Ethyl monochloroacetate; Ethyl alpha-chloroacetate; Ethyl-2-monochloroacetate	1081
Hexachlorocyclopentadiene	1,2,3,4,5,5-Hexachloro-1,3-cyclopentadiene; Perchlorocyclopentadiene	1096
Dichloromonofluoromethane	Fluorodichloromethane; HCFC 21; Fluorocarbon 21	1106

Name	Synonyms	ICSC
Methyl chloroformate	Methyl chlorocarbonate Carbonochloridic acid, methyl ester Chloroformic acid methyl ester Methoxycarbonyl chloride	1110
Methanesulfonyl chloride	Mesyl chloride; Methylsulfonyl chloride; Methanesulfonic acid chloride	1163
Benzyl bromide	alpha-Bromotoluene; Bromophenylmethane	1225
Cyanuric chloride	2,4,6-Trichloro-1,3,5-triazine; Chlorotriazine; Trichlorocyanidine; Tricyanogen chloride; Cyanuric acid trichloride; 2,4,6-Trichloro-s-triazine	1231
1,1,2,2-Tetrabromoethane	Acetylene tetrabromide; Tetrabromoacetylene; sym-Tetrabromoethane	1235
1,1,1,2-Tetrafluoroethane	HFC 134a	1281
Chlorotrifluoroethane	2-Chloro-1,1,1-trifluoroethane; 1-Chloro-2,2,2-trifluoroethane; HCFC 133a	1299
Chlorfenvinphos	O,O-Diethyl-O-{2-chloro-1-(2,4-dichlorophenyl)vinyl}phosphate; 2-Chloro-1-(2,4-dichlorophenyl)vinyldiethyl phosphate	1305
1-Bromopropane	n-Propyl bromide; Propyl bromide	1332
3-Chloro-2-methyl-1-propene	Methallyl chloride; Methyl allyl chloride; gamma-Chloroisobutylene	1341
2,2-Dichloro-1,1,1-trifluoroethane	HCFC 123	1343
Bromoethane	Ethyl bromide	1378
Methyl chloroacetate	Chloroacetic acid methyl ester; Methyl monochloroacetate; Methyl-alpha-chloroacetate	1410
Dibromodifluoromethane	Difluorodibromomethane; Fluorocarbon 12-B2	1419
1,1,1,2-Tetrachloro-2,2-difluoroethane	1,1-Difluoro-1,2,2,2-tetrachloroethane; CFC-112a	1420
1,1,2,2-Tetrachloro-1,2-difluoroethane	1,2-Difluoro-1,1,2,2-tetrachloroethane; CFC-112; Fluorocarbon 112	1421
1-Chloro-1-nitropropane		1423
Dichloroacetylene	Dichloroethyne	1426
Fluoroacetamide	2-Fluoroacetamide; Monofluoroacetamide; Fluoroacetic acid amide	1434
Isoflurane	Ether, 1-chloro-2,2,2-trifluoroethyl difluoromethyl; 2-Chloro-2-(difluoromethoxy)-1,1,1-trifluoroethane	1435
Sevoflurane	1,1,1,3,3,3-Hexafluoro-2-(fluoromethoxy)propane; Ether, fluoromethyl 2,2,2-trifluoro-1-(trifluoromethyl)ethyl	1436
Desflurane	1,2,2,2-tetrafluoroethyl difluoromethyl ether	1437
p-Chloro-o-cresol	para-Chloro-ortho-cresol; Phenol, 4-chloro-2-methyl; 4-Chloro-o-cresol	1476
Methylchlorosilane	Chloro(methyl) silane	1587
n-Butyl chloroformate	Butyl chlorocarbonate; Butyl chloroformate; Chloroformic acid butyl ester; Carbonochloridic acid, butyl ester	1593
Isobutyl chloroformate	Isobutyl chlorocarbonate; 2-Methylpropyl chloroformate; Formic acid, chloro-, isobutyl ester; Carbonochloridic acid, 2-methylpropyl ester	1594
n-Propyl chloroformate	Propyl chloroformate; Propyl chlorocarbonate; Formic acid, chloro-, propyl ester; Carbonochloridic acid, propyl ester	1595
1,4-Dichloro-2-nitrobenzene	2,5-Dichloronitrobenzene; 1-Nitro-2,5-dichlorobenzene; Nitro-p-dichlorobenzene	1618
1-Chloro-3-nitrobenzene	Benzene, 1-chloro-3-nitrom-Chloronitrobenzene	1633
Methoxyflurane	2,2-Dichloro-1,1-difluoroethyl methyl ether; 2,2-Dichloro-1,1-difluoro-1-methoxyethane; Methoflurane; Penthrane	1636
2-Amino-4-chlorophenol	p-Chloro-o-aminophenol; 2-Hydroxy-5-chloroaniline; 4-Chloro-2-aminophenol; C.I. 76525	1652
1-Bromo-3-chloropropane	1-Chloro-3-bromopropane; Trimethylene chlorobromide	1665
1,2-Dibromo-3-chloropropane	3-Chloro-1,2-dibromopropane; DBCP; 1-Chloro-2,3-dibromopropane	0002

Name	Synonyms	ICSC
Phosgene	Carbonyl chloride; Chloroformyl chloride	0007
Allyl chloride	3-Chloro-1-propene; 3-Chloropropylene; Chloroallylene	0010
Benzyl chloride	alpha-Chlorotoluene (Chloromethyl)benzene; Tolyl chloride	0016

▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
1.1.11	Acute/chronic diseases caused by halogen derivatives of aliphatic and aromatic hydrocarbons	T53	NE61
1.1.11	Respiratory tract irritation	J68.3	CA81.Y
1.1.11	Acute chemical pneumonitis and bronchitis	J68.0	CA81.0
1.1.11	Pulmonary oedema	J68.1	CA81.1
1.1.11	Upper respiratory inflammation	J68.2	CA81.2
1.1.11	Burns and corrosions of eye and adnexa	T26.0-T26.1, T26.5-T26.6	NE00 & XA3RB1, XA9K79, XA53T1
1.1.11	Conjunctivitis	H10.2	9A60.Z
1.1.11	Keratoconjunctivitis	H16.2	9A79
1.1.11	Corneal ulcer	H16.0	9A76
1.1.11	Burns and corrosions of external body surface	T20-T25	ND9Z, ND9Y, NE10
1.1.11	Irritant contact dermatitis	L24	EK02.12
1.1.11	Narcotic syndrome consequent to acute systemic poisoning by halogenated derivatives of aliphatic or alicyclic hydrocarbons: methylene chloride, trichloroethylene, tetrachloroethylene, vinyl chloride monomer, chloroacetone, bromoacetone, hexafluoroacetone, halogenated derivatives of benzene	T53.2, T53.3, T53.4, T53.6, T53.7, T59.3, T59.8	PB35, & XM73T7, & XM3NB3, & XM3DA8, & XM6YR0, & XM2N89
1.1.11	Acute neurological syndrome	T59.8, T60.8, X47, X48, Y17	NE61, PB32, PB33, PB36, PH56
1.1.11	Acute/chronic toxic encephalopathy	G92	8D43.0Y
1.1.11	Toxic optic neuropathy	H46	9C40.Y
1.1.11	Toxic liver disease	K71	DB95.Y
1.1.11	Chloracne	L70.8	ED81.1
1.1.11	Effects on endocrine, immune, nervous, and reproductive systems following exposure to derivatives of biphenyls	T53.7, T65.8, X46, X49, Y16, Y19	NE61,PB35, PB36, PH55, PH51, PH56
1.1.11	Toxic optic neuropathy	H46	9C40.Y
1.1.11	Ototoxic hearing loss	H91.0	AB53
1.1.11	Effects on the peripheral nervous system	G62.2	8D43.2Y
1.1.11	Injury of trigeminal nerve	S04.3	NA04.4
1.1.11	Raynaud's phenomenon in the hands and feet	I73.0	BD42.Z
1.1.11	Acro-osteolysis in the terminal phalanges of the hands and feet	M89.5	FB86.2
1.1.11	Distal skin disorders (scleroderma-like syndrome)	L94.8	EE7Y
1.1.11	Liver fibrosis with portal hypertension	K74.0, +K76.6	DB93.Y & DB98.7Z
1.1.11	Renal failure with tubular necrosis	N17.0	GB60.Z
1.1.11	Chronic renal failure	N18.9	GB61.Z
1.1.11	Chemical porphyria	E80.1	5C58.10
1.1.11	Liver angiosarcoma	C22.3	2B56.3
1.1.11	Hepatocellular carcinoma	C22.0	2C12.02
1.1.11	Kidney cancer	C64	2C90.Z
1.1.11	Melanoma	C43	2C30.Z
	Occupational exposure to risk factors	Z57	QD84.Y

1.1.12 Diseases caused by benzene or its homologues	ICD Code T52.1, T52.2 +Z57
General characteristics of the causal agent	Benzene and its homologues belong to the chemical class of (alkyl)-aromatic hydrocarbons and are defined by the general formula: $C_nH_{2n-6.}$ The most important alkyl derivatives of benzene are toluene, xylene and ethylbenzene. Like benzene, alkyl-aromatic compounds are liquid, colourless, with an aromatic, sweet gasoline-like odour. Volatility decreases with the number and size of the alkyl substituents. Vapours are heavier than air and may migrate along the ground, with the possibility of distant ignition. Solubility in water is in the order of 0.1% or less (w/w), decreasing with the number and size of the alkyl substituents. All alkyl-aromatic compounds react more or less violently with oxidants, nitric acid, sulphuric acid and halogens and may thus cause fire or explosion hazards. They attack plastic and rubber materials. *Benzene* (benzol, C_6H_6, molecular mass 78.1, CAS number 71-43-2) is the simplest aromatic hydrocarbon. It is a volatile colourless liquid (boiling point 80° C) whose vapours are heavier than air. *Toluene* (methylbenzene, toluol, $C_6H_5CH_{3,}$ molecular mass 92.1, CAS number 108-88-3, boiling point 110.6°C) is a volatile liquid, easily flammable at ambient temperature and pressure. It has a sweet benzene-like odour. Nowadays, technical grade toluene may contain small amounts of benzene, whilst higher levels of contamination (even in the order of 25%) used to be relevant in the past. *Xylene* (xylol, $C_6H_4(CH_3)_2$, molecular mass 106.2) exists in three isomeric forms of dimethylbenzene: ortho (ortho-Xylene, 1,2-Dimethylbenzene, o-Xylol, CAS number 95-47-6); meta (meta-Xylene, 1,3-Dimethylbenzene, m-Xylol, CAS number 108-38-3); and para (para-Xylene, 1,4-Dimethylbenzene, p-Xylol, CAS number 106-42-3), with boiling points 144.4, 139.1, and 138.3°C, respectively. Technical grade xylene (boiling point 138.5°C) contains a mixture of these isomers together with some ethylbenzene. *Ethylbenzene* ($C_6H_5CH_2CH_3$, molecular mass 106.2, CAS number 100-41-4) is a highly flammable, colourless, volatile liquid with a boiling point of 136.2°C.
Occupational exposures	*Benzene* occurs naturally in crude petroleum. It is present in coal derivatives and petroleum fractions, and distillates. Mixtures of alkylbenzene homologues are employed as technical solvents and are contained in reformed gasoline. Benzene is still present in car fuel in variable amounts (in the order of 1-3%), depending on the quality of the gasoline. The presence of benzene in petrol and as an industrial solvent can result in significant occupational exposure. Benzene and pure alkylbenzene isomers are used as starting materials in the chemical synthesis of a great variety of bulk chemicals (such as styrene, cumene, cyclohexane, nitrobenzene, chlorobenzene, phenol, etc.), and specialty products (such as explosives, intermediates for dyes and pharmaceuticals, etc.). Occupational exposure to benzene and alkylbenzenes may hence occur in the chemical industry for the synthesis of a great variety of chemical products, in the production and handling of gasoline fuels, in the production and use of solvents and thinners for fats, waxes, resins, oils, inks, paints, lacquers, adhesives, glues, plastics, rubber, in scouring of metal parts, in dry cleaning, in the extraction of oils from seeds and nuts, and in photogravure printing. Benzene is also used as a chemical intermediate and in the manufacture of detergents, explosives, pharmaceuticals, and dyestuffs. High levels of occupational exposure to benzene may occur in industries involving benzene production (petrochemicals, petroleum refining, coke and coal chemical manufacturing), rubber manufacturing, and storage or transport of benzene and petroleum products containing benzene. Other workers who may be exposed to benzene because of their occupations include steel workers, printers, shoemakers, laboratory technicians, firefighters, and petrol station workers. Additional occupational exposure to benzene is nowadays possible in the production of benzene via coal tar distillation or from petroleum, in the cleaning of tanks in which benzene has been stored; and through contact with residues of crude oil or with petrol including vehicle emissions. Occupational exposure to alkyl-benzene homologues is possible in several productive activities and in the handling of materials. Among those of greater concern, there are: the rubber industry, the production of benzoic acids (terephthalic acid is a polymer building block made from p-xylene), of explosives, of styrene from benzene and of many other organic compounds; the formulation of solvents and thinners for paints, lacquers, adhesives, glues, and printing inks; the manipulation of gasoline and crude oils.

1.1.12 Diseases caused by benzene or its homologues	ICD Code T52.1, T52.2 +Z57
Occupational exposures	*Toluene* occurs naturally in crude oil. It is a by-product in the production of gasoline and other fuels from crude oil and in the production of coke from coal. Toluene is used for the production of paints, paint thinners, adhesives, fingernail polish, lacquers, and rubber, and in some printing and leather tanning processes, as well as in the production of benzene, plastics, nylon, and polyurethane. It is used in the synthesis of trinitrotoluene (TNT), benzoyl chloride, benzoic acid, and toluene diisocyanate. Toluene is also used to improve octane ratings by addition to gasoline, along with benzene and xylene. Toluene is nowadays used in all the processes in which benzene was usually employed in the past as solvent, because it does not entail haematological effects. In some cases, however, technical toluene is still contaminated by benzene, with levels up to 15%. *Xylene* is primarily produced from petroleum as a synthetic chemical. Nonetheless, it can occur naturally in petroleum and coal tar and form during forest fires, although to a small extent. The most common use of xylene is as a solvent in the printing, leather, and rubber industries. It is widely used as a cleaning agent, a thinner for paint, and in varnishes. To a lesser extent, xylene is used as an ingredient in the coating of fabrics and papers, and as a material in the chemical, synthetic fibres, and plastics industries. Xylene can be found in small amounts in gasoline and airplane fuel. *Ethylbenzene* is primarily produced by the alkylation of benzene with ethylene under liquid phase conditions and a solid alkylation catalyst. Ethylbenzene is used for the production of styrene, as a solvent in paints and lacquers and in the rubber and chemical manufacturing industries. It is found in crude oils and combustion products. Occupational exposure to ethylbenzene alone is rare because ethylbenzene is usually present in complex mixtures such as gasoline, or it is handled in closed systems as in conversion to styrene.
Toxicological profile, main health effects and diagnostic criteria	
Short toxicological profile	Benzene is readily absorbed following inhalation (primarily), oral or dermal exposure. Absorbed benzene is rapidly distributed throughout the body and tends to accumulate in fatty tissues (with a higher partition into lipid-rich organs, such as the brain and bone marrow), extensively bio-transformed (mostly in the liver), and excreted in the urine as several metabolites. Benzene is metabolized to many metabolites by the cytochrome P450 (CYPs) oxidase system. CYP2E1 (Cytochrome P450 Family 2 Subfamily E Member 1) is one of the most important isoenzymes metabolizing benzene, and its oxidative metabolism is needed for the induction of haematotoxic and genotoxic effects of benzene. Since ethanol is able to induce CYP2E1, alcohol consumption can foster benzene toxicity. Excretion of benzene metabolites mostly occurs in the urine, while after inhalation benzene is rapidly eliminated in exhaled air unchanged. Most of absorbed toluene is metabolized in the liver by the P450 system and excreted in urine. Around 20% of absorbed toluene is eliminated in exhaled air. More than 90% of absorbed xylene is transformed via side-chain oxidation to methylhippuric acid and excreted in urine. Ethylbenzene is metabolized to mandelic and phenylglyoxylic acids. The biotransformation occurs preferably at the alkyl substituents, which are progressively mineralized to yield the corresponding benzoic acids. Hydroxylation of the aromatic ring occurs only to a minor extent in alkyl benzenes, but is the main pathway in benzene. The intermediate arene oxide is highly reactive and, together with its conversion products, represents the putative genotoxic agent that causes the effects of benzene on the haematopoietic system. Most metabolites of benzene and its homologues can be used for biological monitoring (see below for further details). Acute occupational exposure to *benzene* can cause narcosis: headache, dizziness, drowsiness, confusion, tremors and loss of consciousness. Benzene is a moderate eye irritant and a skin irritant. Chronic exposure to benzene can reduce the production of both red and white blood cells from bone marrow in humans, resulting in aplastic anaemia. It reduces both B-cell and T-cell proliferation and decreases host resistance to infection. Chromosomal aberrations in human peripheral lymphocytes are associated with occupational exposure to benzene. A number of reports suggest that benzene induces site-specific human chromosome damage [translocations between chromosomes 14 and 18, t(14;18)]. Several case reports have documented how *toluene* as an abused inhaled drug can cause death, central nervous system symptoms, and cardiac, renal, and hepatic toxicities, as well as a foetal alcohol-like syndrome. Some investigations on volunteers exposed to at least 100 ppm of toluene for most of a work day reported intoxication and reduced performance. Studies on populations of rotogravure printers, historically exposed to high concentrations of toluene, showed neurobehavioral, reproductive, developmental, and colour vision changes.

1.1.12 Diseases caused by benzene or its homologues	ICD Code T52.1, T52.2 +Z57
Short toxicological profile	Short-term exposure to high levels of *xylene* has been shown to produce skin and eye irritation, as well as irritation of the respiratory tract mucosae, thus causing difficulty in breathing and impaired lung function. Stomach discomfort and possible alterations in liver and kidney functions have been observed, together with neurological effects, such as headache, dizziness, confusion, delayed response to visual stimuli, impaired memory, and lack of muscle coordination with loss of balance. Short-term exposure to high levels of *ethylbenzene* has been shown to cause eye and throat irritation, and vertigo and dizziness following increasing levels of exposure. Some evidence suggests that ethylbenzene might induce hearing loss. Occupational long-term exposure to ototoxic organic solvents which include mixtures of benzene, toluene, xylene and ethylbenzene have been shown to cause ototoxic hearing loss, regardless of concurrent noise exposure, and chronic encephalopathy. For the further details, refer to item 1.1.38.

Name of the diseases and ICD code: **Acute diseases caused by benzene or its homologues**
(Specific disease code) **+T52.1, T52.2 +Z57**

Respiratory tract irritation (J68), Acute chemical pneumonitis and bronchitis (J68.0), Upper respiratory inflammation (J68.2), Conjunctivitis (H10.2), Corneal ulcer (H16.0), Irritant contact dermatitis (L24), Narcotic syndrome and other neurological effects (T52.1, T52.2), Cardiac arrhythmias (I49.9), Nausea and vomiting (R11), Diarrhoea (K52.9)

Short description of the disease

Benzene is considered very toxic: inhalation of air concentrations in the order of 20,000 ppm has been observed to be fatal in 5-10 minutes. Skin exposure to benzene can result in redness and blisters. Prolonged or repeated skin contact may result in irritant dermatitis. People who breathe in high levels of benzene may develop drowsiness, dizziness, rapid or irregular heartbeat, headaches, tremors, confusion, unconsciousness, up to death. These clinical manifestations may occur within minutes to several hours. Neurological effects appear to be due primarily to the direct effects of benzene on the central nervous system. The anaesthetic action of benzene on the central nervous system is similar to that of other anaesthetic gases, first inducing excitation followed by depression and, if exposure continues, death through respiratory failure. Consuming foods or fluids contaminated with high levels of benzene can cause vomiting, stomach irritation, dizziness, sleepiness, convulsions, rapid heart rate, and death. Benzene can cause death in acute exposures primarily by its anaesthetic properties (respiratory arrest) or by exacerbating fatal arrhythmias.

Lethal doses of inhaled *toluene* vapours have been estimated to be around 4,000 ppm for 1 hour or in the order of 10,000-30,000 ppm for a few minutes.

Xylenes have been observed to produce irritant effects on the eyes, skin, and mucous membranes, together with impaired respiratory function, headache and dizziness, for short-term exposures to concentrations as low as 50 ppm. Chronic exposures have been reported to cause eye irritation, sore throat, and neurological effects (such as anxiety, inability to concentrate, and forgetfulness) at even lower concentrations (around 14 ppm). Eye contact with xylene vapours or liquid xylene can cause irritation, and subsequent photophobia, redness of the conjunctivae, and damage of the conjunctival and corneal epithelium. Following airborne concentrations of about 100-400 ppm, the occurrence of neurological effects such as retardation of response times, memory impairments, and loss of balance have been observed. Tremors, mental confusion, and narcosis have been reported for air concentrations estimated to be in the order of 10,000 ppm. In workers exposed to xylene vapours, nausea and vomiting have been reported.

Evidence on the lethal effects of *ethylbenzene* are scarce, as are data regarding systemic effects of ethylbenzene inhalation. Recognized effects are irritation of the eyes and mucosae of the respiratory tract, and ototoxicity. Haematological alterations, such as increased lymphocyte counts and decreased haemoglobin concentration, have been reported.

1.1.12 Diseases caused by benzene or its homologues ICD Code T52.1, T52.2 +Z57

Diagnostic criteria

Clinical manifestations

- Signs and symptoms:
  - *Central nervous system*

  The symptoms of narcotic syndrome include headache, dizziness, nausea, drowsiness, weakness, confusion, unconsciousness, respiratory depression, memory loss, nausea, hearing and colour vision loss and, in the most severe cases, coma. Unconsciousness may be prolonged, although consciousness is regained rapidly after cessation of exposure. Generally, symptoms of central nervous system toxicity appear immediately after inhalation of benzene levels in the order of 3,000 ppm for a few minutes, and 30 to 60 minutes after ingestion. For toluene concentrations above 200-240 ppm, vertigo, dizziness, difficulty in maintaining equilibrium, and headache can be observed after perhaps 3-7 hours of exposure. Higher concentrations may result in a narcotic coma and sudden death, following cardiac arrest due to ventricular fibrillation with increased sensitivity to catecholamines (this might follow, for example, inhalation of fumes from adhesives containing toluene among other solvents).

  Below is a summary of typical neurological clinical patterns usually observed at corresponding increasing concentration levels of benzene or its homologues.

Concentration (ppm)	**Time of exposure** (hr)	**Health effects**
Benzene		
25	8	No acute clinical symptoms
50~150	5	Headache, lassitude, weakness
500	1	Vertigo, drowsiness, nausea
7500	½	Dangerous to life
Toluene		
2.5		Odour threshold
100	8	No symptoms, possible very mild headache
200	8	Mild irritant effects
400	8	Irritation, headache, dizziness, incoordination
800	3	Pronounced nausea
4000	1	Narcosis
≥5000		Unconsciousness and death
Xylene		
1		Odour threshold
100	4	No effect on reaction time
200	4	Irritant effects, prolonged reaction time, impairment of vestibular, and visual function
300	2	Decreased performance (decrements in psychometric tests such as memory span and choice reaction time)
700	1	Dizziness, headache, feeling of intoxication, and sleepiness
≥5000		Unconsciousness and death

1.1.12 Diseases caused by benzene or its homologues ICD Code T52.1, T52.2 +Z57

- *Respiratory system*

Acute exposure to benzene vapour is irritant to the mucous membranes of the respiratory tract. With massive exposure (e.g. 20,000 ppm for a few minutes), pulmonary oedema and respiratory arrest may ensue. Pulmonary aspiration of ingested liquid benzene may cause severe haemorrhagic inflammation of the lungs.

- *Cardiovascular system*

Exposure to benzene concentrations usually above 1,000 ppm may lower the threshold of the heart muscle to the effects of adrenaline, resulting in life threatening arrhythmias such as ventricular fibrillation (these effects tend to be reversible if exposure is terminated).

- *Skin*

Benzene is a lipid solvent and, as such, it degreases the skin particularly after prolonged or repeated contact and can cause skin irritation. Locally, benzene can produce erythema, a burning sensation, and in more severe cases, oedema and even blistering. Recall that, because of their larger surface area to body weight ratio, child and young workers are more vulnerable than adults to toxicants absorbed through the skin.

- *Gastrointestinal system*

If swallowed, benzene can irritate the stomach, causing nausea, vomiting, and diarrhoea. A lethal oral dose has been estimated to be 100 mL (about 1 g/kg, for a 75 kg male), although as little as 15 mL or 50 mg/kg has been observed to cause death.

- *Eyes*

High concentrations of benzene vapour can cause eye irritation and visual blurring. When splashed in the eyes, benzene may cause burning pain and sloughing of the eye surface.

- *Potential sequelae*

Recovery from moderate exposure to benzene may take 1-4 weeks. During this time, affected subjects may also continue to experience impaired gait, nervous irritability, and breathlessness for about 2 weeks. Cardiac distress and yellow colouration of the skin may persist for up to one month.

- Examinations:
  - The diagnosis of acute benzene toxicity is primarily clinical, based mostly on neurological signs and symptoms, and respiratory effects. However, laboratory testing is useful for monitoring the affected subject and evaluating complications. Routine laboratory studies for all exposed subjects include full blood count, glucose, and electrolyte determinations. Additional tests include electrocardiogram monitoring, urinalysis, determinations of blood urea nitrogen, creatinine, and liver function test. Chest radiography and pulse oximetry (or arterial blood gas measurements) are recommended for severe inhalation exposure or if pulmonary aspiration is suspected.
  - Chest X-rays may reveal a picture of pneumonitis or bronchitis, with increased bronchovascular markings.
  - Pulmonary function tests may show an acute obstructive disease.
  - An ophthalmic examination should be performed, including visual acuity and slit lamp inspection of the cornea. Corneal ulceration may be seen on corneal examination.

Exposure assessment

- History of occupational exposure: confirmed occupational exposure to high concentrations of benzene or its homologues via inhalation, skin and eye contact and, when available, workplace air and biological monitoring data, such as:
  - urinary *S*-phenylmercapturic and *t,t*-muconic acids for benzene;
  - urinary toluene and o-cresol, and blood toluene for toluene;
  - urinary methylhippuric acid for xylene; and
  - urinary mandelic and phenylglyoxylic acids (summed), and ethylbenzene in end-exhaled air for ethylbenzene.

  Urinary markers should be collected at the end of the work shift. It is important to remember that, since cigarette smoke contains benzene, smoking is a relevant confounding factor in the interpretation of biomonitoring results.
- Minimum duration of exposure: few minutes.
- Maximum latent period: 24 hours.

1.1.12 Diseases caused by benzene or its homologues ICD Code T52.1, T52.2 +Z57

Name of the diseases and ICD code: **Chronic diseases caused by benzene** *(Specific disease code)* **+T52.1 +Z57**

Bone marrow depression (aplastic anaemia) (D61.2), Myelodysplastic (preleukemic) syndrome (D46.9)

Short description of the disease

Benzene is a myelotoxicant known to suppress bone marrow cell proliferation and to induce haematological disorders, while its metabolism produces an epoxide (benzene oxide), which may react with cell macromolecules. An early stage of benzene toxicity is leucopaenia (particularly lymphopaenia), which is reversible after the end of the exposure. This condition may progress to irreversible marrow damage: bone marrow failure syndromes (non-carcinogenic haematological effects) due to prolonged exposure to benzene include aplastic anaemia and myelodysplastic syndrome. Whilst frequent short-term exposures at levels in the order of 100 ppm or higher may result in transient blood changes (leucocytosis, polymorphocytosis) with no apparent long-term effects, repeated low-dose exposures (such as around 20 ppm) have been shown to cause cytopaenias (anaemia, leucopaenia and thrombocytopaenia).

Diagnostic criteria

Clinical manifestations

- Signs and symptoms:
  - Classic symptoms include weakness, purpura, pallor, pancytopaenia, breathlessness on exertion, increased occurrence of infections, bruising and haemorrhages, jaundice, splenomegaly, and lymphadenopathy. Pancytopaenia becomes manifest usually after 3-24 months of exposure.
  - Aplastic anaemia (medullary hypoplasia) is characterized by thrombocytopaenia, and leucopaenia, and anaemia.
  - Manifestations of myelodysplastic syndrome (medullary hyperplasia) include thrombocytosis, and leucocytosis, and erythrocytosis.
- Examinations:
  - Full blood count with differential and reticulocyte count may show transient haematological effects or signs of bone marrow failure; red blood cells indices may show anaemia.
  - Bone marrow aspiration and biopsy may show medullary depression.
  - Aplastic anaemia is defined by the presence of a peripheral blood pancytopaenia and a hypocellular bone marrow. Remaining blood cells tend to have normal morphology.

Exposure assessment

- History of occupational exposure: confirmed prolonged or repeated occupational exposure to benzene and, when available, environmental and biological monitoring data (urinary t,t-muconic and s-phenylmercapturic acids). Urinary markers should be collected at the end of the work shift.
- Minimum duration of exposure: depression of bone marrow activity has been observed after few days of exposure even at levels below 50 ppm (160 mg/m^3). Other haematological effects usually need higher levels of exposure for at least one month.
- Maximum latent period: three years.

Name of the diseases and ICD code: **Chronic diseases caused by benzene homologues or mixtures of the same** *(Specific disease code)* **+T52.2 +Z57**

Ototoxic hearing loss (H91.0)

Short description of the disease

Prolonged exposure to ototoxic organic solvents which include mixtures of benzene, toluene, xylene and ethylbenzene, can induce ototoxicity, even in the absence of noise exposure. Noise-induced hearing loss may be potentiated (cranial nerve effects): the incidence of sensorineural hearing loss has been found to be higher than expected in noise-exposed workers who were also exposed to ethylbenzene. The ototoxic effect of toluene and its synergism with noise is not well established.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: tinnitus and mild hearing loss to profound deafness. Difficulty in communicating in noisy environments.
- Examinations: pure tone audiometry shows high frequency sensorineural hearing loss.

Exposure assessment

- History of occupational exposure: confirmed occupational exposure to high concentrations of benzene homologues or mixtures of the same via inhalation, skin and eye contact and, when available, workplace air and biological monitoring data.
- Minimum duration of exposure: few months.
- Maximum latent period: one year.

1.1.12 Diseases caused by benzene or its homologues — ICD Code T52.1, T52.2 +Z57

Chronic toxic encephalopathy (G92)

Short description of the disease

Exposure to mixtures of benzene homologues (e.g. organic solvents), and to toluene in particular, may cause chronic adverse effects to the central nervous system. Solvent-induced encephalopathy, known as chronic toxic encephalopathy or organic brain syndrome due to chronic exposure to solvents, may develop usually insidiously after long-term exposure (often decades), even at not particularly high exposure levels. Chronic solvent encephalopathy is characterized by irreversible impairment of memory, concentration, and mood, accompanied by fatigue and loss of initiative. Attention, learning, psychomotor performance and verbal and non-verbal reasoning, as well as concept formation, can be affected. Loss of colour vision and alterations in visual perception may be part of the clinical picture.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: if exposure is not avoided, the disease progresses through three levels of increasing severity:
  - from *organic affective syndrome* (characterized by depression, irritability, loss of interest in daily activities);
  - to *mild chronic toxic encephalopathy* (characterized by fatigue, mood disturbances, memory and attentional complaints, together with impairment of psychomotor functions such as speed and dexterity); and
  - up to severe chronic toxic encephalopathy (characterized by loss of intellectual ability interfering with occupational or social functioning as well as by impairment of memory, abstract thinking and judgment). Third-level lesions become permanent, although the exposure ceases, and the affected person usually remains severely disabled.
- Examinations:
  - Neuropsychological assessment may show neurobehavioural impairment and should be conducted through the use of tests addressed at exploring the following functions: verbal and visual memory, attention, psychomotor speed, visual analysis, construction, abstraction, and primary intellectual abilities (some examples of specialized behavioural tests to measure neurotoxicity are reported in Table 2 at the end of item 1.1.38).
  - Electroencephalography may show nonspecific abnormalities (such as diffuse slowing).
  - Neuroimaging investigations may show mild cerebral atrophy.

Differential diagnosis

Depression and other psychiatric disorders; sleep and neurodegenerative disorders, vascular disorders of the brain; neoplasms such as brain tumours, metabolic causes such as thyroid disorders and avitaminosis; or even traumatic brain disorders.

Exposure assessment

- History of occupational exposure: confirmed occupational exposure to benzene homologues (toluene in particular) or mixtures of them via inhalation or skin contact and, when available, workplace air monitoring and detection of the compounds or their metabolites in biological fluids.
- Minimum duration of exposure: ten years.
- Maximum latent period: not applicable.

Name of the diseases and ICD code: **Carcinogenic effects of benzene or its homologues**
(Specific disease code) **+T52.1, T52.2 +Z57**

Short description of the disease

There is sufficient evidence in humans for the carcinogenicity of benzene. Benzene causes acute myeloid leukaemia in adults. Positive associations have been observed for non-Hodgkin lymphoma, chronic lymphoid leukaemia, multiple myeloma, chronic myeloid leukaemia, acute myeloid leukaemia in children, and cancer of the lung. There is strong evidence that benzene metabolites, acting alone or in concert, produce multiple genotoxic effects at the level of the pluripotent haematopoietic stem cell resulting in chromosomal changes consistent with those seen in haematopoietic cancer. IARC classifies benzene as carcinogenic to humans (Group 1). For further details on carcinogenic effects of benzene, refer to item 3.1.8.

As regards benzene homologues, the main IARC conclusions are reported below:

- The evidence for the carcinogenicity of ethylbenzene is inadequate in humans and sufficient in experimental animals: it has thus been classified as possibly carcinogenic to humans (Group 2B).
- Toluene and xylenes are not classifiable as to their carcinogenicity to humans (Group 3).

1.1.12 Diseases caused by benzene or its homologues	ICD Code T52.1, T52.2 +Z57
Key actions for prevention	Aromatic hydrocarbons are staple products of the chemical industry, and key components of gasoline and of oil-derived fuels. Moreover, lower aromatic hydrocarbons, such as benzene, spontaneously form as trace intermediates from the combustion processes of most carbon-containing fuels. Therefore, it is unlikely that their use can be discontinued or banned. The only case of a more or less extensive limitation or ban to use in consumer products is that of benzene. Due to the carcinogenicity of benzene, its use as a solvent or co-solvent in formulations such as glues, adhesives, paints, lacquers, and degreasers has been mostly eliminated. This is particularly important that in the production of fine chemicals, closed-circuit reactors and stringent manufacturing procedures, including the substitution of benzene with alternative starting materials whenever possible, are used to reduce and eliminate the exposure. Benzene is generated in the production of gasoline by reforming and aromatization of crude oil fractions, although in most industrial countries its content in the formulated product has been regulated to be well below 5% in volume. What can hardly be reduced is the generation of benzene from non-aromatic hydrocarbons during the use of gasoline in combustion engines, a phenomenon that parallels the generation of polycyclic aromatic hydrocarbons in diesel engines. In all industrial activities where benzene is produced, used or generated as a by-product, primary and secondary prevention measures should be applied to the highest possible level. Workplace and biological monitoring of workers should be implemented on a regular basis. Appropriate engineering, ventilation controls and working practices should be used with personal protective equipment to avoid skin, eye and respiratory exposure to benzene or its homologues. The WHO recommends several risk mitigation procedures to be followed; although mainly developed for public health purposes, they can easily apply to occupational settings as well, in detail: • Eliminate benzene usage by i) promoting the use of alternative solvents in industrial processes, glues and paints; and ii) developing and implementing policies and legislation to remove benzene from consumer products. • Reduce exposure to benzene by: i) minimizing exposure at petrol filling stations as far as possible with the implementation of best practices in location, design and extraction; ii) reducing emissions from vehicle exhausts through means of improved design and regular monitoring of engine settings; iii) separating dwelling spaces from areas where vehicles and benzene-containing products are kept; iv) avoiding, to the extent possible, the use of benzene-containing products; v) discouraging indoor use of unflued oil and gasoline heating; vi) prohibiting smoking inside buildings. • Educate employers and workers by i) raising their awareness regarding sources of exposure to benzene and risk mitigation measures; and ii) conducting educational activities to discourage the use of benzene or petrol for cleaning and degreasing in industry and domestically. Several scientific bodies and regulatory agencies suggest or enforce occupational exposure limits for various aromatic hydrocarbons. The group of experts considered that the following limits of exposure of workplace atmospheric concentrations have been observed to provide a reasonable level of protection for workers' health and have been used in a number of countries: • Benzene: 0.5 ppm as 8hr TWA, 2.5 ppm as short-term exposure. • Toluene: 20 ppm as 8hr TWA. • Xylenes: 100 ppm as 8hr TWA, 150 ppm as short-term exposure. • Ethylbenzene: 20 ppm as 8hr TWA.

1.1.12 Diseases caused by benzene or its homologues ICD Code T52.1, T52.2 +Z57

Further reading

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    - Occupational Acute Neurotoxic Diseases Caused by Chemicals (GBZ76).
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For the chemical entities listed below an entry exists in the collection of International Chemical Safety Cards (ICSC) hosted in the ILO website

Name	Synonyms	ICSC
Benzene	Cyclohexatriene benzol	0015
Toluene	Methylbenzene Toluol Phenylmethane	0078
Ethylbenzene	Ethylbenzol Phenylethane EB	0268
Cumene	(1-Methylethyl)benzene 2-Phenylpropane Isopropylbenzene	0170
O-Xylene	ortho-Xylene 1,2-Dimethylbenzene o-Xylol	0084
M-Xylene	meta-Xylene 1,3-Dimethylbenzene m-Xylol	0085
P-Xylene	para-Xylene 1,4-Dimethylbenzene p-Xylol	0086
1,2,3-Trimethylbenzene		1362
1,2,4-Trimethylbenzene		1433
1,3,5-Trimethylbenzene		1155
Trimethyl benzene mixed isomers	Benzene, trimethyl (isomers) Methylxylene	1389
P-Cymene	1-Methyl-4-isopropylbenzene Dolcymene Camphogen	0617
Diisopropylbenzene mix	Benzene, bis(1-methylethyl) Bis(1-methylethyl)benzene	1714

▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
1.1.12	Acute/chronic diseases caused by benzene or its homologues	T52.1, T52.2	NE61&XM0QY7, NE61&XM2738
1.1.12	Respiratory tract irritation	J68	CA81.Z
1.1.12	Acute chemical pneumonitis and bronchitis	J68.0	CA81.0
1.1.12	Upper respiratory inflammation	J68.2	CA81.2
1.1.12	Conjunctivitis	H10.2	9A60.Z
1.1.12	Corneal ulcer	H16.0	9A76
1.1.12	Irritant contact dermatitis	L24	EK02
1.1.12	Narcotic syndrome and other neurological effects	T52.1, T52.2	PB31&XM0QY7,
1.1.12	Cardiac arrhythmias	I49.9	BC9Z
1.1.12	Nausea and vomiting	R11	MD90
1.1.12	Diarrhoea	K52.9	ME05.1
1.1.12	Bone marrow depression (aplastic anaemia)	D61.2	3A70.11
1.1.12	Myelodysplastic syndrome (preleukaemic syndrome)	D46.9	2A3Z
1.1.12	Ototoxic hearing loss	H91.0	AB53
1.1.12	Chronic toxic encephalopathy	G92	8D43.0Z
1.1.12	Acute myeloblastic leukaemia	C92.0	2A60.3Z
	Occupational exposure to risk factors	Z57	QD84.Y

1.1.13 Diseases caused by nitro- and amino-derivatives of benzene or its homologues ICD Code T65.3 +Z57	
General characteristics of the causal agent	Nitro- and amino-derivatives of benzene or its homologues are a large, heterogeneous class of industrial chemical compounds characterized by the presence in their structure of at least one unit of benzene (or of a benzene alkyl homologue), to which one or more nitro (-NO_2) or/and amino (-NH_2) groups are attached by means of a direct chemical bond. The nitro and the amino functional groups linked to a benzene (or benzene homologue) unit can easily transform into one another by chemical and biochemical processes. The physical and chemical characteristics of individual compounds belonging to both classes differ depending on the presence of other functional groups in their chemical structures. Properties thus span from those of liquids with high volatility, and water solubility in the milligram- to gram-per-litre range (such as nitrobenzene and aniline), to those of high-melting solids with poor water and high organic solvent solubility. Further details are reported below separately for the two classes of benzene derivatives. *Nitro-derivatives of benzene or its homologues* are a class of organic chemicals derived from benzene or its homologues, through replacement of one or more hydrogen atoms by a nitro- group (R-NO_2). Nitro-compounds of major industrial importance include nitrobenzene, dinitrobenzene, the mono- and dinitrotoluenes (DNT, the main constituents of technical dinitrotoluene being 2,4-DNT and 2,6-DNT), trinitrotoluene (TNT), tetryl, mononitro-chlorobenzenes (2-chloro-nitrobenzene, 4-chloronitrobenzene, 1,4-dichloro-2-nitrobenzene, 2,4-dichloro-1-nitroben-zene), nitroanilines, nitro-chloro-toluenes, dinitrophenol, para-nitroanisole, 4-nitrodiphe-nyl, picric acid (trinitrophenol) and dinitrocresol. In the chemical industry, nitro-derivatives are often the chemical precursors of amino-derivatives. *Amino-derivatives of benzene or its homologues* are a class of organic chemicals derived from benzene or its homologues through replacement of at least one hydrogen atom by an amino- (-NH_2) group. Aniline is the simplest aromatic amino-compound, with one amino-group directly bound to a benzene ring. Pure aniline is a colourless and moderately volatile oily liquid with a char-acteristic amine odour. Acetanilide is the acetylated derivative of aniline. Other common single-ring aromatic amines include mono- and dialkyl- anilines (e.g. methyl and dimeth-ylaniline, ethyl- and diethylaniline), chloro-anilines, nitro-anilines, toluidines, chloro-tolui-dines, phenylene-diamines.
Occupational exposures	*Nitro-derivatives of benzene or its homologues (from now on 'nitro-derivatives')* of major industrial importance include nitrobenzene, mono-, di-, and trinitrotoluene. These are or were used as chemical solvents, as starting or intermediate organic compounds in fine chemical syntheses of pharmaceuticals, pesticides, dyes and other specialty chemicals. Also as explosive substances in military ordnance and as explosives in the construction industry. Occupational exposure to nitro-derivatives is thus possible in several chemical and non-chemical industrial applications: production of dyes, pigments, explosives, cosmetics, pesticides, plastics and pharmaceuticals, in the textile and paper industries, in remediation of chemically contaminated areas, and in chemical laboratories. *Nitrobenzene* is the starting material for the production of aniline and for the chemical synthesis of several fine chemical products; it was used as a solvent in the formulation of paints, in consumer goods such as shoe and floor polishes, and in leather dressings to impart a typical almond smell. Some derivatives of nitrobenzene are used in the fragrance industry. *Dinitrobenzene* (mainly 1,3-DNB) and dinitrotoluene (mainly 2,4-DNT and 2,6-DNT) are primarily used as starting materials for the synthesis of fine chemicals such as dyestuffs, pesticides and drugs. *Trinitrotoluene* (2,4,6-TNT) is synthesized for use as a main component of military ordnance and increasingly less as industrial explosive. *4-Nitrodiphenyl* is the chemical precursor of 4-amino-biphenyl.

1.1.13 Diseases caused by nitro- and amino-derivatives of benzene or its homologues
ICD Code T65.3 +Z57

Occupational exposures

Amino-derivatives of benzene or its homologues (from now on 'amino-derivatives') are obtained, in most cases, by chemical reduction of the corresponding nitro-derivatives. Aniline has been produced for more than a century in the manufacture of various products, such as dyestuffs and their intermediates, polyurethane foams, and rubber accelerators. Several compounds are used as intermediates in the syntheses of pharmaceuticals, pesticides, dyes and other specialty chemicals. Some amino-derivatives are employed as antioxidants in vulcanized rubber and as stabilizers in ordnance explosives. Some amino-derivatives carrying two amino groups in the molecular structure, such as 4,4'-diamino-biphenyl (or *p,p*-benzidine), 4,4'-diaminophenyl-methane, and *p*-phenylene-diamine, are (or were) used as bi-functional reagents in the manufacturing of isocyanate polymers and resins (for further details on isocyanates, refer to item 1.1.35). Other di-amino-derivatives (e.g. o-phenylene-diamine derivatives) are used in fur dyeing and in hair-dressing (hair dyeing) in both the professional and informal employment sectors.

The synthesis of specialty chemicals from nitro- and amino-derivatives generates large amounts of waste, containing unreacted materials and by-products, which may be more toxic than the starting materials. Cleaning of chemical reactors, management of dumps, and remediation of contaminated areas are activities likely to entail workers' exposure to these compounds, often at levels of toxicological concern.

Historically, many of these compounds were manufactured in high volumes as feed-stock materials in the production of other chemicals. In some countries the use of amino derivatives with carcinogenic properties has been banned (2-naphthylamine, benzidine, 4-aminodiphenyl and 4-nitrodiphenyl). Up-to-date information on global and national production volumes is difficult to access, but there is a trend in developed countries of elimination, or reduced manufacturing. In developing countries, there may be continued manufacturing and export to developed countries.

Toxicological profile, main health effects and diagnostic criteria

Short toxicological profile

Nitro- and amino-derivatives of benzene are reactive chemicals, and this is reflected in their toxicological effects.

Most nitro- and amino-derivatives of benzene or its homologues are quickly and largely absorbed by vapour and dust inhalation and through skin contact. After absorption, they distribute in the body, and are extensively bio-transformed (metabolic activation) especially by the liver, lung, kidney, bladder, skin and gut microorganisms.

Nitro-derivatives are biologically transformed by nitrogen reduction into the corresponding toxic reactive intermediates aryl-nitroso- and aryl-hydroxylamine compounds. For this reason, nitro-derivatives share many toxicological effects with amino-derivatives, and their metabolites are often more toxic than the nitro-aromatic precursors themselves.

Amino-derivatives are biologically transformed by nitrogen oxidation to yield toxic reactive intermediates, such as the aryl-hydroxylamine metabolites. The azoic dyes, which contain an Ar(1)-N=N-Ar(2) functional group, are converted especially by the gut microorganisms into the aromatic amines Ar(1)-NH_2 and Ar(2)-NH_2, and the entero-hepatic circulation reabsorbs the resulting products for further biotransformation. Aromatic amines and their aryl-hydroxylamine metabolites undergo biological acetylation to neutral compounds, which can also be reabsorbed.

Acetylated aryl-hydroxylamines that derive from aromatic amines and aromatic nitrocompounds are easily bio-transformed by de-acetylation to the corresponding nitrogen electrophiles (the nitrenes), which are reactive with biological nucleophiles such as the DNA (thus possibly initiating genotoxic carcinogenesis), with enzymes such as the cytochromes (thus impairing detoxification by the liver), and with haemoglobin (through which they can generate methaemoglobin). This latter phenomenon is particularly distinctive of poisoning from nitrobenzene and aniline, as well as from most other nitro- and amino-derivatives.

The hydroxylamine metabolites of some amino-derivatives, and to a lesser extent of some nitro-derivatives, bind to the side-chain carboxylic acid groups of body proteins. The resulting covalently bound forms, referred to as "protein adducts", can act as haptens towards the immune system and trigger allergic sensitization not only to the chemicals themselves, but also to compounds which contain the same sub-structures, in particular azo-dyes such as those of textile garments and of industrial processed food and drinks.

1.1.13 Diseases caused by nitro- and amino-derivatives of benzene or its homologues
ICD Code T65.3 +Z57

Short toxicological profile	Health effects related to exposure to nitro- and amino-derivatives of benzene and its homologues thus include (with various degrees of severity): methaemoglobinemia and other haematological alterations, skin and mucosal irritation, liver toxicity, skin sensitization with subsequent allergic contact dermatitis, as well as allergic reactions involving the upper and lower respiratory tract, with rhinitis and asthma, respectively. Some like benzidine are carcinogenic, while others like aniline are probable carcinogens. Because these substances and their active metabolites are excreted in the urine, they cause cancer of the bladder. Aniline for example is metabolically activated to electrophiles that are genotoxic, induce oxidative stress and alter cell proliferation and cell death. For other chemicals in this class that are classed as carcinogens or possibly carcinogenic, the mode of carcinogenicity is not clear.

Name of the diseases and ICD code: **Acute diseases caused by nitro- and amino-derivatives of benzene or its homologues** *(Specific disease code)* **+T65.3 +Z57**

Toxic methaemoglobinemia (D74.8), Toxic haemolytic anaemia (D59.4), Respiratory tract irritation (J68), Acute chemical pneumonitis and bronchitis (J68.0), Chemical pulmonary oedema (J68.1), Upper respiratory inflammation (J68.2), Burn and corrosion of eye and adnexa (T26.0-T26.1, T26.5-T26.6), Conjunctivitis (H10.2), Corneal ulcer (H16.0), Irritant contact dermatitis (L24)

Short description of the disease

The most characteristic sign of acute poisoning by most nitro- (especially nitrobenzene, dinitrobenzene, dinitrotoluene and 4-nitrodiphenyl) and amino-derivatives of benzene or its homologues is methaemoglobinemia, which decreases the oxygen-carrying capacity of the blood. Following methaemoglobinemia, prolonged exposure to most amino-derivatives, nitrobenzene, dinitrobenzene, and 4-nitrodiphenyl can cause haemolytic anaemia, due to breakdown of red blood cells.

Generally, nitro- and amino-derivatives are irritant for skin, eyes and respiratory tract. In particular:

- irritation of the skin follows exposure to nitrobenzene, dinitrobenzene, trinitrotoluene, and amino-derivatives;
- irritation of the mucous membranes is associated with exposure to nitrobenzene, trinitrotoluene, and amino-derivatives;
- irritation of the respiratory tract is linked with exposure to dinitrobenzene and amino-derivatives; and
- local irritation is uncommon in dinitrotoluene exposure.

Nitro- and amino-derivatives are slightly soluble in water: this characteristic can be related to lower respiratory tract symptoms with insidious onset. Effects can be delayed (6 to 24, up to 72 hours), but are often preceded by upper respiratory tract symptoms. Aspiration of *N,N*-diethyl-*m*-toluidine may lead to acute pulmonary oedema, which can also represent a delayed consequence of inhalation.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms:
  - Methaemoglobinaemia is characterized by intense cyanosis (with normal arterial pO_2) accompanied by headache, irritability, dizziness, drowsiness, numbness, vertigo, weakness, fatigue, nausea, vomiting, dyspnoea, chest and abdominal pain, aphonia, air hunger, unconsciousness, seizures, tachycardia, cardiac dysrhythmias, and potentially death.
  - Upper airways irritation usually becomes manifest with sneezing and sore throat.
  - Irritation of the skin is characterized by papular eruption, oedema and desquamation, especially in the case of prolonged or repeated exposure to trinitrotoluene.
  - Eye irritation is usually accompanied by pain and lacrimation and may cause corneal damage.
- Examinations:
  - Typical 'fishy' aniline odour may be detected in the breath and sweat of affected subjects.
  - On physical examination, splenomegaly and sometimes hepatomegaly may be observed.
  - Following methaemoglobinemia and anaemia, jaundice may become evident together with scleral icterus and an enlarged spleen, and the subject may report discolouration of the urine. Blood of the affected subject may assume a chocolate-brown colour.

1.1.13 Diseases caused by nitro- and amino-derivatives of benzene or its homologues ICD Code T65.3 +Z57

- Laboratory findings: haemoglobin levels may be normal or severely reduced; increased mean corpuscular volume, mean corpuscular haemoglobin, and reticulocytosis may be present. Unconjugated bilirubin and liver enzymes levels in serum are usually increased; conjugated bilirubin levels may be normal or only mildly elevated. Other findings may include: increased lactate dehydrogenase and reduced haptoglobin in serum, increased urobilinogen in urine and stool, and haemoglobinuria.
- Chest X-rays may show a picture of acute bronchitis or pneumonitis, with increased bronchovascular markings.
- Pulmonary function tests may show an obstructive picture.
- Physical examination and ophthalmoscopy may detect eye irritation.

Exposure assessment

- History of occupational exposure: confirmed occupational exposure to nitro- or amino-derivatives of benzene or its homologues (by inhalation and skin contact) and, when available, workplace air monitoring and measurements of the compounds or their metabolites in biological fluids, for example:
  - 4,4'-methylenebis (2-chloroaniline) (MOCA) can be monitored by measuring total (free and conjugated) MOCA in end-of-shift urine samples;
  - post-shift urinary aniline represents a good biomarker of aniline exposure; and
  - dinitro-aminotoluene metabolites can be found in urine after trinitrotoluene exposure.
- Minimum duration of exposure: few hours.
- Maximum latent period: few days.

Toxic liver disease (K71), Liver impairment (K72.9)

Short description of the disease

High exposure to trinitrotoluene (TNT) can cause hepatotoxic effects, mediated also by genetic susceptibility (e.g. in case of glucose-6-phosphate dehydrogenase deficiency or sickle cell trait), after absorption through skin and mucous membranes, inhalation, and ingestion. A clinical picture of liver disease usually appears after a period of two to four months from exposure. In some cases, the disease rapidly progresses to fulminant hepatic failure, which may be fatal in up to 25% of affected subjects. In other cases, the clinical presentation of the disease is sub-acute, with ascites and portal hypertension. Many amino-derivatives may cause mild hepatic impairment, characterized by transient liver function abnormalities.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: anorexia, weakness, nausea, vomiting and abdominal pain with hepatomegaly and jaundice. Accompanying sequelae may include skin rash, aplastic anaemia and methaemoglobinemia.
- Examinations:
  - Increases of serum transaminase, alkaline phosphatase, and serum bilirubin concentration can be observed when the disease progresses.
  - Liver failure in fulminant hepatitis commonly results in coagulopathy with disseminated intravascular coagulation, and kidney failure (including hepatorenal syndrome) with increased prothrombin time (PT) or international normalized ratio (INR).
  - Abdominal ultrasound examination may show hepatic steatosis.
  - A variety of histological changes can be observed at liver biopsy, including acute hepatitis, steatosis, fibrosis and centrilobular necrosis.

Exposure assessment

- History of occupational exposure: confirmed occupational exposure to high concentrations of TNT or amino-derivatives via inhalation, skin or eye contact and, when available, workplace air and biological monitoring, such as dinitroaminotoluene metabolites of TNT in urine or urinary aniline in post-shift samples.
- Minimum duration of exposure: few minutes.
- Maximum latent period: four months.

1.1.13 Diseases caused by nitro- and amino-derivatives of benzene or its homologues ICD Code T65.3 +Z57

Name of the diseases and ICD code: **Chronic diseases caused by nitro- and amino-derivatives of benzene or its homologues** *(Specific disease code)* **+T65.3 +Z57**

Allergic contact dermatitis (L23)

Short description of the disease

Amino-derivatives of benzene or its homologues, such as *p*- and *m*-phenylenediamine, nitroanilines, 2-aminophenol, 4,4'-methylenedianiline (MDA), and seldom trinitrotoluene (TNT) and nitrobenzene can induce skin hypersensitivity, and subsequent allergic contact dermatitis (ACD).

The disorder is characterized by an eczematous skin reaction due to a delayed type IV hypersensitivity to these contact allergens. It presents as a pruritic eczema, characterized by erythema and vesicles, which develops within 24-48 hours of exposure at the site of hapten penetration in sensitized individuals. Note that pre-existing skin irritation promotes the development of ACD. Although sensitization can be induced by even a single contact with the compound, in occupational settings it usually takes place after months of repeated contacts, or in some cases, after many years.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: redness, swelling, vesicles, oozing and crusting (acute eczematous reaction) of the skin. The development of the skin lesions is in direct relationship to the work activities, with a pattern of recurrence of the disease on re-exposure to the same agent. Through a cumulative effect, repeated contact can cause a sub-acute form of contact dermatitis characterized by dry, red plaques. If the exposure continues, the dermatitis will become chronic. Features of chronic ACD are dry, thickened and scaly skin, cracking and fissuring of the fingers and palms, chronic nail dystrophy. Itch (pruritus) is usually present.
- Examinations:
  - On physical examination, lesions appear localized at allergen contact sites, but often spread to the surrounding area or even to other body sites. Occupational ACD is mainly found on the hands. Upon exposure to volatile allergens or more commonly by transference from the hands it may occur at the face, neck, and arms.
  - Patch tests should be performed by a specialized physician, according to relevant guidelines (such as those listed in the 'further reading'). This diagnostic approach carries the risk of sensitization, and the testing concentration should be defined according to specific recommendations.

Exposure assessment

- History of occupational exposure: confirmed previous occupational exposure (at least one episode) to amino-derivatives of benzene or its homologues (such as p- and m-phenylenediamine, nitroanilines, 2-aminophenol, 4,4'-methylenedianiline), and occasionally trinitrotoluene and nitrobenzene; and onset of signs and symptoms as a consequence of subsequent exposures. A dose/effect relationship in the onset of allergic contact dermatitis can usually be observed. In general, induction of sensitization needs higher levels of exposure than elicitation.
- Minimum duration of exposure: usually several instances of exposure are required over long periods for sensitization, but even a single contact might be sufficient, in particular for potent sensitizers, such as dinitrochlorobenzene, dinitrofluorobenzene, and *p*-phenylenediamine. For elicitation of ACD in sensitized individuals, skin contact with the compound for between a few minutes and several hours may give rise to skin reactions.
- Maximum latent period: in sensitized subjects any further exposure to the compound causes the onset of clinical signs usually within 12-72 hours, or even later (up to 1-2 weeks).

Sensitizer-induced occupational asthma (J45.0)

Short description of the disease

Some amino-derivatives, such as *p*- and *m*-phenylenediamine, nitroanilines and 2-aminophenol, induce hypersensitivity in the respiratory tract which can result in allergic asthma. Sensitizer-induced occupational asthma is characterized by a latency period of several weeks or months, and occasionally years – between first exposure to one of the above-mentioned compounds at work and the development of immunologically mediated symptoms. Once the subject is sensitized, even very low concentrations of the sensitizing agent can provoke asthma attacks. Clinical patterns include progressive worsening of symptoms through the working week with improvement on rest days. Nasal symptoms due to allergic rhinitis are not consistently present but sometimes may either precede the onset of occupational asthma symptoms or commence at the same time. Eye irritation due to conjunctivitis and skin urticaria may be present.

1.1.13 Diseases caused by nitro- and amino-derivatives of benzene or its homologues ICD Code T65.3 +Z57

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: episodic wheezing, difficulty in breathing, chest tightness and cough. Excess sputum production is common. Note that pre-existing asthma does not exclude the development of sensitizer -induced occupational asthma.
- Examinations:
  - Lung function testing may show evidence of airway obstruction, but the absence of airway obstruction does not exclude a diagnosis of (occupational) asthma. A bronchodilator response may be seen in workers with occupational asthma when given ß2 agonists. Measures of lung function taken before and after a working shift are not sensitive indicators of the presence of occupational asthma and may miss a late asthmatic response.
  - Recording serial peak flow measurements (sPEF) is the initial method of either confirming or refuting a possible occupational cause for asthma. sPEF recording over three weeks with at least 4 recordings a day has very high specificity and moderately good sensitivity for making a diagnosis of occupational asthma. A comparison of measurements collected in conditions of exposure vs. absence of exposure to the suspected causal agent is very useful in reaching a diagnosis.
  - Skin prick (epicutaneous) testing may be positive, in particular when considering potent contact allergens such as *p*-phenylenediamine.
  - Non-specific bronchial reactivity to challenge with a variety of agents (including histamine, methacholine, and mannitol) may be increased in occupational asthma. Additionally, sequential measures of airway reactivity including periods at work and away from work may assist in making a diagnosis.
  - Specific bronchial challenge to the workplace allergen or allergens (in a specialist facility under carefully controlled conditions) may assist in making a diagnosis, although a negative test does not exclude it.
  - Changes in sputum eosinophilia may be helpful in the diagnosis of allergic asthma.

Exposure assessment

- History of occupational exposure: confirmed occupational exposure to amino-derivatives of benzene or its homologues (such as *p*- and *m*-phenylenediamine, nitroanilines and 2-aminophenol).
- Minimum duration of exposure: usually from weeks to years but, in some cases, this period may be as short as a few days.
- Maximum latent period: usually between 3 to 24 months, but may be shorter in atopic subjects and in exceptional cases it may be as short as a few days. In sensitized subjects, the latency between exposure and onset of symptoms is usually no longer than 48 hours.

Allergic occupational rhinitis (J30.4)

Short description of the disease

Some amino-derivatives of benzene or its homologues (e.g. *p*-phenylenediamine and *m*-phenylenediamine, nitroanilines, 2-aminophenol), dinitrobenzene, tetryl (2,4,6-Trinitrophenylmethylnitramine) and *p*-nitroaniline induce hypersensitivity in the upper respiratory tract which may cause allergic upper airways disorders, such as allergic rhinitis.

The disorder follows a sensitization for one (or more) of the above mentioned compounds, and is characterized by inflammation of the nasal mucosae, congestion, rhinorrhoea and sneezing. In general, a proportion of up to 40% of rhinitis patients may manifest asthma, and about 70% asthma patients also suffer from rhinitis.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: rhinorrhoea, sneezing, lacrimation, red eyes, itchy eyes, nose and throat, nasal cavity obstruction, watery and pale nasal mucosae, congested conjunctivae.
- Examinations:
  - Specific inhalation challenge testing can be used to identify the allergen involved.
  - Anterior rhinoscopy should be used to examine the nasal mucosae, which may appear pale and boggy.
  - Rhinomanometric measurements can be used to measure nasal obstruction.

1.1.13 Diseases caused by nitro- and amino-derivatives of benzene or its homologues ICD Code T65.3 +Z57

Exposure assessment

- History of occupational exposure: confirmed occupational exposure to amino-derivatives of benzene and its homologues (e.g. *p*-phenylenediamine and *m*-phenylenediamine, nitroanilines, 2-aminophenol), dinitrobenzene, tetryl (2,4,6-trinitrophenylmethylnitramine) or p-nitroaniline. Symptoms typically appear in relation to the exposure, and disappear when exposure ends. Recurrence is thus observed after re-exposure to the same agent.
- Minimum duration of exposure: usually few weeks, since occupational allergic upper airways disorders require a sensitization period. In exceptional cases, minimum duration of exposure may be as short as a few days.
- Maximum latent period: in sensitized individuals usually no more than 48 hours, but the exposure that triggers symptoms may occur years after sensitization has occurred.

Skin pigmentation (L81.9)

Short description of the disease

Prolonged or repeated exposure to TNT or dinitrobenzene (DNB) may cause their nitro groups to react with the melanin pigment in the skin, creating a typical discolouration syndrome.

Diagnostic criteria

Clinical manifestations

- A bright yellow-orange staining of the hands, arms, feet and face may accompany other disorders caused by TNT or DNB described above.

Exposure assessment

- History of occupational exposure: confirmed repeated occupational exposure to high concentrations of TNT or DNB via inhalation, skin or eye contact and, when available, workplace air and biological monitoring, such as dinitroaminotoluene metabolites of TNT in urine.
- Minimum duration of exposure: few days.
- Maximum latent period: few weeks.

Aplastic anaemia (D61.2)

Short description of the disease

Intensive exposure to TNT after few months can result in aplastic anaemia. In workers exposed to TNT in munition plants, aplastic anaemia with purpura has been reported.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms:
  - Main complaints are weakness, fatigue, increased frequency of infections, and of mucosal and skin bleeding.
  - Aplastic anaemia (with medullary hypoplasia) is characterized by thrombocytopaenia, and leucopaenia, and anaemia.
- Examinations:
  - Physical examination may reveal skin and mucous membrane pallor, purpura, and petechiae.
  - Full blood count with differential and reticulocyte count may show transient haematological effects or signs of bone marrow failure; red blood cells indices may show anaemia.
  - Bone marrow aspiration and biopsy may show medullary depression.
  - Aplastic anaemia is defined by the presence of a peripheral blood pancytopaenia and a hypocellular bone marrow. Remaining blood cells have more or less normal morphology.

Exposure assessment

- History of occupational exposure: confirmed prolonged occupational exposure to high concentrations of TNT via inhalation, skin or eye contact and, when available, workplace air and biological monitoring, such as dinitroaminotoluene metabolites of TNT in urine.
- Minimum duration of exposure: few months.
- Maximum latent period: six months (historically longer latency periods have been described, up to years).

1.1.13 Diseases caused by nitro- and amino-derivatives of benzene or its homologues ICD Code T65.3 +Z57

Name of the diseases and ICD code: **Carcinogenic effects of nitro- and amino-derivatives of benzene or its homologues** *(Specific disease code)* **+T65.3 +Z57**

The IARC classifications of some amino and nitro derivatives of benzene are summarised in the following table. The carcinogenic effects of these substances is described in more detail in item 3.1.9.

A number of these substances are classified as carcinogens or possible carcinogens. For example 4-amino-biphenyl, benzidine and *o*-toluidine are believed to cause cancer of the bladder. *In vitro* experiments of MOCA and aniline indicate that they are genotoxic. Both cause a variety of tumours in animal experiments, but there is only limited evidence of their carcinogenicity in humans. MOCA is classed as a carcinogen on the strength of this mechanistic and animal evidence, while aniline is classed as a probable carcinogen.

IARC Classification of amino derivatives of benzene

Chemical name	CAS number	IARC Classification
4-aminobiphenyl	92-67-1	1
MOCA	101-14-4	1
benzidine	92-87-5	1
o-toluidine	95-53-4	1
aniline	62-53-3	2A
2-amino-4-chlorophenol	95-85-2	2B
3,3'-dichlorobenzidine	91-94-1	2B
o-dianisidine	119-90-4	2B
N,N-dimethylaniline	121-69-7	3

IARC Classification of nitro derivatives of benzene

Chemical name	CAS number	IARC Classification
1,4-dichloro-2-nitrobenzene	89-61-2	2B
2-chloronitrobenzene	88-73-3	2B
2,4-dinitrotoluene	121-14-2	2B
2,6-dinitrotoluene	606-20-2	2B
nitrobenzene	98-95-3	2B
para-nitroanisole	100-17-4	2B
2,4,6-trinitrotoluene	118-96-7	3
4-nitrobiphenyl	92-93-3	3
p-nitrotoluene	99-99-0	3

Key
Group 1: Carcinogenic to humans
Group 2A: Probably carcinogenic to humans
Group 2B: Possibly carcinogenic to humans
Group 3: Unclassifiable as to carcinogenicity in humans

Bladder cancer (C67)

Short description of the disease

This disease is observed for exposure to benzidine, 4-aminobiphenyl, MOCA and o-toluidine. All these compounds have been classified as carcinogenic to humans by the IARC (Group 1). For a detailed description on carcinogenic effects of benzidine and its salts, and toxic nitro- and amino-derivatives of benzene and its compounds, refer to items 3.1.2 and 3.1.9, respectively.

Key actions for prevention	These and other chemicals have multiple synonyms and commercial product names. When making risk assessments it is wise to confirm their identity using a unifying system. There are many such systems, but perhaps the most commonly used are the Chemical Abstract Service (CAS) numbers, and European Inventory of Existing Commercial Chemical Substances (EINECS) numbers. For example, the CAS number for the probable carcinogen aniline is 62-53-3, while its EINECS number is 200-539-3. From the point of view of occupational health, o-toluidine, o-dianisidine, 2-amino-4-chlorophenol, benzidine, MOCA, 3,3'-dichlorobenzidine and 4-aminodiphenyl are among the most important amino-benzene compounds because of their carcinogenic potential. Strict precautions necessary for handling carcinogens apply to different members of this family.

1.1.13 Diseases caused by nitro- and amino-derivatives of benzene or its homologues ICD Code T65.3 +Z57	
Key actions for prevention	The hierarchy of controls should be employed (elimination, substitution, engineering controls, and lastly personal protective equipment). As the first tier, due to the carcinogenic properties of some nitro- and amino-derivatives of benzene or its homologues, the more toxic compounds such as 4-aminobiphenyl and benzidine have been banned from production and use in most countries, and substitutes with lesser toxicity developed. Consumer protection issues caused the ban of several related azo-dyes, which were suspected of, or demonstrated as having carcinogenic or allergenic properties, thus effectively stopping the production and use of some aromatic amines and of their precursors. Workers and supervisors should be educated to be aware of the nature and extent of the hazard posed by the production and use of nitro- and amino-aromatic compounds, and work in a clean, safe manner. Adequate plant and equipment design for both operating and maintenance, and accurate job analysis are minimum pre-requisites to ensure workers' safety and health. In particular, measures include appropriate equipment design, ventilation as close to the point of generation as possible, with air-pollution control, adequate handling procedures, and specific measures for the prevention of workers' exposure through spillage. Best available technologies allow performing the chemical reactions involving the most dangerous compounds in closed-circuit batch reactors with as much segregation as possible of the reagents, solvents, raw reaction mixtures, purified products and reaction by-products. In parts of the process where this cannot be totally achieved (such as in loading and unloading reactors), workers need to be protected with coveralls, gloves and face masks. Dust, mist from hot charges, leaking lines, steaming operations, hot drainage ditches and so on may cause gross exposure and contamination of the work environment. Work clothing should be changed daily and plants should be provided with facilities for an obligatory bath or shower at the end of the working period. Protective clothing and equipment must withstand permeation of chemicals for the expected exposure time. Any contaminated skin or clothing should be washed or removed immediately and the individual kept under appropriate medical supervision. Routine plant maintenance should include a preliminary thorough cleaning of the machinery before maintenance staff access, and appropriate disposal of waste. An effective programme to prevent health impairment due to exposure to nitro- and amino-derivatives should include exposure control and medical supervision. Measurement of airborne or surface contamination is useful to check consistent operation safety and minimal chance of skin contact. The group of experts considered that the following limits of exposure of workplace atmospheric concentrations have been observed to provide a reasonable level of protection for workers' health and have been used in a number of countries: • 2 ppm as 8hr TWA for m-Nitrotoluene, o-Nitrotoluene, o-Toluidine. • 0.1 mg/m^3 as 8hr TWA for *o*-Phenylenediamine, *p*-Phenylenediamine, *m*-Phenylenediamine, 2,4,6-Trinitrotoluene, 1,4-Benzenediamine dihydrochloride. • 0.1 mg/m^3 as STEL and as an airborne concentration which should never be exceeded (ceiling value) for 1,3-bis (aminomethylbenzene).

1.1.13 Diseases caused by nitro- and amino-derivatives of benzene or its homologues ICD Code T65.3 +Z57

Further reading

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For the chemical entities listed below an entry exists in the collection of International Chemical Safety Cards (ICSC) hosted in the ILO website

Name	Synonyms	ICSC
Aniline	Aminobenzene	0011
2-Chloronitrobenzene	1-Chloro-2-Nitrobenzene	0028
Benzidine	(1,1'-Biphenyl)-4,4'-diamine; 4,4'-Diaminobiphenyl; p-Diaminodiphenyl; Biphenyl-4,4'-ylenediamine	0224
Ortho-Toluidine	1-Amino-2-methylbenzene; 2-Aminotoluene; o-Methylaniline	0341
1,4-Benzenediamine dihydrochloride	1,4-Phenylenediamine dihydrochloride; 1,4-Diaminobenzene dihydrochloride; 4-Aminoaniline dihydrochloride; p-Phenylenediamine dihydrochloride	0386
2,4-Dinitrophenol	1-Hydroxy-2,4-Dinitrobenzene	0464
3,3'-Dichlorobenzidine	3,3'-Dichlorobiphenyl-4,4'-Diamine	0481
Nitrobenzene	P-Nitrophenyl	0065
m-Dinitrobenzene	1,3-Dinitrobenzene	0691
2,4-Dinitrotoluene	1-Methyl-2,4-Dinitrobenzene	0727
2,6-Dinitrotoluene	1-Methyl-2,6-Dinitrobenzene	0728
4-Aminobiphenyl	4-Aminodiphenyl; p-Biphenylamine; Xenylamine; Biphenyl-4-amine; Biphenyl-4-ylamine; (1,1'-Biphenyl)-4-amine	0759
4-Nitro-N-phenylbenzenamine	4-Nitrodiphenylamine; p-Nitrodiphenylamine; p-Nitrophenylphenylamine; 4-Nitro-N-phenylaniline	0804
p-Phenylenediamine	1,4-Diaminobenzene; 1,4-Benzenediamine; p-Aminoaniline	0805
n,n-Dimethylaniline	Dimethylphenylamine	0877
n-Methylaniline	Monomethylaniline	0921
o-Nitrotoluene	2-Nitrotoluene; 1-Methyl-2-nitrobenzene; o-Methylnitrobenzene o-Mononitrotoluene ONT	0931
o-Nitrotoluene	4-Nitrotoluene; 1-Methyl-4-nitrobenzene; p-Methylnitrobenzene PNT	0932
2,4,6-Trinitrotoluene	2-Methyl-1,3,5-trinitrobenzene; 1-Methyl-2,4,6-trinitrobenzene; TNT	0967
m-Phenylenediamine	m-Diaminobenzene; 1,3-Benzenediamine 3-Aminoaniline; 1,3-Phenylenediamine	1302
Benzylamine	Aminotoluene; Phenylmethylamine; Benzenemethanamine; Monobenzylamine	1338
Benzyldimethylamine	N,N-Dimethylbenzenemethanamine; N-Benzyldimethylamine; Dimethylbenzyla-mine; Benzyl-N,N-dimethylamine; N-(Phenylmethyl)dimethylamine	1340
n-Ethylaniline	N-Ethyl-N-Phenylamine	1385
m-Nitrotoluene	3-Methylnitrobenzene; Toluene, m-nitro 3-Nitrotoluene	1411
o-Phenylenediamine	o-Diaminobenzene 1,2-Benzenediamine; 2-Aminoaniline; 1,2-Phenylenediamine	1441
1,3-Bis(Aminomethyl)benzene	1,3-Benzenedimethanamine; 1,3-bis-Aminomethylbenzene; m-Phenylenebis(methylaine); m-Xylylenediamine; m-Xylene alpha, alpha'-diamine	1462
2-Nitro-p-Phenylenediamine	2-Nitro-1,4-benzenediamine; 1,4-Diamino-2-nitrobenzene; 2-Nitro-4-aminoaniline	1542
2,4-Diaminoanisole	1,3-Benzenediamine; 4-methoxy; 4-Methoxy-3-phenylenediamine; 4-Methoxy-m-phenylenediamine C.I. Oxidation Base 12	1578
o-Dianisidine	3,3'-Dimethoxybenzidine	1582
n,n-Diethylaniline	Benzenamine	1609
1,4-Dichloro-2-Nitrobenzene	Nitro-*p*-dichlorobenzene	1618
N-(1,3-dimethylbutyl)-N'-phenyl-p-Phenylenediamine	N-(4-Methyl-2-pentyl)-N'-phenyl-1,4-diaminobenzene; 1,4-Benzenediamine, N-(1,3-dimethylbutyl)-N'-phenyl; *p*-Phenylenediamine, N-(1,3-dimethylbutyl)-N'-phenyl-; 6PPD	1635
2-Amino-4-chlorophenol	5-Chloro-2-hydroxyaniline	1652

▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
1.1.13	Acute/chronic diseases caused by nitro- and amino-derivatives of benzene or its homologues	T65.3	NE61& XM83H3
1.1.13	Toxic methaemoglobinaemia	D74.8	3A93
1.1.13	Toxic haemolytic anaemia	D59.4	3A21.Y
1.1.13	Respiratory tract irritation	J68	CA81.Z
1.1.13	Acute chemical pneumonitis and bronchitis	J68.0	CA81.0
1.1.13	Chemical pulmonary oedema	J68.1	CA81.1
1.1.13	Upper respiratory inflammation	J68.2	CA81.2
1.1.13	Burn and corrosion of eye and adnexa	T26.0-T26.1, T26.5-T26.6	NE00
1.1.13	Conjunctivitis	H10.2	9A60.Z
1.1.13	Corneal ulcer	H16.0	9A76
1.1.13	Irritant contact dermatitis	L24	EK02
1.1.13	Allergic contact dermatitis	L23	EK00
1.1.13	Sensitizer-induced occupational asthma (occupational allergic asthma)	J45.0	CA23.0
1.1.13	Occupational allergic rhinitis	J30.4	CA08.0Z
1.1.13	Toxic liver disease	K71	DB95.Z
1.1.13	Liver impairment	K72.9	DB97.Y
1.1.13	Skin pigmentation	L81.9	EK5Y
1.1.13	Aplastic anaemia	D61.2	3A70.Z
1.1.13	Bladder cancer	C67	2C94.Z
	Occupational exposure to risk factors	Z57	QD84.Y

1.1.14 Diseases caused by nitroglycerine or other nitric acid esters	ICD Code T65.5 +Z57
General characteristics of the causal agent	Nitric acid esters are a class of organic chemicals represented by the general formula R-ONO_2 (R being an alkyl or cycloalkyl group) and formally derived from alcohols (R-OH) by substitution of the hydroxyl group -OH with a nitrate ester -ONO_2 group. Major representatives of this class are the nitric acid esters of aliphatic polyalcohols such as glycols, glycerol, sugars, and polysaccharides. *Nitroglycerine* (NG), CAS number 55-63-0, is the oldest nitro-ester isolated and used as an explosive from the mid-1800s. Pure NG is highly explosive and appears as a colourless to yellow, oily, viscous liquid or as pale-yellow crystals. It starts decomposing at 50 to 60°C and explosively decomposes above 218°C. It is slightly soluble in water and miscible with acetone, ether, benzene, and many other organic solvents. It can be absorbed through the skin. *Ethylene glycol dinitrate* (EGDN), CAS number 628-96-6, is a clear colourless to yellowish, oily liquid, heavier than water, soluble in alcohol and ether (not in water) and explosive above 114°C. It is less explosive than nitroglycerine and characterized by a high percutaneous absorption. *Propylene glycol dinitrate* (PGDN), CAS number 6423-43-4, is a colourless liquid with a characteristic odour, heavier than water and slightly soluble (0.13 g/100 ml). It decomposes above 121°C. An odour threshold of around 0.2 ppm has been reported. *n-Propyl nitrate*, CAS number 627-13-4, is a pale-yellow liquid with a sweet, sickening odour. An odour threshold of 50 ppm has been reported. *Nitrocellulose*, CAS number 9004-70-0, is a light fabric material, which contains variable amounts of nitrate substitution. Average substitution of one alcohol function per glucose residue yields flammable but not explosive materials, while increasing substitution to a maximum of three nitrate ester residues per glucose residue yields explosive materials.
Occupational exposures	Most nitro-esters are employed as explosives both for civil purposes (mining, earthwork and demolition) and in the military field as propellants for projectiles and rockets and as blast agents. Small quantities are used in the pharmaceutical industry. Nitroglycerine is highly explosive and still used by itself for this purpose in certain applications (e.g. in oil-well drilling). More often, it is used with EGDN to make dynamite or with guncotton to make cordite or other smokeless powders and in rocket propellants. EGDN is mainly used as an explosive; when mixed with nitroglycerine, EGDN lowers its melting point and reduces the hazard associated with the use of frozen dynamite. Most of the data on the toxic effects of EGDN on workers come from such mixtures. Since EGDN is 160 times more volatile than NG and since the usual mixtures in dynamite are 60-80% EGDN and 20-40% NG, the vapour exposures are primarily to EGDN. PGDN is the principal constituent of Otto Fuel II, a torpedo propellant. *n*-Propyl nitrate has been used as a fuel ignition promoter, in rocket fuels, and as an intermediate in organic synthesis. A quantitatively minor use of nitroglycerine and isosorbide (a nitrate-class drug) is as pharmaceutical agent releasing nitrogen oxide for the treatment of heart disease, given both orally (nitroglycerine) and as controlled-release trans-dermal formulations (isosorbide). Low-nitration nitrocellulose dissolved in acetone is employed as a bright lacquer in wood finishing; an older, now discontinued use was in the movie industry; nitrocellulose disks or sheets are used for blotting in biochemical laboratories. High-nitration cellulose is a starting material for the manufacturing of industrial and military explosives. All workers involved in the preparation and production of the above mentioned compounds could be exposed to nitroglycerine and other nitric acid esters.
Toxicological profile, main health effects and diagnostic criteria	
Short toxicological profile	Nitro-aliphatic esters are quickly absorbed by all routes, and their main pharmacological effect is almost immediate vasodilatation of central and peripheral arteries. The vasodilatation of cerebral arteries provokes acute headaches, which were first noticed by chemical workers in the early years of nitroglycerine production as an explosive. On the other hand, subjects with hitherto intractable angina noticed an easing of chest pain: the neutralized tailings of the production of nitroglycerine were thus marketed as oral drops or sublingual pills for pharmaceutical use. Furthermore, the local vasodilatory effect exerted by nitroglycerine when absorbed through the skin was exploited to cure frostbites. Only towards the end of the 20th century, the true pharmacological mechanism was clarified, with the discovery of nitric oxide (NO) as the active diffusible transmitter. The sensitivity of the endothelial cells to the action of NO released from the biotransformation of nitroglycerin is, however, transient due to 'desensitization' of the receptors. The biotransformation of nitric acid esters into nitrate and further into nitrite ions can generate methaemoglobinemia.

1.1.14 Diseases caused by nitroglycerine or other nitric acid esters ICD Code T65.5 +Z57

Short toxicological profile

It has been known for a long time that combining alcohol intake and nitrate esters exposure may worsen headaches and, in some cases, induce temporary psychiatric disorders with aggressive behaviour, as described in several reports of cases that mainly occurred amongst Navy sailors. Although the released NO is able to generate highly carcinogenic N-nitrosamines from endogenous amines, there is no evidence of carcinogenicity of aliphatic nitrate esters.

The health effects of short-term or intermittent exposure to NG or EGDN in the workplace include headache, dizziness, nausea, palpitations, and a decrease in systolic and diastolic pressure. All these symptoms are associated with vasodilatation. Most workers do not experience these symptoms after repeated daily exposures to NG or EGDN as they develop tolerance. The disappearance of these symptoms in workers exposed on successive days of the work week indicates that vasodilatation from NG or EGDN has been counteracted by compensatory vasoconstriction. Discontinuation of exposure to NG or NG-EGDN mixtures of workers with a personal history of prolonged, high-level exposure has been associated with angina pectoris and even sudden death, observed in particular during weekends or holidays. The compensatory vasoconstriction in workers who have developed tolerance to nitro-esters continues in the absence of exposure to a vasodilatating agent. It has been postulated that this vasoconstriction leads to spasms of the coronary arteries and that these spasms are related to angina pectoris and sudden deaths that occur during periods when workers are not exposed to nitro-esters. Although this mechanism has not been conclusively proven, exposed workers may have an increased risk of death from heart disease. Skin irritation and sensitization (dermatitis) can result from dermal contact with NG or EGDN.

Taken together, the available toxicokinetic data from studies of humans and animals and from the pharmaceutical use of nitroglycerine are sufficient to conclude that nitroglycerine can easily penetrate the skin and be absorbed in sufficient amounts to cause circulatory and vascular effects up to death after removal from exposure because of continued vascular tolerance.

Name of the diseases and ICD code: **Acute diseases caused by nitroglycerine or other nitric acid esters**
(Specific disease code) **+T65.5 +Z57**

Acute toxic encephalopathy (G92), Vascular headache (G44.1), Angina pectoris (I20)

Short description of the disease

Most acute effects, consequent to inhalation, ingestion or skin absorption of nitroglycerine or other nitric acid esters, are mainly caused by vasodilation and can affect the cardiovascular system, the blood, and the nervous system. These effects are enhanced by alcohol consumption.

Acute poisoning due to absorption of high doses, in particular of nitroglycerine (occurring especially in industrial workers), is characterized by: flushing of the face, headache, nausea, vomiting, fatigue, mental confusion, dizziness, orthostatic hypotension with reflex tachycardia and, in the most severe poisonings, seizures and convulsions. In addition, methaemoglobinemia and cyanosis can appear.

A transient loss of vision reportedly occurred before acute toxic effects from nitroglycerine exposure. Most workers rapidly adapt to the hypotensive action of nitroglycerine, but discontinuation of exposure may interrupt this adaptation.

Subacute exposure causes vasodilatation, tachycardia, hypotension, and reduced pulse pressure. This can be followed by bradycardia and collapse.

When these effects are less severe, a tolerance is established within a week. Thereafter the symptoms generally disappear or become rather mild. When the exposure is interrupted for a short period (e.g. for about a day), no significant reduction in tolerance is noted. After a longer period of absence, however, the symptoms reappear on subsequent re-exposure to the agent.

1.1.14 Diseases caused by nitroglycerine or other nitric acid esters ICD Code T65.5 +Z57

Diagnostic criteria

Clinical manifestations

- Signs and symptoms:
  - Most of the immediate signs and symptoms may appear within a few minutes to one hour or more after exposure to the nitroglycerine, in detail: headache, flush, hypotension, reduced blood pressure, post-exposure angina pectoris, and methaemoglobinemia. In cases of severe poisoning, confusion, hallucinations, and maniacal manifestations have been observed. Headache is generally preceded by a sensation of warmth and fullness in the head, starts at the forehead, and moves upward towards the occiput. It may extend down to the back of the neck and remain for hours or several days. Walking or attempting to stoop enhances the pain. Palpitations and facial flushes can be present. Tremor of the hands is common. In very severe cases, the signs can involve the heart muscle, with a reduced contractility. There may be delirium and convulsions or sudden collapse.
  - Mental disturbances: drowsiness, stupor, insomnia, languor, and fear can occur but are relatively minor issues. More important are the effects of the very severe headaches, mental confusion, dizziness, mental excitement, pugnaciousness, hallucinations, and maniacal manifestations.
  - When EGDN was first introduced into the dynamite industry, the only changes noticed were similar to those affecting workers exposed to nitroglycerine: headache, sweating, face redness, arterial hypotension, heart palpitations, and dizziness, especially at the beginning of work, on Monday mornings and after an absence.
  - EGDN causes arterial dilation, increased heart rate, and reduced blood and pulse pressure. Cases of sudden death have been reported amongst workers in contact with nitroglycerine; however, death has usually been attributed to the action of the EGDN mixed with nitroglycerine in the manufacture of dynamite.
  - The acute and subacute effects of nitroglycerine or other nitric acid esters are enhanced by alcohol consumption, with the production of a neuropsychiatric syndrome with aggressive behaviours.
  - Most workers rapidly adapt to the hypotensive action of nitroglycerine, but discontinuation of exposure (even for a few days, such as at the weekend) may interrupt this adaptation, and some workers may suffer nausea when resuming work on Monday mornings.
  - Methaemoglobinaemia due to PGDN exposure produces intense cyanosis and is accompanied by headache, irritability, nervousness, dizziness, drowsiness, numbness, vertigo, weakness, fatigue, nausea, vomiting, dyspnoea, chest and abdominal pain, aphonia, air hunger, unconsciousness, seizures, tachycardia, cardiac dysrhythmias and possible death. Normally, methaemoglobin levels are < 1% of haemoglobin. Cyanosis occurs at methaemoglobin levels > 10%, and hypoxia occurs at methaemoglobin levels > 20-25%.
- Examinations:
  - Electrocardiography may show arrhythmia or ischaemia.
  - Long-term blood pressure monitoring might help uncover blood pressure variations in presence/absence of exposure.
  - A chocolate-brown colouration of the blood samples can be a critical clue.
- Differential diagnosis:
  - Angina pectoris due to other causes.
  - Drug use of glyceryl trinitrate should be taken into consideration.

Exposure assessment

- History of occupational exposure: confirmed acute occupational exposure to nitroglycerine or other nitric acid esters by inhalation, skin/eye contact, or accidental ingestion and, if available,
  - Detection of the compounds or their metabolites in biological fluids, such as blood plasma or whole blood levels of nitroglycerine or other nitric acid esters and their metabolites. Ethylene glycol dinitrate or its metabolites can be measured in urine. Blood methaemoglobin levels should be monitored, especially in workers exposed to PGDN.
  - Workplace air monitoring of nitroglycerine or other nitric acid esters concentrations.
- Minimum duration of exposure: few minutes.
- Maximum latent period: few hours.

Irritant contact dermatitis (L24)

Contact with nitric acid esters can cause irritation of the skin and mucous membranes, accompanied by burning sensation, pruritus, redness and erythema. Nitroglycerine may produce moderate irritation: eruptions of the palms and interdigital spaces and ulcers under the nails have been observed in workers handling nitroglycerine. For more details on the clinical features and exposure assessment criteria of irritant contact dermatitis, refer to item 2.2.2.

1.1.14 Diseases caused by nitroglycerine or other nitric acid esters ICD Code T65.5 +Z57

Name of the diseases and ICD code: **Chronic diseases caused by nitroglycerine or other nitric acid esters**
(Specific disease code) **+T65.5 +Z57**

Chronic toxic encephalopathy (G92), Angina pectoris (I20)

Short description of the disease

Sudden removal of workers exposed for long periods (5-10 years) to nitroglycerine has resulted in life-threatening health effects and deaths, mainly due to the development of tolerance (acclimatisation, tachyphylaxis) to the vasodilatory action of the substance, resulting in a semi-permanently altered health status characterized by blood pressure changes and compensatory vasoconstriction. Withdrawal from exposure to the vasodilating agent (i.e., on a weekend or holiday leave) can therefore be associated with angina pectoris and death. At necropsy, often no significant signs of atherosclerotic changes in the heart have been observed. The cases with withdrawal symptoms reported have occurred after exposure to nitroglycol or to a mixture of nitroglycol and nitroglycerine.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms:
  - In acclimatized subjects, any break in exposure, either during sleep or during the following first physical efforts of the day after arriving at work, can cause malaise, weakness, vomiting, dizziness, headache, and impaired vision.
  - Neurological disorders, such as tremors, neuralgia, hallucinations, can occur.
  - Workers exposed to nitroglycerine have reduced tolerance for alcohol, and concurrent ethanol ingestion appears to potentiate nitroglycerine toxicity resulting in abnormal behaviour characterized by irritable and destructive moods.
  - Chronic exposure to these substances can increase anaemia. Exposure to nitroglycerine can cause leucopaenia.
  - After continuous exposure to these agents for a number of years, chest pain may follow, usually 24-72 hours after interrupting the exposure. Symptoms disappear shortly after reexposure.
- Examinations:
  - Electrocardiography might indicate ischaemia.
  - Full blood count could assist in excluding the presence of anaemia.
  - Long-term blood pressure monitoring might highlight blood pressure alterations in the presence/absence of the exposure.
  - Chocolate-brown blood can be a critical clue; methaemoglobin assay can document methaemoglobinemia mainly due to PGDN.

Exposure assessment

- History of occupational exposure: confirmed prolonged or repeated occupational exposure to nitroglycerine or other nitric acid esters mainly by inhalation or skin absorption and, if available,
  - Detection of the compounds or their metabolites in biological fluids, such as blood plasma or whole blood levels of nitroglycerine or other nitric acid esters and their metabolites. Ethylene glycol dinitrate or its metabolites can be measured in urine. Blood methaemoglobin levels should be monitored, especially in workers exposed to PGDN.
  - Workplace air monitoring of nitroglycerine or other nitric acid esters concentrations.
- Minimum duration of exposure: five years.
- Maximum latent period: six months.

Other chronic diseases caused by nitroglycerine or other nitric acid esters

Raynaud's phenomenon (I73.0)

Some authors have reported that workers who handle dynamite can develop numbness in the fingers, paraesthesia, or Raynaud's phenomenon. The cause of these symptoms is not known, but some suggest that they might be related to nerve damage secondary to peripheral stagnation of blood flow due to the vasodilatory action of nitroesters.

Allergic contact dermatitis (L23)

This disease is recognized and compensated in some national systems as a consequence of exposure to nitric acids, where the maximum latent period after cessation of exposure is 6 months. For further details on clinical features and exposure assessment criteria of allergic contact dermatitis, refer to item 2.2.1.

1.1.14 Diseases caused by nitroglycerine or other nitric acid esters	ICD Code T65.5 +Z57
Key actions for prevention	The pre-eminent industrial hazard of aliphatic nitric esters, rather than intoxication, is catastrophic explosion occurring in production plants due to runaway reactions, in manufacturing plants of ordnance or commercial explosives through electric sparks, during fires of painting facilities, or in storage of old movie films. The main preventive primary interventions are represented by the avoidance of dispersion of the compounds in the working environment and of workers' skin contact. Personal protective equipment should always be used. Exposure of pregnant workers to nitroglycerine or nitric acid esters is not advisable. The group of experts considered that the following limits of exposure of workplace atmospheric concentrations have been observed to provide a reasonable level of protection for workers' health and have been used in a number of countries: Nitroglycerine, ethylene glycol dinitrate, and propylene glycol dinitrate: 0.05 ppm as 8hr TWA, exposures to EGDN and nitroglycerine should be considered additive; *n*-Propyl nitrate: 25 ppm as 8hr TWA. The recommended standard for workplace exposure to NG/EGDN is designed to prevent significant changes in the diameters of cerebral blood vessels during initial exposure, as indicated by the development of throbbing headaches or by decreases in blood pressure, thereby preventing the development of the compensatory vasoconstrictive mechanisms that may eventually result in more serious effects. The possible condition of tolerance deserves consideration before abruptly removing a subject from a situation of prolonged exposure to nitroglycerine or other nitric acid esters.

1.1.14 Diseases caused by nitroglycerine or other nitric acid esters ICD Code T65.5 +Z57

Further reading

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For the chemical entities listed below an entry exists in the collection of International Chemical Safety Cards (ICSC) hosted in the ILO website

Name	Synonyms	ICSC
Nitroglycerine	NG; Glyceryl trinitrate; Glycerol trinitrate; 1,2,3-Propanetriol trinitrate; Nitroglycerol; Trinitroglycerin; Blasting oil	0186
Ethylene glycol dinitrate	EGDN; EGN; 1,2-Ethanediol dinitrate; Ethylene dinitrate; Ethylene nitrate; 1,2-Dinitroethane; Glycol dinitrate; Nitroglycol	1056
Propylene glycol dinitrate	PGDN; 1,2-Propanediol dinitrate; 1,2-Propylene glycol dinitrate; Propylene dinitrate	1392
n-Propyl nitrate	Nitric acid, propyl ester; Monopropyl nitrate	1513
Nitrocellulose	Cellulose nitrate; Cellulose tetranitrate; Pyroxillin	1560

▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
1.1.14	Acute/chronic diseases caused by nitroglycerine or other nitric acid esters	T65.5	NE61 &XM8T02 &XM5NZ1 &XM0WA9 &XM4PQ8
1.1.14	Angina pectoris	I.20	BA40.Z
1.1.14	Acute/chronic toxic encephalopathy	G92	8D43.0Y
1.1.14	Vascular headache, not elsewhere classified	G44.1	8A84.Z
1.1.14	Irritant contact dermatitis	L24	EK02
1.1.14	Raynaud's phenomenon	I73.0	BD42.Z
1.1.14	Allergic contact dermatitis	L.23	EK00.Z

1.1.15 Diseases caused by alcohols, glycols, or ketones	ICD Code T51, T52.3, T52.4 +Z57
General characteristics of the causal agent	*Alcohols* are a class of aliphatic hydrocarbon derivatives in which one hydroxyl group (-OH) replaces one hydrogen atom. Alcohols with 1 to 4 carbon atoms, referred to as "*lower alcohols*", are methanol, ethanol, the isomers 1-propanol and 2-propanol, and the four isomers of butyl alcohol (butanol): 1-butanol, 2-butanol, iso-butanol and tertiary butanol. Lower alcohols are more or less miscible with water and with organic solvents (in particular, methanol and ethanol are completely miscible with water). *Glycols* are a chemical class of aliphatic hydrocarbon derivatives in which two hydroxyl groups (-OH) replace two hydrogen atoms on different carbon atoms. Lower glycols of industrial interest are ethylene glycol (ethanediol), propylene glycols (1,2- and 1,3-propanediol), butylene glycol (1,4-butanediol) and diethylene glycol. Long-chain polyols belong to the same class of glycols but contain more hydroxyl groups (usually one for each carbon atom). Lower glycols, similarly to alcohols and ketones, are more or less miscible with water and with organic solvents. Ethylene, diethylene and propylene glycols are completely miscible with water. *Ketones* are a chemical class of aliphatic hydrocarbon derivatives in which one carbonyl group (>C=O) replaces one internal methylene group ($-CH_2-$). Lower ketones of industrial interest are acetone, methyl-ethyl ketone (MEK), methyl-*n*-butyl ketone (MBK), methyl isobutyl ketone (MIBK), cyclohexanone, and methyl-cyclohexanone. Lower ketones are more or less miscible with water and with organic solvents (in particular, acetone is completely miscible with water). When the hydrocarbon portion of the compound contains four or less carbon atoms, alcohols and ketones are usually volatile liquids, while glycols are viscous liquids with a low vapour pressure. Boiling points range from 64°C for methanol to 230°C for 1,4-butandiol. Lower alcohols and ketones are flammable: the temperature on combustion is, however, colder than that of other combustibles such as volatile hydrocarbon gases and liquids.
Occupational exposures	Lower alcohols, glycols, and ketones, and others, such as ethers and ether-glycols, esters and acetals as well as their technical mixtures, are often referred to commercially as "oxygenated solvents" and are widely employed in many technological applications as solvents and as industrial chemical reagents. Occupational exposure to these and other chemical compounds belonging to these chemical groups is thus possible in their production as chemicals, in their use as starting products or solvents in industrial chemical syntheses, in the manufacturing of industrial or consumer products, and in handling of formulated products which contain them. **ALCOHOLS** Lower alcohols are used in industry mainly as water-miscible solvents and detergents. Specific alcohols are used in organic syntheses. *Methanol*, CAS number 67-56-1, is industrially manufactured from syngas (a fuel gas mixture of hydrogen and carbon monoxide). It is used as a chemical reagent in the manufacture of formaldehyde and many other chemicals (notably methyl derivatives); as a solvent for nitrocellulose, ethyl cellulose, and various natural and synthetic resins; as a denaturant for ethanol; and as antifreeze and in automotive windshield washer fluid. *Ethanol*, CAS number 64-17-5, is a component of fermented and distilled alcoholic beverages such as beer and cider [alcohol concentration usually lower than 8% volume per volume (v/v)], wine (alcohol concentration usually lower than 14% v/v), liquors (alcohol concentration usually lower than 28% v/v), spirits (alcohol concentration usually higher than 28% v/v). Ethanol obtained from fermentation of cereals is also used as a solvent in the perfume industry and in some preserved foods. Ethanol from petrochemical manufacture is usually obtained from ethylene and is used in organic synthesis. Ethanol for industrial use is usually denatured by adding toxic and ill-tasting substances to avoid its food use. This is often a cause of accidental intoxications, usually involving groups of people. *n-Propanol* (or 1-propanol), CAS number 71-23-8, is manufactured industrially by oxo synthesis from ethylene and syngas (hydroformylation) that generates propionaldehyde, which is further reduced to n-propanol. Its main industrial uses are as a chemical reagent and as a solvent for waxes, vegetable oils, resins, cellulose esters, and ethers. Other uses with a potential for occupational exposure include the formulation of degreasing, polishing, and brake fluids. More recently, health workers started using it as an alternative to ethyl alcohol for hand disinfection.

1.1.15 Diseases caused by alcohols, glycols, or ketones	ICD Code T51, T52.3, T52.4 +Z57
Occupational exposures	*iso-Propanol* (or 2-propanol, or isopropyl alcohol), CAS number 67-63-0, is industrially manufactured by acid-catalysed hydration of petrochemical propene or by hydrogenation of acetone (a by-product of the production of phenol through the cumene hydroperoxide reaction). The majority of isopropyl alcohol is used as a solvent, both in industry and in consumer products. Among industrial uses with a potential for exposure are the preparation and use of cleaning solvents for glues, paints, oils, and grease and its usage as de-icing agent of liquid fuels. It is used in the fractional crystallization ("winterization") of waxes to separate high-melting triglycerides ("stearins") from food oils. An ultra-high-purity grade of isopropyl alcohol devoid of high-boiling impurities is used in semiconductor processing, while a medical grade is used in surgical catgut (regenerated collagen) packaging as an aqueous solution to impart flexibility. A 70% solution of iso-propanol in water is widely used as rubbing alcohol in health-care, household (rubbing and spray polish for glass panes) and personal care products (skin lotions, hair care and shaving products, home aerosols). Occupational exposures mostly occur by inhalation, whereas exposure to consumer products is primarily by skin contact and can involve workers in healthcare and in the informal sector. *n-Butanol* (or n-butyl alcohol), CAS number 71-36-3, is industrially produced mainly together with iso-butyl alcohol, by catalytic hydroformylation of propylene to yield n-butyraldehyde and isobutyraldehyde. n-Butanol is used in the adhesives and plastics industry and to manufacture butyl acetate (a widely used industrial solvent for paints with a strong fruit-like smell), butyl-ether and butyl-ether acetate solvents, and butyl-ester acrylate and methacrylate (which are important monomers in the polymers). As a solvent, n-butanol finds wide applications in cosmetics (fingernail basecoats, undercoats, polishes, enamels, and their removers; degreasers), in the manufacture of gums, dyes, resins (including those for paper and paperboard coatings for food packaging materials), cellophane, paints, lacquers, and varnishes and in the biological extraction of egg yolks, flavours, oils, antibiotics, hormones, and vitamins. It is also found in automotive brake fluid, perfumes, rubber cement, wood treatments, and ground cement. It has utility as a flavouring agent in butter, cream, fruit, and alcoholic beverages. *sec-Butanol* (or rac-butanol), CAS number 78-92-2, is industrially synthesized by hydration of n-butene and is primarily used as an intermediate in the manufacture of methyl ethyl ketone (MEK). Minor reported uses are as a solvent for lacquers, enamels, vegetable oils, gums and other natural resins, in industrial cleaning agents, polishes, penetrating oils and paint removers, in hydraulic brake fluids, and in the synthesis of flotation agents. Optically active sec-butanol is produced by fermentation of carbohydrates; in addition to being present in fermented alcoholic beverages, it is used as a chemical reagent in the production of fine chemicals (flavours and perfumes). *iso-Butanol*, CAS number 78-83-1, is industrially manufactured along with n-butanol starting with catalytic hydroformylation of propylene (see above). Its main industrial uses are the chemical synthesis of iso-butyl acetate (a paint solvent), of diisobutyl-phthalate (a plasticiser for polymers), and of esters for fruit flavouring essences. Minor uses include the formulation of lacquer solvents and paint removers. Limited use with a potential for occupational exposure occurs in chemical laboratories as solvent for liquid chromatography. *tert-Butanol*, CAS number 75-65-0, is solid at room temperature, a unique characteristic among lower alcohols. Industrial tert-butanol is produced by hydration of isobutylene and as a by-product during the production of propylene oxide from isobutene. Its use as a solvent is limited in the pharmaceutical and fine chemicals industry. It is used as a dehydrating agent although its main industrial use is in the synthesis of methyl-tert-butyl and ethyl-tert-butyl ether (MTBE and ETBE, respectively, that are anti-knock additives for gasoline), of tert-butyl chloride (a chemical intermediate for the synthesis of fine chemicals), and of 2,5-ditert-butyl phenol (an antioxidant for hydrocarbons and polymers). tert-Butanol is an authorized denaturant for ethanol. *Isoamyl alcohol*, CAS number 123-51-3, is the main constituent of fusel-oil (or fuselol), a high boiling ("tailing") product of alcoholic carbohydrate fermentation, from which it is recovered by fractional distillation. It is mainly used as chemical reagent for fine chemicals (photographic chemicals and pharmaceutical products), as a component of paint stripper and in chemical laboratory analyses (e.g. it is used in an official method for measurement of butterfat in milk). *Methyl isobutyl carbinol* (or MIBC), CAS number 108-11-2, has been a solvent for dyestuffs, oils, gums, resins, waxes, and cellulose esters. It has been used in flotation processes and brake fluid. *Cyclohexanol*, CAS number 108-93-0, is industrially produced by hydrogenation of phenol and is the starting material for the production of adipic acid in the manufacture of nylon. Minor uses include the synthesis of other fine chemicals, lacquers, paints, varnishes, degreasers, plastics and plasticizers, soaps and detergents, textiles, and insecticides.

1.1.15 Diseases caused by alcohols, glycols, or ketones	ICD Code T51, T52.3, T52.4 +Z57
Occupational exposures	*Methyl-cyclohexanol* (mixed isomers), CAS number 25639-42-3, has been used as a solvent for cellulose esters and ethers, a lubricant antioxidant, a blending agent for soaps and detergents, in the textile and artificial silk industry, and as a degreasing agent. *Isooctyl alcohol* (ethyl-hexyl alcohol), CAS number 26952-21-6, is a technical but chemically inappropriate name for 2-ethyl-hexanol. This alcohol is synthesized by the aldol condensation of n-butyraldehyde (itself produced by hydroformylation of propylene), followed by hydrogenation of the resulting hydroxyl-aldehyde. Its main use is the production of phthalate plasticizers and of non-ionic detergents and surfactants; a minor fraction is used as a technical solvent in synthetic drying oils, cutting and lubricating oils, and hydraulic fluids. *Hexafluoro-isopropyl alcohol* (or hexafluoro-isopropanol), CAS number 920-66-1, is industrially prepared by catalytic hydrogenation of hexafluoroacetone (see below). It is an important building block for the manufacture of specialty products, such as water-repellent poly-acrylate resins and esters used for textile waterproofing, and of the inhalation anaesthetic sevorane. *Propargyl alcohol*, CAS number 107-19-7, is industrially produced by the copper-catalysed addition of formaldehyde to acetylene (Reppe synthesis), as a by-product of the industrial synthesis of 2-butyne-1,4-diol [being itself the industrial precursor of 1,4-butandiol (or butyl-glycol)], and represents an important building block for fine chemicals. The main industrial use of propargyl alcohol is in electroplating, as a corrosion inhibitor and electroplating brightening additive. *Glycidol*, CAS number 556-52-5, is industrially prepared by epoxidation of allyl alcohol. Among its main uses is the preparation of glycidol esters, which are in turn formulated into epoxy resins, especially for coatings. It is used in industry as chemical reagent for fine organic synthesis. **GLYCOLS** Glycols find several different uses in industry and technology. 1,2-, 1,3- 1,4-glycols are employed as starting materials for the production of condensation polymers with dicarboxylic acids (polyester fibres such as polyethylene terephthalate); ethylene and propylene glycols are employed in formulations for antifreeze or liquid coolants; in brake fluids, lubricants, de-icing, mould-release agents and ink solvents, as textile softening agents and plasticizers (diethyleneglycol). *Ethylene glycol*, CAS number 107-21-1, is industrially produced mainly by hydration of ethylene oxide (a Group 1 IARC human carcinogen, see item 3.1.19) and in minor amount from ethylene chlorohydrin. The main industrial use of ethylene glycol is as a building block for polymers, especially in the manufacture of polyethylene terephthalate: this is a fully recyclable material with uses both as a textile fibre (as Dacron or Terylene) and as a mouldable plastic, especially to manufacture containers for food liquids and aluminized plastic sheets (Mylar). Ethylene glycol also finds use as a chemical intermediate in organic synthesis. The main technological uses of ethylene glycol are as a drying agent; as a component of automotive fluids such as antifreeze, coolants, hydraulic fluids, and de-icing agents; as a solvent in inks, stain removers, polishes and adhesives, as a water-compatible co-formulant for pesticides, in fire extinguishers, as a foam stabilizer in consumer products; as a heat-transfer fluid in air conditioning units and solar energy systems. *α-Propylene glycol* (1,2-propanediol), CAS number 57-55-6, is industrially prepared from propylene through epoxydation of petrochemical propylene and base-catalysed "opening" of propylene oxide. The industrial product is a racemic mixture and is used as a chemical feedstock to produce unsaturated polyester resins (reaction with maleic anhydride and isophthalic acid to yield thermosetting plastics) or the alcohol component of polyurethanes, by further reaction with propylene oxide. Other bulk uses include that as a component of de-icing fluids for air transport. *β-Propylene glycol* (1,3-propanediol), CAS number 504-63-2, is industrially prepared mostly by hydroformylation of petrochemical ethylene and hydrogenation of the obtained 3-hydroxypropionaldehyde (Shell process) or by hydratation of acrolein (Degussa process). It is mostly used as a building block for condensation polymers (polytrimethylene terephthalate or Eastman's Tritan (that is used as a substitute of bisphenol A-polycarbonate to produce Nalgene bottles) and as a component of water-compatible solvents and paint removers.

1.1.15 Diseases caused by alcohols, glycols, or ketones	ICD Code T51, T52.3, T52.4 +Z57

Butylene glycol (1,4-butanediol), CAS number 110-63-4, is the only one of the four isomers of butanediol to have an industrial significance. Industrial butylene glycol is prepared by several routes: from acetylene and formaldehyde (BASF-Reppe process); by hydroformylation of propylene (LyondellBasell process); from maleic anhydride (Davy process). Industrial uses include as a component of water-based solvent mixtures and as a building block for condensation polymers (polybutylene terephthalate). 40% of the production is used to produce tetrahydrofuran (a cyclic ether used as water-soluble solvent) that is one precursor of elastomeric polyurethane fibres, such as spandex (elastane). Minor uses include as reagent in the industrial synthesis of fine chemicals.

Diethylene glycol, CAS number 111-46-6, is industrially produced mainly as a by-product in the hydration of ethylene oxide to obtain ethylene glycol. The main industrial use of diethylene glycol is as a building block for polymers, especially in the manufacture of diethylene glycol esters and of polyurethanes (in the plastics and lacquer industries; for further details, see item 1.1.35); of plasticizers for polymers, of glycol-ethers and of explosives (diethylene glycol nitrate; for further details, see item 1.1.14). Technological uses include that as a plasticizer to impart flexibility to polyesters; as a softening agent for vinyl resins and a textile finishing agent for wool, rayon, cotton, and silk; as a humectant (moistening agent) for corks, tobacco, medical bandages; as an anti-freeze auxiliary (a 40% solution in water freezes at -18°C and a 50% solution at -28°C) in water fire extinguishers (Sprinkler); as a de-icer for aircraft and take-off/landing runways; as a hygroscopic water remover and industrial dryer in a variety of applications (e.g. a brake fluid constituent as a rubber-swell inhibitor, to increase the water tolerance of the fluid); as a component of household products, such as in mildew removers. In most applications diethylene glycol replaces the much more toxic ethylene glycol.

Pentaerythritol (2,2-Bis(hydroxymethyl)1,3-propanediol), CAS number 115-77-5, is industrially prepared by aldol condensation of formaldehyde and acetaldehyde. Its main bulk chemical use is as a building block for the preparation of resins and lacquers and for the synthesis of high-duty lubricants (pentaerythritol esters and alkyl-ethers) and of the industrial and military explosive PETN (see item 1.1.14).

KETONES

Lower ketones are employed as solvents in cleaning and degreasing, in formulating inks, resins, varnishes, lacquers, certain glues, surface coatings, paint removers, and automotive care products. Some ketones are used as starting materials in industrial organic syntheses.

Acetone, CAS number 67-64-1, is a widely used industrial solvent and chemical intermediate. In addition to its formulation in paints, varnishes, and lacquers, it is used as a solvent for cements in the leather, photography, fibre, and rubber industries. It is also used for cleaning and drying precision parts. Workers potentially exposed to acetone include bronzers, painters, chemical process plant workers, adhesive makers, varnish and stain makers, lacquer and oil processors, film makers, and those engaged in commercial and household maintenance. Acetone is used as an intermediate in the manufacture of methyl isobutyl ketone, mesityl oxide, acetic acid, diacetone alcohol, halomethanes, and certain explosives.

Methyl ethyl ketone (MEK, butanone), CAS number 78-93-3, is industrially prepared by catalytic oxidation of 2-butanol. It finds industrial use mainly as a solvent; one specialty use is in welding polystyrene (which is soluble in this solvent) in the surface coating industry; in the de-waxing of lubricating oils; and in the manufacture of colourless synthetic resins, artificial leather, rubbers, lacquers, varnishes, and glues. MEK is seldom used alone in industrial applications; it is usually found in mixtures with acetone, ethyl acetate, *n*-hexane, toluene, or alcohols.

3-Methyl-2-butanone (Methyl isopropyl ketone, MIPK), CAS number 563-80-4 is industrially prepared as a small-volume chemical from methyl isobutyl carbinol. It finds a limited use as a solvent for nitrocellulose lacquers.

Methyl propyl ketone, CAS number 107-87-9, is industrially prepared as a small-volume chemical by oxidation of 2-pentanol and finds limited use as a solvent. Small-volume specialty uses are as a flavouring agent, and in organic synthesis.

Diethyl ketone (3-pentanone), CAS number 96-22-0, is industrially prepared as a small-volume chemical by thermal decarboxylation of calcium propionate (Piria synthesis). It finds little, if any, use as a solvent, and small-volume specialty uses in organic synthesis.

1.1.15 Diseases caused by alcohols, glycols, or ketones	ICD Code T51, T52.3, T52.4 +Z57

Methyl n-butyl ketone (2-hexanone), CAS number 591-78-6, is industrially prepared as a specialty chemical from acetyl chloride and butyl-magnesium chloride or catalytically from acetic acid and ethylene. Methyl n-butyl ketone is used as a solvent for cellulose nitrate, vinyl polymers and copolymers, and natural and synthetic resins in a wide variety of materials, including paints, lacquers, ink thinners, nitrocellulose, glues, resins, oils, fats, and waxes, and in printing of plasticized fabric. Technical grade methyl n-butyl ketone has typically been produced in a concentration of 70%, with the remaining 30% composed of methyl isobutyl ketone.

Methyl isobutyl ketone (MIBK), CAS number 108-10-1, is industrially manufactured from acetone through three consecutive reactions, which are integrated in a single production unit (Uhde-Sasol process). Firstly, acetone undergoes an aldol condensation to give diacetone alcohol; diacetone alcohol readily dehydrates to give mesityl oxide; mesityl oxide is hydrogenated to give MIBK. Due to its poor solubility in water, MIBK is used as a process solvent for extraction from aqueous solutions, such as extraction of gold, silver and other precious metals from cyanide solutions at gold mines. MIBK is used as a component of cellulose and polyurethane lacquers and paint solvents. Methyl amyl alcohol is prepared from MIBK, and MIBK is an authorized denaturant for industrial ethyl alcohol due to its unpleasant taste.

Methyl n-amyl ketone, CAS number 110-43-0, is a natural product that occurs in clove and cinnamon bark oil but is produced commercially via catalytic dehydrogenation of 2-hydroxyheptane. Methyl n-amyl ketone is used as a solvent in metal roll coatings and in synthetic resin finishes and lacquers, as a flavouring agent, and in perfumes.

Methyl isoamyl ketone (5-methyl-2-hexanone, MIAK), CAS number 110-12-3, is industrially produced by condensation of acetone with isobutyraldehyde, in a similar pathway to that of MIBK. It is mainly employed as a solvent for cellulose esters, acrylics, and vinyl copolymers.

Cyclohexanone, CAS number 108-94-1, is a major chemical product, which is industrially obtained by oxidation of cyclohexanol and is used predominantly for the synthesis of adipic acid and of caprolactame for the production of nylon polycondensation fibres. Minor uses are as a solvent in insecticides, paints, paint and varnish removers, natural and vinyl rubbers, and in the textile and tanning industries. Other specialty applications include its use as a solvent adhesive or sealer for polyvinyl chloride plastic, which is used in medical devices and other items. It is one of the dispersants of ferric oxide powder ("*carrier*") for the production of electronic magnetic media, such as video tapes.

Ethyl-n-butyl ketone (EBK), CAS number 106-35-4, is industrially synthesized by reductive condensation of propanal with 2-butanone. It occurs naturally in breads and other baked goods. EBK is employed as a solvent for nitrocellulose and polyvinyl resins and for baked-on or air-dried finish mixtures. EBK is used as a fragrance in soaps, perfumes, detergents, creams, and lotions.

Dipropyl ketone, CAS number 123-19-3, is industrially prepared by passing butyric acid over precipitated calcium carbonate at 450°C (this is a flow-reactor modification of the Piria synthesis, see above). It is employed as a solvent for nitrocellulose, oils, resins, and polymers, and in lacquers and flavourings.

Ethyl amyl ketone (5-Methyl-3-heptanone), CAS number 541-85-5, is used as a solvent for nitrocellulose-alkyd, nitrocellulose-maleic, and vinyl resins.

Diisobutyl ketone (2,6-Dimethyl-4-heptanone), CAS number 108-83-8, is used as a solvent for synthetic resins, coating compounds, nitrocellulose, lacquers, and rubber. It is also used in organic syntheses.

Methyl vinyl ketone (MVK), CAS number 78-94-4, is industrially prepared by the condensation of acetone and formaldehyde, followed by dehydration. MVK polymerizes spontaneously upon storage and therefore is typically stored with hydroquinone (see item 1.1.33), which inhibits polymerization. MVK is a building block for styrene-MVK polymers that are useful as photo-biodegradable polymers in packaging applications. It is a versatile synthetic reagent for the synthesis of fine chemicals, such as natural products (synthetic vitamin A) and pesticides (vinclozolin). Chemically, it is an "*activated ketone*" and a strong electrophile ("*alkylating agent*").

Mesityl oxide, CAS number 141-79-7, is industrially obtained by acid condensation of acetone and employed as such as a solvent (for synthetic rubber, vinyl chloride-acetate copolymers, cellulose esters and ethers, oils, gums, resins, lacquers, inks), as a stain and paint remover. It is the precursor to industrially prepared methyl-isopropyl ketone by catalytic hydrogenation. As a consumer product, it finds use as an insect repellent.

1.1.15 Diseases caused by alcohols, glycols, or ketones	ICD Code T51, T52.3, T52.4 +Z57
	Isophorone, CAS number 78-59-1, is an unsaturated cyclic ketone that has been used as a solvent for polyvinyl resins, nitrocellulose resins, epoxy and alkyd resins, and polyacrylates, and for a variety of fats, oils, and gums. Its primary use has been as a solvent for vinylic resins applied by roller coating. However, it has also been used in pesticides and herbicides and as a chemical intermediate. *Diacetone alcohol* (4-Hydroxy-4-methylpentan-2-one, DAA), CAS number 123-42-2, is industrially manufactured by potassium hydroxide catalysed condensation of acetone (the technical grade solvent contains as much as 15% by volume of unreacted acetone). DAA is the intermediate for the preparation of mesityl oxide and MIBK. It is used as a solvent for nitrocellulose, cellulose acetate, celluloid, pigments, waxes, fats, and oils. Other technical uses include the formulation of antifreeze and hydraulic brake fluids. *Diacetyl* (2,3-butanedione), CAS number 431-03-8, is a naturally occurring flavouring substance found in some foods including butter, caramel, coffee, cocoa, and honey. It has been identified in a number of daily products other than butter (e.g. cheese, yogurt, milk), in several flowers and plant extracts, in aromatic components of tobacco smoke, beer and wine. Synthetic diacetyl produced by dehydrogenation of 2,3-butanediol is used as a food additive, mainly as a flavouring agent to impart a butter-like taste to popcorn margarine, candies, and a wide range of other products. Other uses for diacetyl include those as reactant/starting material in chemical laboratories, as analytical reagent, antimicrobial/preservative, photoinitiator/photosensitizer in polymerizations. *Hexafluoroacetone*, CAS number 684-16-2, is industrially prepared from hexafluoropropene. Its main industrial use is as the precursor to prepare hexafluoro-isopropyl alcohol and a specialty solvent for polymers (acetal resins, polyamides, polyglycolide, polyacetals) and polyols, or as a polymer adhesive.
Toxicological profile, main health effects and diagnostic criteria	
Short toxicological profile	Most alcohols, glycols and ketones with simple alkyl or cyclo-alkyl structure can be inhaled as airborne vapours and mists (according to their physical characteristics of volatility) through the respiratory tract, and be more or less completely absorbed. Depending on their nature and concentration, and on the duration of exposure, irritation of the airways can occur. Absorption through the skin is possible since these compounds and complex mixtures of them are often used in formulations and in consumer products. In the case of the less volatile compounds, skin absorption is the most likely route. Especially for industrial methanol and ethanol, there is the possibility of accidental or deliberate ingestion as illegal alcoholic drinks, usually with severe consequences. Following absorption, they are usually bio-transformed in the liver and often enter into the pathways of the fundamental cell metabolism, such as glycolysis and the Krebs cycle, the biosynthesis of fatty acids, and other biochemical pathways of mineralization. In some cases, their intermediate bio-transformed forms are chemically reactive and can impair biological mechanisms by overloading the biochemical pathways, through inactivation of key enzymes or other specific mechanisms. Some compounds, such as methyl-vinyl ketone, diacetone alcohol, and mesityl oxide are themselves highly reactive electrophiles that can inactivate key enzymes. Other compounds, such as 2-hexanol and methyl-*n*-butyl ketone, yield the strongly reactive metabolite hexane-2-5-dione, which is a specific peripheral neurotoxic agent. The un-metabolized fraction of these compounds is excreted in the urine or undergoes very simple biotransformation into conjugates, especially glucuronides and sulphates. During exposure and in the early hours after cessation of exposure, the elimination of the more volatile compounds and of some bio-transformed forms occurs by exhalation in the expired air, as typical of ethyl alcohol and acetone.

1.1.15 Diseases caused by alcohols, glycols, or ketones	ICD Code T51, T52.3, T52.4 +Z57
Short toxicological profile	**ALCOHOLS** *Methanol* is absorbed quickly from the lungs and the skin and is rapidly distributed to the liver, where it is bio-transformed to formaldehyde and to formic acid or formate (i.e., the anion derived from formic acid). Massive ingestion (as it is the case when drinking methanol as a component of uncontrolled or illegal spirits) causes systemic acidosis, which can rise to life-threatening levels. The most dangerous long-term effect of non-fatal intoxication from methanol is a specific blindness or serious visual impairment. *Ethanol* is a fundamental component of fermented alcoholic beverages. As a nutrient component of food, ethanol is completely mineralized to carbon dioxide, but excessive ingestion causes an overload of the metabolic capacity of the liver, which can be damaged by chronic abuse (alcoholic steatosis and cirrhosis). Un-metabolized alcohol crosses the blood-brain barrier and reaches the brain, where it displays its neurotoxic effects, both acutely (drunkenness) and following chronic abuse (e.g. Korsakoff psychosis). Abuse of alcohol as a drink is a common problem and has long-term effects for the alcohol user and for the offspring, especially if the user is a female of reproductive capacity. Alcohol drinking is classified by IARC as a Group 1 human carcinogen (malignant tumours of the oral cavity, pharynx, larynx, oesophagus and liver). Exposure to ethyl alcohol at occupational levels mostly occurs through the airways, where it causes mild irritation. Concentrated ethanol splashes that reach the eyes can cause chemical burns and severe ocular damage. *n-Propanol*, absorbed through the airways and through the skin at occupationally relevant concentrations and doses, is quickly metabolized to propionaldehyde and propionic acid, which enter the carbon mineralization pathway. It is reported as a milder skin irritant than ethyl alcohol and thus it is used as an alternative hand disinfectant to ethyl alcohol. Overexposure through ingestion is unlikely due to its strongly unpleasant taste. *iso-Propanol* is absorbed through the airways and the skin; overexposure through ingestion is unlikely due to its strongly unpleasant taste. It is quickly metabolized to acetone, which is mostly eliminated in the urine and with exhaled air, to which it imparts the characteristic "solvent-like" off-smell that is typical of uncompensated diabetes. In a minor amount, acetone enters the carbon mineralization pathway. *n-Butanol* is absorbed through the airways, although its strong odour is sufficient to alert to inadvertent exposure; skin absorption is slow and over-exposure through ingestion is unlikely due to its strongly unpleasant taste, although it is a trace component of alcoholic beverages. Most toxicological information comes from studies performed on butyl acetate, a common industrial solvent that is quickly and completely hydrolysed in vivo to n-butyl alcohol. The dose absorbed at occupationally relevant concentrations is quickly metabolized to butyraldehyde and butyric acid, which enter the carbon mineralization pathway. Minor amounts are excreted in the urine as glucuronide and sulphate conjugates. It does not show cumulative neurotoxicity. *sec-Butanol* is well absorbed by inhalation and by skin contact, but a large fraction (> 50%, up to 80%) of the inhaled dose is eliminated through the exhaled air. The retained dose is eliminated rapidly from the blood with an elimination half-life of about 2.5 hours. It is extensively metabolized, although less than other lower alcohols, when present in mixtures. Approximately 1% of the dose is excreted as glucuronide. The acute effects of administration are due to its "*alcohol-like*" narcotic effect. It is not a significant skin irritant. *iso-butanol* is very similar to n-butyl alcohol in its effect, although its vapour pressure (higher than n-butyl alcohol) increases absorption by inhalation. Absorption also occurs by skin contact. Most biotransformation occurs by conversion to carboxylic acid (isobutyric acid) and by glucuronidation. *tert-Butanol* is the only four-carbon alcohol that is solid at ambient temperature: therefore its absorption through the skin is likely negligible and it is a mild skin irritant. No other effects on humans have been reported and no reports of human poisoning are known. It is bio-transformed much less than the other isomers, and a substantial fraction of the dose is excreted as the glucuronide. Data on carcinogenicity, teratogenicity, or effects on reproduction are not adequate for toxicological evaluations. *Isoamyl alcohol* is absorbed through the skin more than by inhalation due to its low volatility and causes human skin erythema and irritation of eyes and upper respiratory tract. It causes central nervous system depression and is deemed to be toxic by ingestion of around 30 mL for an adult individual. It is bio-transformed mainly by oxidation to the aldehyde and the carboxylic acid that are mineralized in the Krebs cycle. Elimination of the glucuronide in the urine is a minor pathway, in the order of less than 10% of the dose. It is not considered to show synergy with ethanol in inducing ethanol-metabolizing enzymes and liver cytochromes, although this behaviour has only been studied in animal models.

1.1.15 Diseases caused by alcohols, glycols, or ketones	ICD Code T51, T52.3, T52.4 +Z57

Methyl isobutyl carbinol is absorbed more through the skin than by inhalation (due to its low volatility) and causes only slight skin erythema and irritation of the eyes. It is mainly biotransformed to the glucuronide and in a small proportion is eliminated in the urine as methyl-isobutyl ketone.

Cyclohexanol is absorbed both by inhalation and through the skin and is an eye, nose and throat irritant. While its main biotransformation process is glucuronidation prior to urinary excretion, a small fraction of the dose is hydroxylated to the 1,2-diol prior to excretion. Its oxidation to cyclohexanone (see below) is of poor efficiency.

Isooctyl alcohol is absorbed more through the skin than by inhalation (due to its low volatility) and causes only slight irritation. Its biodegradation, yet little studied, is likely to occur through oxidation to the aldehyde and carboxylic acid, and further mineralization through the Krebs cycle. The unmodified compound is likely eliminated in a small proportion of the dose as the glucuronide.

Hexafluoro-isopropyl alcohol is a volatile liquid that is easily absorbed by inhalation and through the skin and mucosae. At all contact sites it is an irritant due to its acid character.

Propargyl alcohol is well absorbed by inhalation and absorption through the skin is reported as limited, due to its volatility. It is a poor substrate of alcohol dehydrogenases, but is extensively metabolized in the liver, where it causes depletion of glutathione and organ damage. Most of the dose is eliminated as carbon dioxide and in urine.

Glycidol has been shown to be carcinogenic in experimental animals, although no evidence is available in humans. The IARC thus classified it as probably carcinogenic to humans (Group 2A).

GLYCOLS

Ethylene glycol is rapidly absorbed by the gastrointestinal tract, while dermal absorption is slow. Due to its very low vapour pressure, exposure by inhalation is generally not associated with toxicity. Acute systemic toxicity from ethylene glycol has been described after ingestion of concentrations in the order of at least 1 mg/kg body. Ethylene glycol is metabolized in the liver to a variety of compounds of increasing toxicity, such as glycol-aldehyde, glycolic acid, glyoxylic acid, and finally oxalic acid, with only a small fraction of absorbed ethylene glycol excreted unchanged in the urine. The metabolites are responsible of the systemic toxicity of ethylene glycol, since they inhibit several fundamental biochemical processes, such as oxidative phosphorylation and cellular respiration, glucose and serotonin metabolism, protein synthesis, DNA replication, and the synthesis of ribosomal RNA. The accumulation of organic acid metabolites, especially of glycolic acid, results in an anion gap metabolic acidosis that affects many cellular functions. Acute systemic ethylene glycol poisoning causes a depression of the central nervous system followed by metabolic acidosis, pulmonary oedema, renal failure with the formation of oxalate crystals, and death, in the most severe cases.

α-Propylene glycol has a negligible vapour pressure, therefore absorption of toxicologically relevant doses through inhalation is unlikely. Dermal and ocular exposures do not appear to elicit significant irritation and cause sensitization, nor does dermal absorption appear to cause absorption of toxicologically relevant doses. The biotransformation of doses absorbed in occupationally relevant conditions is not likely to interfere with human metabolism, since the absorbed substance enters the cellular pool of nutrient substrates (oxidation to lactic and pyruvic acid).

β-Propylene glycol is an oily substance with negligibly low volatility and a scarce absorption through the skin. The biotransformation of doses absorbed in occupationally relevant conditions is not likely to interfere with human metabolism, since the absorbed substance enters the cellular pool of nutrient substrates (oxidation to malonic acid).

Butylene glycol (1,4) is an oily substance with very low volatility and negligible absorption through the skin, that does not appear to pose significant occupational hazard. Of note is its neurobehavioral and neurotoxic effects (fatal cases reported) when it is ingested in gram-sized doses, as a recreational abuse substance that is a metabolic precursor to gamma-hydroxy-butyrolactone (GHB).

1.1.15 Diseases caused by alcohols, glycols, or ketones	ICD Code T51, T52.3, T52.4 +Z57

Diethylene glycol has been reported to represent a health hazard mainly by acute oral exposure. Due to its low volatility, there is no information available in humans on the effects of exposure through inhalation. No data is available on its potential eye irritating or sensitizing properties in humans. Diethylene glycol has mild if any irritating effects on the human skin. Most toxicological information on the acute toxic effects of diethylene glycol derives from observation of the consequences of its past use as a solvent in the formulation of pharmaceutical drugs, such as a sulphanilamide. Ingestion of concentrations in the order of 0.5 to 1 g/kg body weight led to severe intoxication with acute and potentially fatal renal failure. Initial effects include nausea, vomiting, headache, polyuria, and abdominal and back pains. Laboratory analysis shows signs of metabolic acidosis (increased anion gap), increased levels of the serum aminotranferases and creatinine, and elevated white blood cell count. If untreated, renal failure may develop within a few days, followed by coma, convulsions and death in severe cases. Autopsy has revealed lesions in the kidneys and the liver.

KETONES

Acetone is absorbed by inhalation and from the skin, where it causes mild irritation from removal of skin lipids and can enhance absorption of other substances. At high airborne concentration, it is an irritant of upper airways. Its systemic toxicity is very low and health- and life-threatening doses are unlikely to be absorbed. Since it is a natural product of human primary metabolism, generated by enzymatic decarboxylation of acetoacetate (itself a metabolic product of the mitochondrial beta-oxidation of fatty acids), most of absorbed acetone is mineralized by conversion to acetyl-CoA, while a fraction of 30-70% is eliminated with exhaled air. The same is true for endogenously generated excess acetone, as occurs chronically in uncontrolled metabolic diseases (such as diabetes) and physiologically during prolonged fasting.

Methyl ethyl ketone is absorbed by inhalation and from the skin, where it causes mild irritation and produces dermatitis by removal of skin lipids. It is a mild narcotic, and there is a report of retrobulbar neuritis in a young worker exposed to this solvent. MEK is also an oxidation biotransformation product of 2-butanol.

Methyl isopropyl ketone is absorbed by inhalation and from the skin and is a mild skin irritant but not a sensitizer. It is a trace product of human metabolism and, as such, it is detected in exhaled breath air. Its main likely biotransformation product is the glucuronide of the corresponding secondary alcohol.

Methyl propyl ketone is absorbed by inhalation and from the skin, and a significant fraction is eliminated with exhaled air, while the remaining dose is excreted as metabolites, likely as conjugates with glucuronic acid. It is a major biotransformation product of *n*-pentane.

Diethyl ketone is absorbed by inhalation and from the skin and is a mild irritant of skin and mucosae. There is little toxicological information on this substance, but it is likely eliminated with exhaled breath air and in the urine, as the glucuronide of the corresponding secondary alcohol.

Methyl-n-butyl ketone is absorbed as an airborne vapour and through the skin. Its biotransformation route of main toxicological concern leads to the specific peripheral neurotoxic agent hexane-2,5-dione. This compound is well known as the final metabolite of hexane (see item 1.1.21), generated through the microsomal hydroxylation at the (n-1) methylene position at both ends of the hydrocarbon chain to yield in sequence 2-hexanol, MNBK, 2-hydroxy-5-keto-hexane and finally hexane-2,5-dione. The lipophilic end metabolite reacts with the epsilon-amino group of lysine in the hydrophobic proteins of the nerve axon, to generate 2,5-dimethyl-N-proteinyl-pyrrole adducts. In turn, these compounds easily oxidize and generate cross-links of the protein that ultimately lead to structural and functional degeneration of the distal axonal portion of motor neurons. The outcome is a progressive, irreversible retrograde paralysis of hands, feet and limbs.

Methyl isobutyl ketone is absorbed by inhalation and from the skin, towards which it is not significantly irritant. It is not neurotoxic. Its main biotransformation products are 4-hydroxy-4 methyl-2-pentanone (hydroxylation at secondary carbon) and 4-methyl-2-pentanol (reduction of carbonyl group).

Methyl n-amyl ketone is mainly absorbed by skin contact, due to its low volatility. Co-exposure with hepatotoxic solvents, such as chloroform, appears to potentiate the toxicity of the latter.

1.1.15 Diseases caused by alcohols, glycols, or ketones	ICD Code T51, T52.3, T52.4 +Z57
	Methyl isoamyl ketone can be absorbed through the skin rather than by inhalation, due to its poor volatility and oily liquid character. Reported or anticipated adverse effects in humans only refer to the onset of skin irritation and of allergy following repeated contact. *Cyclohexanone* is absorbed by inhalation and by skin contact and its main biotransformation product is the glucuronide of cyclohexanol, with trace amounts of the diol glucuronide-sulphate and of cyclohexyl mercapturic acid. Cyclohexanone depresses the central nervous system and is narcotic at high concentrations. It is irritating to mucous membranes, eyes, and skin. *Ethyl-n-butyl ketone* can be absorbed by skin contact, rather than by inhalation, due to its poor volatility and oily liquid character. It can potentially be bio-transformed to a higher homologue of 2,5-hexanedione, and some experiments show potentiation of the neurotoxicity between MBK and EBK. *Dipropyl ketone* is absorbed as an airborne vapour and through the skin. It is mostly an eye and skin irritant. *Ethyl amyl ketone* can be absorbed by skin contact, rather than by inhalation, due to its poor volatility and oily liquid character. Evidence on its toxicity is scarce and it does not appear to be a skin irritant or sensitizer. It can potentially be bio-transformed to a higher homologue of 2,5-hexanedione, but there is no published literature information on this aspect. *Diisobutyl ketone* is mostly absorbed through skin contact, rather than through inhalation. It is not a primary skin irritant, but skin defatting occurs on repeated contact. Little is known on its biotransformation and excretion that possibly entails reduction to the alcohol and conjugation to the glucuronide. The structure of DIBK precludes metabolism to the neurotoxic metabolite 2,5- hexanedione. *Methyl vinyl ketone* is most likely absorbed by inhalation and through the skin and is an irritant due to its strong electrophile character. *Isophorone* is efficiently absorbed by skin contact, which is the most likely way of exposure due to its low volatility. Absorbed isophorone is mostly converted into a number of biotransformation products, derived from hydroxylation of the allylic methyl group (isophorol) and further conversion to a carboxylic acid that is excreted into the urine as the glucuronide. Although isophorone features an activated carbonyl group, its reactivity towards DNA is poor. *Diacetone alcohol* is absorbed by inhalation and through the skin. Prolonged skin contact is irritant and there is a literature record of a delayed irreversible kidney damage in worker who was exposed to a mixture of diacetone alcohol and ethanol. Due to its possible conversion to mesityl oxide by dehydratation, it is possible that the effects are in part due to this strong electrophile. *Mesityl oxide* is a high-boiling, viscous solvent, so that the most relevant route of exposure is by skin contact. It has a strong peppermint odour and due to its electrophilic chemical reactivity, it is a mild irritant of the mucosae and upper airways. It is known that co-exposure to ethyl alcohol enhances its central narcotic effects. Its reaction with sulphur amino acids and peptides, such as cysteine and glutathione, followed by a further biotransformation of the generated thiol conjugates, generates off-smelling compounds that are mainly excreted in exhaled air and sweat, and are likely responsible for its insect repellency. *Diacetyl* is absorbed through inhalation and is a recognized lung toxicant, responsible for a severe *bronchiolitis obliterans* in a group of food workers formerly employed at a microwave-popcorn production plant. *In vitro*, diacetyl is an uncoupler of oxidative phosphorylation and it is known to react with the guanido group in the side chain of arginine, but the relationship of these observations with the development of specific lung toxicity is not known. *Hexafluoroacetone* is likely absorbed from both inhalation and skin contact. There is little information, except for generic warning to use it as a chemical that requires special handling.

1.1.15 Diseases caused by alcohols, glycols, or ketones ICD Code T51, T52.3, T52.4 +Z57

Name of the diseases and ICD code: **Acute diseases due to direct contact with alcohols, ketones or their vapours** *(Specific disease code)* **+T51, T52.4 +Z57**

Respiratory tract irritation (J68), Acute chemical pneumonitis (J68.0), Upper respiratory inflammation (J68.2), Conjunctivitis (H10.2), Corneal ulcer (H16.0), Corneal scar and opacity (H17.9), Corneal oedema (H18.2)

Short description of the disease

Exposure to high concentration of alcohols or ketones (and their vapours) can cause irritation of eyes and respiratory tract, with rhinitis, laryngitis, and bronchitis. High exposures to ketone vapours may lead to chemical pneumonitis.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms:
  - Exposure to inhaled high concentrations of alcohols or ketones (and their vapours) can lead to symptoms of lung and upper respiratory tract irritation, including sneezing, rhinorrhoea, redness of the throat, epistaxis, nasal itching and soreness, coughing, wheezing, inspiratory pain, bronchitis, and pneumonitis.
  - In case of contact with the eyes and adnexae, alcohols or ketones (and their vapours) may produce a local inflammation (conjunctivitis) up to corneal ulcers, with alteration, reduction or loss of vision.
- Examinations:
  - Chest X-rays may reveal a picture of pneumonitis or bronchitis, with increased bronchovascular markings.
  - An ophthalmic examination should be performed, including visual acuity and slit lamp inspection of the cornea. Corneal ulceration may be seen on corneal examination.

Exposure assessment

- History of occupational exposure: confirmed occupational exposure to alcohols, ketones or their vapours via inhalation, ingestion or dermal and mucous membranes contact.
- Minimum duration of exposure: minutes.
- Maximum latent period: 48 hours.

Name of the diseases and ICD code: **Acute diseases caused by alcohols**
(Specific disease code) **+T51 +Z57**

Acute systemic poisoning by methanol (T51.1), Toxic optic neuropathy due to methanol toxicity (H46), Visual disturbances and blindness due to methanol toxicity (H53-H54)

Short description of the disease

Methanol may be acutely toxic following inhalation of very high doses, percutaneous exposure or ingestion, the latter being very uncommon in occupational settings. Acute toxicity from methanol manifests as central nervous system depression, followed by a latent period of varying duration, from 8 to 36 hours, and occasionally up to 48 hours. Subsequently, metabolic acidosis develops, superimposed with headache, nausea and features of ocular toxicity. Ocular toxicity may range from photophobia, amblyopia, and misty or blurred vision to markedly reduced visual acuity and complete blindness; ingestion of doses in the order of 4-10 mL methanol in adults may cause severe damage. Coma and death may occur after very high exposures. The minimal lethal dose following ingestion is considered to be in the range of 300-1000 mg/kg. When non-fatal, severe intoxication may cause permanent damage to the central nervous system (CNS), manifest as a Parkinsonian-like condition and permanent blindness.

The timeline of methanol poisoning can usually be summarized as follows (see below for further details):

1. Central nervous system depression.
2. Asymptomatic latent period.
3. Severe metabolic acidosis with gastrointestinal symptoms.
4. Ocular toxicity followed by blindness, coma and in extreme cases death.
5. Ocular and neurological sequelae in survivors.

1.1.15 Diseases caused by alcohols, glycols, or ketones ICD Code T51, T52.3, T52.4 +Z57

Diagnostic criteria

Clinical manifestations

- Signs and symptoms:
  - *Central nervous system involvement:* headache, vertigo, lethargy, and confusion occur commonly in mild to moderate methanol intoxication. The occurrence of coma and convulsions during severe cases of methanol poisoning suggests the presence of cerebral oedema. In addition to blindness, survivors of severe methanol intoxication may develop a Parkinson-like extrapyramidal syndrome characterized by rigidity, bradykinesia, mild tremor, masked faces, lethargy, and mild dementia.
  - *Ocular toxicity:* the ophthalmologic symptoms and signs of methanol poisoning range from blurred vision and altered visual fields to complete blindness. Blurred vision, decreased visual acuity, photophobia, and "feeling of being in a snow field" were common complaints in over one-half of patients in an epidemic of methanol poisoning. Visual impairment usually takes the form of central scotoma or complete blindness secondary to optic nerve atrophy.
  - *Gastrointestinal system involvement*: methanol typically produces nausea, vomiting, and abdominal pain. Abdominal pain may be severe as a result of the development of pancreatitis, which is a common complication of severe methanol poisoning, with an increase of serum amylase. Elevation of hepatic aminotransferases is usually mild and transient.
  - *Kidney involvement:* although the occurrence of myoglobinuria is a rare complication of methanol poisoning, if present it may cause renal dysfunction. Subjects with a hospital admission methanol concentration of 400 mg/dL have been reported to develop acute renal failure in association with myoglobinuria (renal dysfunction peaked on the eighth day and returned to normal within one month).
  - *Sequelae of methanol poisoning:* permanent damage (residual scotomata) can result although complete blindness is avoided. Difficulties in speech and motor sequelae have afflicted those patients who survived the initial, severe metabolic acidosis (see below).
- Examinations:
  - *Ophthalmic exam:* in case of methanol toxicity the pupils are dilated, the sclerae are congested, and there is pallor of the optic disc with central scotoma.
  - *Alterations of the acid-base balance:* the presence of severe metabolic acidosis with increased anion and osmolar gaps strongly suggests the presence of methanol intoxication. The anion gap is the difference between the sum of the measured cations and the sum of the measured anions. Under normal circumstances, this gap represents negatively charged proteins (albumin), fatty acids, and inorganic anions (sulphates, phosphates). Normally, the anion gap is about 12-16 mmol/L, but the actual concentrations vary between laboratories depending on the accuracy of laboratory measurements. The generation of formate and, to a lesser extent, lactate contributes to the anion gap during methanol intoxication. A profound metabolic acidosis occurs during severe methanol poisoning. Most seriously intoxicated patients with a serum bicarbonate level<18 mEq/L had serum methanol concentrations over 50 mg/dL (500 mg/L). In all symptomatic patients, arterial pH should be measured.
  - *Serum concentrations of methanol and formate:* a variety of factors complicate the correlation of serum methanol concentrations to clinical effects, including differences in sample collection, individual variabilty, concentration of toxic metabolites, and ethanol ingestion. Clinical symptoms and mortality correlate more closely with metabolic acidosis and formate concentration rather than with serum methanol concentrations. Diagnosis may be aided by the analysis of formate in serum, although elevated concentrations of formate in serum is not specific for methanol intoxication, because exposure to formate itself may have occurred.
  - *Haematological and biochemical abnormalities:* isoamylase analysis indicates that a substantial portion of the amylase elevation may result from inflammation of the salivary glands, and therefore, the presence of an elevated serum amylase does not necessarily imply the presence of pancreatitis. Case reports indicate that myoglobinuric renal failure may complicate methanol poisoning. Pancreatitis, including severe necrotizing pancreatitis, is a common complication of severe methanol intoxication. In a series of 22 cases of methanol intoxication, 11 patients developed evidence of pancreatic damage and 1 patient died of acute necrotizing pancreatitis. Elevation of the mean corpuscular volume occurs during severe methanol poisoning, probably as a result of generalized cellular swelling. The haemoglobin, haematocrit, and leucocyte counts are usually normal.
  - *Imaging studies:* the most consistent radiographic finding following severe methanol intoxication is bilateral necrosis of the putamen. In cases of severe methanol intoxication, non-enhanced CT at the time of admission can demonstrate hypodensity in the putamen, and less often, in the caudate nucleus. However, CT imaging of the brain frequently is normal when performed within the first 24 hours after methanol ingestion. Although initial MRI scans may not demonstrate optic abnormalities despite the presence of blindness on clinical examination, case reports indicate that repeating MRI scans one month after methanol poisoning demonstrate atrophy of the optic chiasm and pre-chiasmatic optic nerves.

1.1.15 Diseases caused by alcohols, glycols, or ketones ICD Code T51, T52.3, T52.4 +Z57

- *Electrophysiological tests:* in an electroretinogram, the negative a-wave reflects photoreceptor activity and the b-wave reflects the conduction of impulses through the bipolar cell layer including Müller glial cells. A reduction of the a- and b-wave amplitude occurs during acute and chronic methanol intoxication. Reversible retinal and optic nerve dysfunction can occur during the early stage of methanol poisoning.

Exposure assessment

- History of occupational exposure: confirmed occupational exposure to very high doses of methanol, either through inhalation, percutaneous absorption, or ingestion (the latter being very uncommon in occupational settings).
- Minimum duration of exposure: some minutes.
- Maximum latent period: 48 hours.

Acute systemic poisoning by isopropyl alcohol (T51.2)

Short description of the disease

Different studies have documented acute human toxicity following poisoning by isopropanol. In particular, after irritation of eyes, nose and throat, neurobehavioral effects with postural imbalance have been observed. Acute isopropanol intoxication has a rapid onset (less than one hour) and peak effects typically occur within several hours of exposure. If serious nervous system effects occur, they may persist for up to 24 hours.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms:
  - The major symptoms of acute isopropanol intoxication include irritation of upper respiratory tract, shortness of breath, dizziness, incoordination, headache, confusion, flushing, hypothermia, contracted pupils and ocular ataxia.
  - Vomiting, haematemesis, diarrhoea, and hypotension may occur following ingestion of large quantities of isopropanol.
  - Extremely high intakes of isopropanol may result in aspiration pneumonia, respiratory depression, lung, spleen and liver congestion, tachycardia, severe confusion, severe hypotension, shock, impaired reflexes, kidney and liver dysfunction, and coma.
- Examinations:
  - Abnormalities at laboratory testing may include hyperglycaemia, elevated protein levels in cerebrospinal fluid, presence of acetone in the blood, urine, and exhaled breath, acetonaemia and acetonuria without metabolic acidosis, and a significant osmolality gap.
  - Chest X-rays may show atelectasis.

Exposure assessment

- History of occupational exposure: confirmed occupational exposure to high concentrations of isopropanol and its vapours, especially through inhalation.
- Minimum duration of exposure: several minutes.
- Maximum latent period: 48 hours.

Irritant contact dermatitis (L24)

Contact of alcohols (especially methanol and n-propanol) with unprotected skin for at least 30 minutes can cause skin irritation. For more details on clinical features and exposure assessment criteria of irritant contact dermatitis, refer to item 2.2.2.

Allergic contact dermatitis (L23)

Allergic contact dermatitis may develop as a consequence of contact to certain compounds, in particular isopropyl alcohol that is a sensitizer. Symptoms may appear during exposure, within 48 hours, or after few days at the latest. For more details on clinical features and exposure assessment criteria of allergic contact dermatitis, refer to item 2.2.1.

1.1.15 Diseases caused by alcohols, glycols, or ketones ICD Code T51, T52.3, T52.4 +Z57

Name of the diseases and ICD code: **Acute diseases caused by glycols** *(Specific disease code)* **+T52.3 +Z57**

Acute systemic poisoning by ethylene glycol (T52.3), Acute toxic encephalopathy due to ethylene glycol (G92)

Short description of the disease

A single exposure to high doses of ethylene glycol may lead to the onset of central nervous system symptoms, i.e., headache, lightheadedness and disturbances of equilibrium at the end of a working day. These symptoms usually disappear after the end of the exposure. Ingestion of ethylene glycol (unlikely in normal occupational conditions) can cause severe intoxication with systemic manifestations, central nervous system depression, encephalopathy and death.

Diagnostic criteria

As a general statement, recall that a history of exposure to ethylene glycol in case of metabolic acidosis with an osmolal and anion gap is diagnostic for poisoning.

Clinical manifestations

- Signs and symptoms: severe ethylene glycol poisoning may progress through three stages: CNS depression, cardiopulmonary toxicity, and renal toxicity. Permanent sequelae may then persist.
  - *Stage 1 (CNS depression)*

  CNS depression begins soon after exposure, lasting for up to 12 hours after ingestion. This depression appears similar to ethanol intoxication, but without the characteristic odour of alcohol. Initially, the inebriation, euphoria, ataxia, slurred speech, sleepiness, irritation, restlessness, and disorientation are due to the unmetabolized ethylene glycol.

  After glycoaldehyde metabolic production (at 4-12 hours) and metabolic acidosis onset, CNS depression can become manifest with seizures, coma, cerebral oedema, and gastrointestinal irritation (nausea and vomiting).

  An osmolal gap, without metabolic acidosis, or an anion gap may be seen before significant metabolism of ethylene glycol occurs. As ethylene glycol is metabolized, the osmolal gap decreases. Signs of metabolic acidosis due to the metabolites may become apparent late.
  - *Stage 2 (Cardiopulmonary toxicity)*

  12-24 hours after ingestion, tachycardia, tachypnoea, and hyper/hypotension may appear, possibly evolving to pulmonary oedema, pneumonitis, congestive cardiac failure, and shock.

  Synthesis of oxalic acid may lead to deposition of calcium oxalate crystals in the meninges, blood vessel walls, lung, myocardium and kidney, with consequential tissue injury in some very severe cases. Tetany from hypocalcaemia and hyperventilation may also occur. Metabolic acidosis with elevated anion gap and decreased osmolal gap persists. Most deaths from ethylene glycol poisoning occur during this stage.
  - *Stage 3 (Renal toxicity)*

  Kidney damage is usually observed 24-72 hours after ingestion. This stage can be characterized by flank pain, costovertebral angle tenderness, oliguric renal failure, hyperkalaemia, and hypocalcaemia.

  Acidosis and acute renal failure may result from deposition of calcium oxalate crystals in the kidneys accompanied by proteinuria, haematuria, crystalluria, and increased serum blood urea nitrogen (BUN) and creatinine.

  Calcium oxalate crystals may appear in the urine as early as stage 1, but absence of these crystals does not rule out the diagnosis of ethylene glycol poisoning. Note that, in this stage, anion and osmolal gaps may be normal.
  - *Sequelae*

  Possible sequelae of severe poisonings by ethylene glycol after one or more weeks include myoclonic jerks, convulsions, coma, and death. Cerebral oedema and deposition of calcium oxalate crystals in the walls of small blood vessels in the brain contribute to this CNS toxicity. Note that recovery in survivors is usually rapid and complete. However, in some cases facial palsy, hearing loss, dysphagia, opthalmoplegia, and visual disturbances can persist even weeks after exposure, indicating cranial nerve damage.

1.1.15 Diseases caused by alcohols, glycols, or ketones ICD Code T51, T52.3, T52.4 +Z57

- Examinations:
  - Physical examination may document nonspecific signs of moderate/severe poisoning, such as tachypnoea, tachycardia, mild hypertension, and low-grade fever.
  - A complete neurologic examination should be performed, with special attention for mental status, gait, and balance.
  - All patients with known or suspected ethylene glycol ingestion require the following tests to investigate electrolyte and acid-base balance: arterial blood gas analysis, serum blood glucose, serum electrolytes.
  - Other helpful laboratory tests may include: serum BUN and creatinine, calcium and magnesium levels, liver function tests, and urinalysis (with special attention to crystalluria).
  - A measured osmolality by the freezing point depression method is needed to detect an osmolal gap. Results of these laboratory tests will confirm the presence and degree of metabolic acidosis and allow calculation of the anion and osmolal gaps.
  - Electrocardiogram and chest X-rays might show cardiopulmonary impairment, while electroencephalography might show signs of CNS depression.

Exposure assessment

- History of occupational exposure: confirmed work-related exposure to high levels of ethylene glycol (mainly through accidental ingestion) and, if available, urinary and blood concentration of oxalic acid and ethylene glycol.
- Minimum duration of exposure: minutes.
- Maximum latent period: 48 hours.

Acute systemic poisoning by diethylene glycol (T52.3), Acute toxic encephalopathy due to diethylene glycol (G92)

Short description of the disease

Diethylene glycol is toxic primarily to the kidney and nervous system and can produce a wide variety of signs and symptoms after ingestion. Intoxicated subjects typically develop acute renal failure (ARF) in some cases accompanied by metabolic acidosis. Other effects include encephalopathy, coma, and death. The lack of information on the short- and long-term effects of diethylene glycol exposure is matched by a scarcity of information on the manner in which diethylene glycol is metabolized and eliminated after ingestion and how it causes its specific end-organ effects in humans.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms:
  - The initial symptoms of diethylene glycol intoxication are nausea, headache and vomiting.
  - With continued exposure, severe abdominal pain, polyuria followed by oliguria, anuria and renal failure may appear. Hepatotoxicity is common.
  - After accidental oral exposure to diethylene glycol, drowsiness, headache, impaired consciousness, progressive obtundation, coma and death haven been reported. Drowsiness may be delayed until approximately 24 hours after ingestion. In addition, meningism, cerebral oedema and haemorrhages, bulbar palsy, (partial) facial and ascending paralysis, and demyelinating lesions of the central and peripheral nervous systems have been reported, as well as tremor and seizures. Symptoms related to CNS impairment usually occur 1-3 weeks after ingestion.
  - Diethylene glycol can cause respiratory arrest and pulmonary oedema.
- Examinations:
  - Electromyography may reveal widespread acute denervation in arm and leg muscles.
  - Magnetic resonance imaging may demonstrate enhancement of cranial nerves III and V.
  - Pathologic examinations post mortem shows central and peripheral nervous system lesions, including axon damage followed by severe demyelination of virtually all cranial and peripheral nerves sampled, and sparing of central myelin.
  - Kidney function tests might document acute renal failure.

Exposure assessment

- History of occupational exposure: confirmed work-related exposure to high levels of diethylene glycol (mainly through accidental ingestion).
- Minimum duration of exposure: some minutes.
- Maximum latent period: 48 hours.

1.1.15 Diseases caused by alcohols, glycols, or ketones ICD Code T51, T52.3, T52.4 +Z57

Irritant contact dermatitis (L24)

Short description of the disease

Glycols are slight irritants for the skin, after exposure of at least several days through skin contact. The first manifestations should appear during exposure or within 48 hours at the latest.

For further details on clinical features of irritant contact dermatitis, refer to item 2.2.2.

Name of the diseases and ICD code: **Acute diseases caused by ketones** *(Specific disease code)* **+T52.4 +Z57**

Acute systemic poisoning by acetone (T52.4), Acute toxic encephalopathy (G92)

Short description of the disease

The data for systemic, neurological, and immunological effects are derived from medical evaluations of workers after single-day exposures and case reports. The systemic effects include respiratory irritation, cardiovascular, gastrointestinal, and haematological effects, with no indications of hepatic or renal involvement.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms:
  - Possible immunological effects consist of increased white blood cell and eosinophil counts, and decreased phagocytic activity of neutrophils.
  - Neurological effects consist of headache, lightheadedness, unconsciousness, dizziness, confusion, slurred speech, lack of energy, general weakness, lethargic state, behavioural changes (increase in anger and hostility), and coma in the most severe cases.
  - Information in humans after oral exposure is derived from case reports of intentional or accidental ingestion. Effects included erosions in the buccal cavity, development of diabetes-like symptoms, coma, and some of the above-mentioned neurological effects.
  - When exposure occurs through inhalation, irritation of nose, throat, trachea, and lungs usually develops.
  - Effects of dermal/ocular exposure consists of eye irritation, and degenerative changes in the epidermis.
  - Subjects exposed by inhalation and dermally from applications of casts using acetone as a setting agent developed increased pulse rate, vomiting and nausea, and neurological effects, including coma.
  - Shortened menstrual cycle has been reported in females exposed to very high concentrations during a working-day time.
- Examinations:
  - Neurobehavioral investigations might show delayed visual and choice reaction time.
  - Auditory tone discrimination test might show increases in response; false negatives are possible.

Exposure assessment

- History of occupational exposure: confirmed occupational exposure to acetone or its vapours and, when available, measurement of its concentrations in venous blood and alveolar breath. A positive nitroprusside reaction can help identifying ketones in urine testing.
- Minimum duration of exposure: minutes.
- Maximum latent period: some weeks.

Acute poisoning by methyl ethyl ketone (T52.4), Acute toxic encephalopathy (G92)

Short description of the disease

Methyl ethyl ketone (MEK) is more irritating than acetone to mucous membranes. It has low acute toxicity, but it potentiates the neurotoxicity of *n*-hexane and methyl-*n*-butylketone.

Diagnostic criteria

Clinical manifestations

Symptoms following acute exposure to MEK include irritation of the eyes, nose, and throat. MEK inhalation may results in slight excitement, followed by somnolence or unconsciousness. Headache, dizziness, and nausea can also be observed, but these effects have been attributed to concomitant exposures to solvents, since human volunteers did not report these symptoms.

1.1.15 Diseases caused by alcohols, glycols, or ketones ICD Code T51, T52.3, T52.4 +Z57

Exposure assessment

- History of occupational exposure: confirmed occupational exposure to MEK or its vapours via inhalation and, when available, measurements of its concentration in urine where it can be found at low levels.
- Minimum duration of exposure: minutes.
- Maximum latent period: 48 hours.

Acute systemic poisoning by methyl isobutyl ketone (T52.4), Acute toxic encephalopathy (G92)

Short description of the disease

Workers exposed to methyl isobutyl ketone report irritant and neurological symptoms.

Diagnostic criteria

Clinical manifestations

- Irritation of the eyes and nasal mucosae.
- Weakness, loss of appetite, headache, stomachache, nausea, and vomiting.
- Sore throat, insomnia, somnolence, heartburn, intestinal pain, and liver enlargement were observed in some workers.

Exposure assessment

- History of occupational exposure: confirmed occupational exposure to MIBK or its vapours via inhalation and, when available, measurements of its concentration in urine.
- Minimum duration of exposure: some hours.
- Maximum latent period: 48 hours.

Irritant contact dermatitis (L24)

Skin contact for a few minutes with ketones (methyl vinyl ketone in particular) may cause irritation of the skin and mucous membranes. For details on clinical features and exposure assessment criteria of irritant contact dermatitis, refer to item 2.2.2.

Allergic contact dermatitis due to methyl vinyl ketone (L23)

Exposure to methyl vinyl ketone may cause allergic reactions. Usually, at least two episodes of skin contact are necessary to cause sensitization. For details on clinical features and exposure assessment criteria of allergic contact dermatitis, refer to item 2.2.1.

Name of the diseases and ICD code: **Chronic diseases caused by alcohols** *(Specific disease code)* **+T51 +Z57**

Chronic toxic encephalopathy (G92)

Short description of the disease

Chronic exposure to alcohols, and to methanol vapours in particular (ICD code T51.1), can cause chronic toxic encephalopathy (e.g. Korsakoff psychosis, Wernicke's encephalopathy).

Diagnostic criteria

Clinical manifestations

Headache, giddiness, insomnia, gastric disturbances, and, in the most severe cases of methanol poisoning, bilateral blindness.

Exposure assessment

- History of occupational exposure: confirmed occupational exposure to alcohols, methanol in particular, and their vapours and, when available, biological monitoring of their concentrations in blood, urine, and alveolar breath. As regard urinary samples, if the distribution of exposure concentration is unknown or likely to fluctuate widely during the work shift, then sampling must be conducted over the whole shift (8hr urine collection) or at the end of a representative exposure period. If it is known that exposure does not fluctuate widely, then end-of-shift sampling is satisfactory.
- Minimum duration of exposure: ten years (probably even less for methanol).
- Maximum latent period: three years.

1.1.15 Diseases caused by alcohols, glycols, or ketones ICD Code T51, T52.3, T52.4 +Z57

Name of the diseases and ICD code: **Chronic diseases caused by ketones** *(Specific disease code)* **+T52.4 +Z57**

Obliterative bronchiolitis due to diacetyl (J68.4)

Short description of the disease

Obliterative bronchiolitis (*bronchiolitis obliterans*, popcorn lung) is a rare respiratory disease characterized by inflammation and scarring of the small airways of the lung, which can lead to severe and permanent respiratory impairment. The possibility of an association between ketones and this disease was suggested by the finding of a moderate to severe fixed obstructive lung disease consistent with this rare illness occurred among former workers of a microwave popcorn production plant in Missouri, USA. An investigation at this plant carried out by the USA National Institute for Occupational Safety and Health (NIOSH) revealed a higher prevalence of bronchial obstruction on spirometry testing. Increasing cumulative exposure to diacetyl, the predominant butter flavouring chemical present in the air of the plant, was associated with an increased prevalence of abnormal lung function.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: the main respiratory symptoms are cough and shortness of breath on exertion, which typically do not improve significantly when removing the exposure (such as at the end of the work shift, during weekends or on vacations). The onset of symptoms is gradual but severe symptoms can occur suddenly (at least in some cases). Several workers that have developed the disease in the setting of butter flavouring exposure during microwave popcorn production (or during the manufacture of flavourings themselves) have experienced a slow onset of symptoms similar to post-transplant patients.
- Examinations:
  - Lung function testing typically shows obstruction [low forced expiratory volume in one second (FEV_1) and reduced ratio between FEV_1 and forced vital capacity (FVC)] that does not improve with use of an inhaled bronchodilator. In moderate to severe disease, increased residual volume may occur.
  - The chest X-ray is usually normal, but high-resolution lung computed tomography (CT) with inspiratory and expiratory views may show heterogeneous aeration on the expiratory view.
  - The diagnosis can be confirmed by identifying bronchiolitis in an open (or thoracoscopic) lung biopsy specimen. However, the pathologic process in the lung is patchy in distribution, and it is only with great care, special stains, and the examination of many biopsy sections that the typical lesion can be identified. Since the process of obtaining the tissue is invasive and the yield is not certain, the need of a lung biopsy for a tissue diagnosis has to be evaluated with great care.

Exposure assessment

- History of occupational exposure: confirmed repeated or prolonged occupational exposure to diacetyl.
- Minimum duration of exposure: uncertain (bronchiolar fibrotic lesions observed in some cases associated with occupational diacetyl exposure have reportedly occurred within a span of a few months following the start of exposure).
- Maximum latent period: uncertain (many suspected cases reportedly occurred many years after first occupational exposure and in workers with relatively low diacetyl exposures).

Polyneuropathy caused by methyl isobutyl ketone (G62.2)

Short description of the disease

Exposure to methyl isobutyl ketone may lead, similarly to exposure to *n*-hexane, to polyneuropathy due to the neurotoxic activity of the main metabolite of both substances, 2,5-hexanedione. For this common aetiology, the clinical and histopathological pictures are similar. The disease usually appears after no less than one year of exposure. Main features are a symmetrical sensory or sensory-motor lesions starting from the most distal parts of the extremities. Recovery after the end of the exposure is usually, although not always, observed.

1.1.15 Diseases caused by alcohols, glycols, or ketones ICD Code T51, T52.3, T52.4 +Z57

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: numbness in the feet and hands are the first symptoms to appear, followed by muscle weakness (in particular at the lower legs and feet). Tendon reflexes may show only mild changes but hyporeflexia may be present. Distal paraesthesia, sensory anomalies, and muscle atrophy are usually present. In the most severe cases, paralysis of the respiratory muscles can occur.
- Examinations:
  - Electromyography (EMG) shows axonal disorders; the motor conduction velocity and the sensory conduction velocity are reduced, the distal motor latency is modified and the sensory potential amplitude is diminished, in addition to signs of denervation in affected muscles and small or absent sensory nerve action potentials.
  - Biopsies of peripheral nerves may show demyelination and infiltration of leucocytes.
  - Electroencephalography (EEG) is usually normal. In the most severe cases, however, it is possible to detect dysrhythmias, widespread or subcortical discomfort and irritation.
- Differentiation from non-occupational peripheral polyneuropathies, from the clinical point of view, is based on the symmetry of the paralysis, on the extreme rareness of sensory loss, and on the absence of changes in the cerebrospinal fluid.

Exposure assessment

- History of occupational exposure: confirmed occupational exposure to mixtures of ketones containing methyl isobutyl ketone (MIBK) via inhalation or dermal contact and, when available, environmental measures of the ketone concentration in the air of the working environment, as well as biological monitoring of urinary 2,5-hexanedione in samples collected after the end of the work shift.
- Minimum duration of exposure: one year.
- Maximum latent period: three years.

Key actions for prevention	Most alcohols, glycols and ketones used as industrial solvents actually replace more hazardous hydrocarbon solvents, such as has occurred in the formulation of adhesives and paints, degreasers, and consumer products and in some extraction processes. There is a constant pressure to substitute pure organic solvents with water-solvent mixtures to decrease the risk of fires. In most applications, (such as in painting) solvent-solute mixtures are evenly distributed on the substrates by gas-assisted spraying; the solvent is expected to evaporate at ambient temperature, and more efficiently when heated. This process intrinsically causes the production of a large amount of solvent-contaminated ambient air in workplaces and the concomitant exposure of workers. Whenever possible, such as in car production, air spray painting is performed in enclosures (by remote-controlled devices), where localized aspiration allows a reduction in the volume of waste air, to recover the organic solvent for recycling or safe disposal, and to abate residual solvent by chemical (water scrubbing, adsorption on charcoal and subsequent thermal desorption and combustion) and biological (bio-filtration) means. Respiratory and body protection of workers is used whenever they need to enter painting booths and when painting, paint removal, and other spray applications are performed in open spaces. Often, due to the large amount of released solvent vapours, filter masks are not adequate since the filters quickly saturate. These factors need to be considered especially for workers in the informal sector, whose access to accurate information on the chemical nature of the solvents they use (most often, complex technical mixtures of chemicals) and to directions for safe use is often very limited. In addition, re-use and recycling of solvent containers, their uncontrolled dumping and even the use of scrap containers for civil and household use can lead to inadvertent acute and massive exposure, often with health and life-threatening consequences. The use of correct labelling (understandable in the local languages), of warning signs and pictograms, and of safe-closure and non-reusable containers can help to avoid the most serious accidents. Many countries enforce, and some professional associations suggest, exposure limits for safe exposure to most of the chemical compounds used as industrial reagents and solvents. The group of experts considered that the following limits of exposure of workplace atmospheric concentrations (either considered as 8hr TWA or as STEL have been observed to provide a reasonable level of protection for workers' health and have been used in a number of countries.

1.1.15 Diseases caused by alcohols, glycols, or ketones	ICD Code T51, T52.3, T52.4 +Z57
Key actions for prevention	**ALCOHOLS** Methanol: 200 ppm as 8hr TWA, 250 ppm as STEL Ethanol: 1000 ppm as STEL n-Propanol: 100 ppm as 8hr TWA Isopropyl alcohol: 200 ppm as 8hr TWA, 400 ppm as STEL n-Butanol: 20 ppm as 8hr TWA sec-Butanol: 100 ppm as 8hr TWA iso-Butanol: 50 ppm as 8hr TWA tert-Butanol: 100 ppm as 8hr TWA Isoamyl alcohol: 100 ppm as 8hr TWA Methyl isobutyl carbinol: 25 ppm as 8hr TWA, 40 ppm as STEL Cyclohexanol: 50 ppm as 8hr TWA Methyl-cyclohexanol: 50 ppm as 8hr TWA Isooctyl alcohol: 50 ppm as 8hr TWA Propargyl alcohol: 1 ppm as 8hr TWA Glycidol: 2 ppm as 8hr TWA **GLYCOLS** Ethylene glycol: 25 ppm as 8hr TWA (vapour and aerosol), 50 ppm as STEL (vapour), 10 mg/m^3 as STEL (inhalable aerosol) Pentaerythritol: 10 mg/m^3 as 8hr TWA **KETONES** Acetone: 250 ppm as 8hr TWA; 500 ppm as STEL Methyl ethyl ketone: 200 ppm as 8hr TWA; 300 ppm as STEL 3-Methyl-2-butanone: 20 ppm as 8hr TWA Methyl propyl ketone: 150 ppm as STEL Diethyl ketone: 200 ppm as 8hr TWA; 300 ppm as STEL Methyl n-butyl ketone: 5 ppm as 8hr TWA; 10 ppm as STEL Methyl isobutyl ketone: 20 ppm as 8hr TWA; 75 ppm as STEL Methyl n-amyl ketone: 50 ppm as 8hr TWA Methyl isoamyl ketone: 20 ppm as 8hr TWA; 50 ppm as STEL Cyclohexanone: 20 ppm as 8hr TWA; 50 ppm as STEL Ethyl-n-butyl ketone: 50 ppm as 8hr TWA; 75 ppm as STEL Dipropyl ketone: 50 ppm as 8hr TWA Ethyl amyl ketone: 10 ppm as 8hr TWA Diisobutyl ketone: 25 ppm as 8hr TWA Methyl vinyl ketone: 0.2 ppm as STEL Mesityl oxide: 15 ppm as 8hr TWA; 25 ppm as STEL Isophorone: 5 ppm as STEL Diacetone alcohol: 50 ppm as 8hr TWA Diacetyl: 0.01 ppm as 8hr TWA; 0.02 ppm as STEL Hexafluoroacetone: 0.1 ppm as 8hr TWA

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Further reading

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   d. Annex I 120. Methylether, ethyl ether, Isopropyl ether, vinyl ether, dichloroisopropylether, guaiacol, methyl ether and ethyl ether of ethylene glycol. P 94-5.
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1.1.15 Diseases caused by alcohols, glycols, or ketones ICD Code T51, T52.3, T52.4 +Z57

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For the chemical entities listed below an entry exists in the collection of International Chemical Safety Cards (ICSC) hosted in the ILO website

ALCOHOLS

Name	Synonyms	ICSC
Methanol	Methyl alcohol, Carbinol, Wood alcohol	0057
Acetone	2-Propanone, Dimethyl ketone, Methyl ketone	0087
1-Butanol	n-Butanol, n-Butyl alcohol, Propyl carbinol, Butan-1-ol, Butyl alcohol	0111
2-Butanol	sec-Butyl alcohol, Butan-2-ol, 1-Methyl propanol, Methyl ethyl carbinol, Butylene hydrate	0112
Isobutanol	2-Methyl-1-propanol, Isopropyl carbinol, Isobutyl alcohol	0113
tert-Butanol	tert-Butyl alcohol, 2-Methyl-2-propanol, Trimethyl carbinol	0114
Glycidol	2,3-Epoxy-1-propanol, Oxirane methanol, 3-Hydroxypropylene oxide	0159
Cyclohexanol	Cyclohexyl alcohol, Hexahydrophenol, Hexalin	0243
2,5-Hexanediol	2,5-Dihydroxyhexane	0280
Methylcyclohexanol	Hexahydromethylphenol, Hexahydrocresol	0292
1-Methylcyclohexanol		0293
2-Methylcyclohexanol	o-Methylcyclohexanol, 2-Hexahydromethylphenol, o-Hexahydromethylphenol	0294
3-Methylcyclohexanol	m-Methylcyclohexanol, 3-Hexahydromethylphenol, m-Hexahydromethylphenol	0295
4-Methylcyclohexanol	p-Methylcyclohexanol, 4-Hexahydromethylphenol, p-Hexahydromethylphenol	0296
2-Hexanol	sec-Hexyl alcohol, Butylmethylcarbinol	0488
Isooctyl alcohol	Isooctanol (mixed isomers), Methylheptyl alcohol (mixed isomers)	0497
2-Methyl-1-butanol	2-Methyl butanol-1, sec-Butylcarbinol	0506
1-Pentanol	n-Amyl alcohol, n-Butyl carbinol, n-Pentyl alcohol	0535
3-Pentanol	Diethyl carbinol, sec-n-Amyl alcohol	0536
1-Propanol	Propyl alcohol, Propan-1-ol	0553
Isopropyl alcohol	2-Propanol, Propan-2-ol, Isopropanol, Dimethylcarbinol	0554
Triisopropanolamine	Tri-2-propanolamine, Tris(2-hydroxypropyl)amine, 1,1',1"-Nitrilotripropan-2-ol	0592
3,5,5-Trimethylhexanol	3,5,5-Trimethylhexylalcohol, Isononyl alcohol	0608
Methyl isobutyl carbinol	4-Dimethyl butan-2-ol, 4-Methyl-2-pentanol, Methyl amyl alcohol	0665
Propargyl alcohol	2-Propyn-1-ol	0673
Furfuryl alcohol	2-Furanmethanol, 2-Furancarbinol, 2-Hydroxymethylfuran, Furfural alcohol	0794
Isoamyl alcohol	3-Methyl-1-butanol, Isopentyl alcohol, Isobutylcarbinol	0798
2-Ethylhexanol	2-Ethyl-1-hexanol, 2-Ethylhexyl alcohol	0890
Phenethyl alcohol	2-Phenylethane-1-ol, Benzeneethanol, Phenylethyl alcohol	0936
1-Octanol	n-Caprylic alcohol, n-Octanol, Heptyl carbinol, 1-Hydroxyoctane, n-Octyl alcohol	1030
Triethanolamine	2,2',2"-Nitrilotriethanol, Trihydroxytriethylamine	1034

Name	Synonyms	ICSC
1-Heptanol	Heptane-1-ol, n-Heptyl alcohol, 1-Hydroxyheptane, n-Heptanol	1082
2-Heptanol	sec-Heptyl alcohol, Amyl methyl carbinol, 1-Methylhexanol, 2-Heptyl alcohol, 2-Hydroxyheptane	1083
1-Hexanol	Hexyl alcohol, n-Hexanol, n-Hexyl alcohol, 1-Hydroxyhexane, Amyl carbinol, Caproyl alcohol	1084
1,4-Butanediol	1,4-Butylene glicol, 1,4-Dihydroxybutane, 1,4-Tetramethylene gycol, Tetramethylene 1,4-diol	1104
2-Octanol	Capryl alcohol, 1-Methyl-1-heptanol, 2-Hydroxy-n-octane, Hexylmethylcarbinol	1170
Nonoxynol-9	Nonoxynol-9, Nonyl phenoxypolyethoxyethanol	1558
N-Methyl diethanolamine	2,2`-(Methylimino)bis-ethanol, Diethanolmethylamine, Bis(2-hydroxyethyl)methylamine	1600
1-(2-Butoxypropoxy) -2-propanol	Dipropylene glycol monobutyl ether, Dipropylene glycol butyl ether, DPGnBE, 1-(2-Methyl-2-butoxy-ethoxy)-2-propanol	1616

GLYCOLS

Name	Synonyms	ICSC
Ethylene glycol	1,2-Ethanediol, 1,2-Dihydroxyethane	0270
Propylene glycol	1,2-Propanediol, Methyl ethylene glycol, 1,2-Dihydroxypropane	0321
Diethylene glycol	Ethylene diglycol, 2,2'-Dihydroxyethyl ether, 3-Oxypentane-1,5-diol, 2,2'-Oxydiethanol, 2,2'-Oxybisethanol	0619
Hexylene glycol	2-Methyl-2,4-pentanediol, 2,4-Dihydroxy-2-methylpentane	0660
Dipropylene glycol	2,2'-Dihydroxydipropyl ether, 1,1'-Dimethyldiethylene glycol, 1,1'-Oxydipropan-2-ol Bis(2-hydroxypropyl) ether	1055

KETONES

Name	Synonyms	ICSC
Acetone	2-Propanone, Dimethyl ketone, Methyl ketone	0087
Methyl ethyl ketone	Ethyl methyl ketone, 2-Butanone, MEK, Methyl acetone	0179
Benzophenone	Diphenyl ketone, Benzoylbenzene, Phenyl ketone	0389
Cyclohexanone	Ketohexamethylene, Pimelic ketone, Cyclohexyl ketone	0425
Cyclopentanone	Ketocyclopentane, Adipic ketone	0427
2-Hexanone	Methyl n-butyl ketone, n-Butyl methyl ketone, MBK	0489
Diisobutyl ketone	2,6-Dimethyl-4-heptanone, Isovalerone, 2,6-Dimethylheptan-4-one	0713
Methyl isoamyl ketone	5-Methylhexan-2-one, MIAK, 2-Methyl-5-hexanone	0815
Methyl propyl ketone	2-Pentanone, Ethyl acetone, MPK	0816
3-Pentanone	Diethyl ketone, Dimethylacetone, Methacetone	0874
Ethyl n-butyl ketone	3-Heptanone, Butyl ethyl ketone	0889
Methyl n-amyl ketone	2-Heptanone, Amyl methyl ketone, Methyl pentyl ketone	0920
Hexafluoroacetone	1,1,1,3,3,3-Hexafluoro-2-propanone, Perfluoroacetone	1057
4-Methoxy -4-methyl-2-pentanone	4-Methoxy-4-methylpentan-2-one, 4-Methyl-4-methoxy-2-pentanone, 4-Methoxy-4-methylpentanone-2	1098
2,3-Butanedione	Diacetyl, Dimethylglyoxal, Dimethyl diketone, 2,3-Diketobutane, Butanedione	1168
5-Methyl-3-heptanone	5-Methyl heptan-3-one, 3-Heptanone, 5-methyl, Ethyl amyl ketone, Ethyl sec-amyl ketone	1391
Dipropyl ketone	Heptan-4-one, Butyrone	1414
Methyl vinyl ketone	3-Buten-2-one, Methylene acetone	1495

▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
1.1.15	Acute/chronic diseases caused by alcohols	T51	NE61&XM6U34
1.1.15	Respiratory tract irritation	J68	CA81.Z
1.1.15	Upper respiratory inflammation	J68.2	CA81.2
1.1.15	Conjunctivitis	H10.2	9A60.Z
1.1.15	Corneal ulcer	H16.0	9A76
1.1.15	Corneal scar and opacity	H17.9	9A77.Z
1.1.15	Corneal oedema	H18.2	9A78.2Z
1.1.15	Acute systemic poisoning by methanol	T51.1	NE61&XM7KD9
1.1.15	Toxic optic neuropathy due to methanol toxicity	H46	9C40.1Z &XM7KD9
1.1.15	Visual disturbances and blindness due to methanol toxicity	H53-H54	9D5Y,9D90.4 &XM7KD9
1.1.15	Acute systemic poisoning by isopropyl alcohol	T51.2	NE61&XM5531
1.1.15	Irritant contact dermatitis	L24	EK02
1.1.15	Allergic contact dermatitis	L23	EK00
1.1.15	Chronic toxic encephalopathy	G92	8D43.0Z
	Occupational exposure to toxic agents in other industries Solids, liquids, gases or vapours	Z57.5	QD84.2

ILO	Disease name	ICD-10	ICD-11
1.1.15	Acute diseases caused by glycols	T52.3	NE61& XM0W28
1.1.15	Acute systemic poisoning by ethylene glycol	T52.3	NE61&XM1762
1.1.15	Acute toxic encephalopathy due to ethylene glycol	G92	8D43.0Z &XM1762
1.1.15	Acute systemic poisoning by diethylene glycol	T52.3	NE61&XM55M8
1.1.15	Acute toxic encephalopathy due to diethylene glycol	G92	8D43.0Z &XM55M8
1.1.15	Irritant contact dermatitis	L24	EK02

ILO	Disease name	ICD-10	ICD-11
1.1.15	Acute/chronic diseases caused by ketones	T52.4	NE61&XM9UX0
1.1.15	Respiratory tract irritation	J68	CA81.Z
1.1.15	Acute chemical pneumonitis and bronchitis	J68.0	CA81.0
1.1.15	Upper respiratory inflammation	J68.2	CA81.2
1.1.15	Conjunctivitis	H10.2	9A60.Z
1.1.15	Corneal ulcer	H16.0	9A76
1.1.15	Corneal scar and opacity	H17.9	9A77.Z
1.1.15	Corneal oedema	H18.2	9A78.2Z
1.1.15	Acute systemic poisoning by acetone	T52.4	9A78.2Z
1.1.15	Acute poisoning by methyl ethyl ketone (MEK)	T52.4	NE61&XM7U59
1.1.15	Acute systemic poisoning by methyl isobutyl ketone (MIBK)	T52.4	NE61&XM9LD3
1.1.15	Acute toxic encephalopathy	G92	NE61&XM5H65
1.1.15	Irritant contact dermatitis	L24	8D43.0Z
1.1.15	Allergic contact dermatitis due to methyl vinyl ketone	L23	EK02
1.1.15	Obliterative bronchiolitis due to diacetyl	J68.4	EK00
1.1.15	Polyneuropathy caused by methyl isobutyl ketone	G62.2	CA81.Y

1.1.16 Diseases caused by asphyxiants like carbon monoxide, hydrogen sulfide, hydrogen cyanide or its derivatives	ICD Code T58, T59.6, T57.3 +Z57
General characteristics of the causal agent	Asphyxiant gases are toxic chemical agents that hamper respiratory gas exchange. They are classified separately from inert gases based on their physiological effects. Inert gases (such as nitrogen, rare gases, and gaseous hydrocarbons) can be potentially lethal when occurring in excessive concentrations in breathable air with decreased ambient oxygen levels (e.g. following accidental spillage of liquid nitrogen, liquid petroleum gas or helium occuring in confined spaces). On the contrary, the toxicity of asphyxiants is based on different biochemical mechanisms, such as prevention of the transportation of oxygen by the blood (carbon monoxide), inhibition of cellular respiration (carbon monoxide, hydrogen sulfide, and hydrogen cyanide) and other specific mechanisms (mainly featured by carbon monoxide and hydrogen sulfide). *Carbon monoxide* (CO), CAS number 630-08-0, molecular mass 28.0, is an odourless, tasteless, colourless and non-irritant gas with a density close to that of air. Apart from being produced naturally by the human body as a signalling molecule, CO is generated by the incomplete combustion of organic material. It diffuses easily through walls and ceilings, mixes well with air (forming explosive mixtures above a volume concentration of 12.5% in air), and has a self-ignition temperature of 609°C. Although it is not very reactive under ordinary conditions, CO corrodes some metals (such as nickel) even at ambient temperature by reacting to form volatile, explosive, and toxic metal carbonyls. *Hydrogen sulfide* (H_2S), CAS number 7783-06-4, molecular mass 34.1, is a weakly acidic, colourless, flammable gas with a very characteristic odour of rotten eggs. At high concentrations or by continuous exposure, it rapidly paralyzes the sense of smell, to the point that the exposed subject is no longer aware of high ambient concentrations (thus representing a potentially fatal exposure). It is heavier than air and displaces oxygen. It burns in air, and even distant ignition can be sparked by electrical charges generated by its own flow or movement. Its combustion products (sulphur oxides) are even more acidic, irritant, and toxic at high concentrations or by prolonged contact. H_2S corrodes some plastics and many metals, including silver, by generating a porous, dark, non-protective layer of metal sulfide. H_2S reacts violently with strong oxidants, causing fire and explosion hazards. H_2S is produced by the human body as a signalling molecule, in small quantities. *Hydrogen cyanide* (HCN, Hydrocyanic acid, Prussic acid, Formonitrile, [liquefied]), CAS number 74-90-8, molecular mass 27.03, is a weakly acidic, colourless gas, slightly soluble in ether, miscible with water and alcohol, with a characteristic odour of bitter almonds (which approximately one-third of the general population cannot detect), and with a density close to that of air. HCN can be easily condensed to the liquid state under ambient conditions (at 26°C). In workplaces, HCN can be present as either a gas or a liquid. It reacts violently with oxidants and with hydrogen chloride in alcoholic mixtures, causing fire and explosion hazards. Sodium cyanide is a white crystalline powder that produces hydrogen cyanide in contact with acids or acid salts. Potassium cyanide is a white deliquescent solid that produces hydrogen cyanide in contact with acids or acid salts. Calcium cyanide is a white crystalline solid whose aqueous solution gradually liberates hydrogen cyanide.
Occupational exposures	*Carbon monoxide* is widely employed in large amounts in the chemical industry as syngas, a mixture of hydrogen, carbon monoxide, and carbon dioxide, which is typically generated in the chemical plant in close proximity to the reactor where it is employed. All combustion of organic materials that occurs in low ambient levels of air or oxygen end up producing carbon monoxide at higher or lower concentrations. Potentially fatal occupational exposures can occur in poorly ventilated engine rooms such as in ships and heating plants, in motor vehicle garages, in coal and fuel furnaces, and in incineration facilities for solid wastes. Firing of demolition explosives, such as in tunnel construction works, and accidental fires also generate large amounts of carbon monoxide. The main occupations exposed to carbon monoxide are thus firefighters, garage personnel, road tunnel workers, metallurgical workers, gas, petroleum, and chemical industries, heating facilities, car mechanics exposed to motor vehicle exhaust, and workers engaged in incineration processes. Since methylene chloride is metabolised to carbon monoxide, occupational exposure to this chlorinated solvent may contribute to exposure to this gas, resulting in increased carboxyhaemoglobin levels. It is important to recall that exposure to cigarette smoke is a common source of personal exposure to carbon monoxide, independently from the occupational setting.

1.1.16 Diseases caused by asphyxiants like carbon monoxide, hydrogen sulfide, hydrogen cyanide or its derivatives	ICD Code T58, T59.6, T57.3 +Z57
Occupational exposures	*Hydrogen sulfide* has limited industrial uses, but it is formed in the hydrodesulphurization of natural gas and crude oil in the petrochemical industry. As a by-product, it is decomposed to yield pure elemental sulphur, which currently represents the valuable starting material for the production of sulphuric acid and has almost completely eliminated the use of mined sulphur. Hydrogen sulfide is generated from the rotting of natural organic waste, as in the anaerobic fermentation of manure to obtain biogas and in sewage-water treatment plants. It occurs as a by-product in the production of artificial cellulose fibres with viscose carbon disulfide (see item 1.1.10 for more details). Alkali sulfides are employed in the extraction of non-ferrous metals, as a reducing agent in the hide and leather industry, and in textile and leather dyeing. Other sources of occupational exposure to hydrogen sulfide are the production of sucrose from sugarcane and sugar-beet, the production of viscose cellulose, some operations in farming such as stirring of manure and opening of fermentation tanks, and inspection of waste-water canals, sludge pits, burials, and cemeteries. The circumstances of acute exposure to hydrogen sulfide in enclosed spaces can easily give rise to accidents with multiple fatalities when workers try to assist the affected person creating a chain of subsequent intoxications, when appropriate respiratory protection is not available. *Hydrogen cyanide* is widely employed in large amounts in the industrial synthesis of several nitrogen-containing organic compounds such as acrylonitrile and adiponitrile, and is usually generated in the chemical plant often by the catalysed reaction of ammonia and methane, i.e., the Andrussow process, upstream and in close proximity to the reactor where it is employed. In these conditions, the potential for exposure is usually minimal since most interventions in the areas of the chemical plant where exposure is possible are carried out through remote controlled actuators. HCN adsorbed on diatomaceous earth or wood dust, stored in tightly sealed containers, and mixed with strong odorising chemicals to warn the operators, has been long used to rapidly kill rodents in large storage areas mainly in the tanks of grain carrier ships and barges, and occasionally ground silos. This procedure is relatively safe when performed by well-trained operators who use industrially formulated devices. On the contrary, in the informal sector, the same procedure is occasionally performed by extemporarily mixing sodium or potassium cyanide and strong acids and can generate very hazardous and potentially fatal conditions for the operators. This procedure is inefficient for sanitizing areas where the carcasses of the rodents cannot be easily spotted and removed and has been replaced by the use of baits medicated with anticoagulant rodenticides (see item 1.1.36 for more details), although in this case, the effect of the pesticide is delayed. Sodium cyanide is employed in gold mining for the exploitation of low-concentration or diffuse ores, such as auriferous sand. Gold is selectively converted to the cyano-aurate complex by a mixture of alkali cyanide and air, and the precious metal is recovered in the elemental state by destroying the complex. In this process, workers are exposed both to alkali cyanides and to released hydrogen cyanide. Potassium cyanide is used to electrolytically refine platinum, for metal colouring, and to separate gold, silver, and copper from platinum. Calcium cyanide is used as a fumigant, as it releases hydrogen cyanide when exposed to air. It is used as a stabilizer for cement, in stainless steel manufacture and as herbicide, rodenticide, fertilizer, and defoliant. All combustion processes of nitrogen-containing organic materials such as wool, grains, polyamide and polyurethane fibres, and foams generate harmful and potentially lethal concentrations of hydrogen cyanide.

1.1.16 Diseases caused by asphyxiants like carbon monoxide, hydrogen sulfide, hydrogen cyanide or its derivatives — ICD Code T58, T59.6, T57.3 +Z57

Toxicological profile, main health effects and diagnostic criteria

Short toxicological profile

Carbon monoxide is rapidly absorbed by breathing and binds very strongly to the iron in the haeme group of haemoglobin and to other similar cellular targets, such as the cytochromes of the respiratory chain. CO has a > 200-fold greater affinity for haemoglobin than oxygen, a fact that explains most of its toxic effect. The level of carboxyhaemoglobin (HbCO) is proportional to the dose of environmental CO breathed by the subject and during the period shortly after poisoning can be used both to confirm an episode of intoxication and to estimate the airborne concentration as well as the duration of the exposure. Increased levels of HbCO cause tissue hypoxia and trigger other cytotoxic mechanisms in specific cells. In the heart, impairment of the respiratory chain can precipitate ischaemia in subjects with pre-existing heart disease, even at levels that are tolerated by healthy subjects. In neurones, carbon monoxide itself or CO-induced hypoxia triggers the excitotoxic release of glutamate and neuronal death. The strong yet reversible binding of CO to haeme iron can be displaced just by shifting the chemical equilibrium with a much higher concentration of oxygen in the tissue. This effect is accomplished by treating the intoxicated subject with oxygen at a higher partial pressure than in ambient air. Carbon monoxide released from its binding with haeme iron can be eliminated with the exhaled air or biochemically mineralized to formic acid, a cause of systemic acidosis, which can be controlled by infusion of bicarbonate, and to carbon dioxide.

Hydrogen sulfide is a natural product of human metabolism and a demonstrated neurotransmitter gas, which is involved in cerebral and cardiovascular function. H_2S is synthesized endogenously in a variety of mammalian tissues via two pyridoxal-5'-phosphate-dependent enzymes responsible for the metabolism of L-cysteine: cystathionine β-synthase (CBS) and cystathionine γ-lyase. The systemic toxicity of H_2S is comparable to that of hydrogen cyanide (see below) since the hydrosulfide anion binds to iron in the mitochondrial cytochrome-c oxidase enzyme even more strongly than cyanide thus impairing cellular respiration.

The biological half-life of exogenously administered hydrogen sulfide is of a few minutes. There are three known pathways of H_2S degradation: mitochondrial oxidation to thiosulfate, which is further converted to sulfite and sulfate; cytosolic methylation to dimethylsulfide; and sulfhaemoglobin formation after binding to haemoglobin.

Note that concentrations of H_2S above 100 ppm cause olfactory paralysis and thus inhibit the worker from perceiving the presence of the compound in the environment.

Hydrogen cyanide is very rapidly absorbed both by breathing and in the stomach, generated from cyanides absorbed by ingestion. A hydrogen cyanide concentration of 300 mg/m³ in the air will kill a human within about 10 minutes. The mechanism responsible for the very rapid onset of toxicity is the binding of the cyanide anion to the iron in the haeme group of haemoglobin and to the cytochromes of the respiratory chain. The only known detoxification pathway of cyanide is biotransformation into the much less toxic thiocyanate anion by the action of the inducible enzyme rhodanese. Enzymic induction of rhodanese is ineffective in counteracting acute intoxication, but it has a biological role in dealing with small amounts of cyanide, which is naturally present in some vegetables, in particular fruit seeds, where cyanide is stored as the benzaldehyde cyanohydrin glucoside amygdalin.

The cyanide anion binds strongly to the cobalt ion of cobalamin (vitamin B12). For this reason, very large doses of hydroxocobalamin, far exceeding those of the physiological pool, quickly administered by rapid intravenous infusion are used in the cocktail of antidotes for HCN poisoning, which also includes inhalation of amyl nitrite and infusion or oral administration of sodium thiosulphate. The same treatment is used to treat subjects intoxicated by organic nitriles, such as acrylonitrile.

1.1.16 Diseases caused by asphyxiants like carbon monoxide, hydrogen sulfide, hydrogen cyanide or its derivatives ICD Code T58, T59.6, T57.3 +Z57

Name of the diseases and ICD code: **Acute diseases caused by asphyxiants**
(Specific disease code) **+T58, T59.6, T57.3 +Z57**

Respiratory tract irritation (J68), Acute chemical pneumonitis and bronchitis (J68.0), Pulmonary oedema (J68.1), Upper respiratory inflammation (J68.2), Reactive airways dysfunction syndrome (RADS) (J68.3), Irritant-induced occupational asthma (J68.3)

Short description of the disease

Effects of the inhalation of hydrogen sulfide and cyanide on the respiratory tract range from mild irritation of mucous membranes lining the airways up to chemical pneumonitis, upper airways inflammation, cough and bronchospasm, irritant asthma, RADS, severe non-cardiogenic pulmonary oedema, and respiratory failure.

Occupational exposure to hydrogen sulfide even at low concentrations can irritate airways (rhinorrhoea, sneezing, and sore throat); for higher concentrations, more severe effects can be observed, such as bronchopneumonia and pulmonary oedema (wheezing, shortness of breath, chest tightness, haemoptysis, and a feeling of suffocation).

Differing from hydrogen cyanide and sulfide, carbon monoxide does not produce irritant effects.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: cough, sore throat, dyspnoea, tachypnoea, wheezing, tachycardia, and chest pain. Pulmonary oedema and respiratory failure can occur in the most severe cases.
- Examinations:
  - Chest X-rays can show a picture of acute bronchitis, pneumonitis or oedema.
  - Pulmonary function tests may show a picture of acute obstruction.

Exposure assessment

- History of occupational exposure: confirmed acute occupational exposure to hydrogen sulfide or hydrogen cyanide and, if available, detection of the compounds, their metabolites or early effect indicators in biological fluids (e.g. blood and urinary thiosulphate, urinary thiocyanate and blood thiocyanate/cyanide and carboxyhaemoglobin) as well as workplace air monitoring.
- Minimum duration of exposure: few minutes.
- Maximum latent period: few minutes for hydrogen sulfide; 24 hours for hydrogen cyanide.

Burns and corrosions of eye and adnexa (T26.0-T26.1, T26.5-T26.6), Conjunctivitis (H10.2), Keratoconjunctivitis (H16.2), Corneal erosion (H16.0), Retinal haemorrhage (H35.6), Irritant contact dermatitis (L24), Frostbite (T35), Chemical burns and corrosions of external body surface (T20-T25), Burns and corrosions of internal organs (T28.0-T28.2, T28.5-T28.7)

Short description of the disease

Direct contact of asphyxiant gases (or their liquid phase) with skin and mucosae can cause irritation, up to burns and corrosion.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms:
  - Acute *carbon monoxide* poisoning can result in erythematous skin lesions, in particular intraepidermal or subepidermal vesicles (bullae), retinal haemorrhages, and visual alterations. Conjunctival petechiae may be present.
  - *Hydrogen sulfide* at low concentrations can irritate eyes and cause conjunctivitis, keratoconjunctivitis and, at higher concentrations, punctate corneal erosion. Symptoms include stinging, redness, foreign body sensation and acute eye pain, photophobia and lacrimation. A single high exposure to H_2S irritates the skin, causing local redness and swelling. H_2S in the liquid phase may be corrosive and cause frostbite, a cryogenic injury resembling a burn; frostbite of the lips and mouth may result from contact with the liquid. Prolonged contact will result in corrosion of the skin. For further details on the clinical features of frostbite, refer to item 1.2.6(1).
  - Skin and eye irritation may follow contact with the liquid phase of hydrogen cyanide.

1.1.16 Diseases caused by asphyxiants like carbon monoxide, hydrogen sulfide, hydrogen cyanide or its derivatives ICD Code T58, T59.6, T57.3 +Z57

- Examinations:
  - An ophthalmic examination should be performed, including visual acuity and slit lamp inspection of the cornea. Corneal ulceration and cystic changes may be seen on corneal examination.
  - Evidence of various degrees of irritation and burns of skin and mucous membranes at physical examination.

Exposure assessment

- History of occupational exposure: confirmed acute occupational exposure to carbon monoxide, hydrogen sulfide, or hydrogen cyanide and, if available, detection of the compounds, their metabolites or early effect indicators in biological fluids (e.g. HbCO, blood and urinary thiosulphate, blood thiocyanate/cyanide and urinary thiocyanate) as well as workplace air monitoring.
- Minimum duration of exposure: few seconds for hydrogen sulfide; few minutes for carbon monoxide and hydrogen cyanide.
- Maximum latent period: 48 hours.

Toxic encephalopathy due to carbon monoxide (G92)

Short description of the disease

Carbon monoxide toxicity depends on the good affinity of this compound for haemoglobin, with the synthesis of carboxyhaemoglobin and the inhibition of oxygen transport to the organism. Carboxyhaemoglobin can be easily measured in blood, and specific symptoms of poisoning can be anticipated based on the proportion of HbCO out of total haemoglobin. Toxic encephalopathy following poisoning by CO is very similar to the one due to solvents (see item 1.1.38) and can manifest with symptoms ranging from headache and dizziness to increased respiratory rate and, eventually, death. This disorder has also been called “organic brain syndrome” or “organic brain disease”.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms (per cent values refer to HbCO/Hb concentrations):
  - 10-30%: headache, dizziness, weakness, malaise, nausea, confusion, disorientation, visual disturbances and a cherry-pink colour of the skin.
  - 30-50%: dyspnoea under physical exercise, increased pulse and respiratory rate.
  - >50%: immediate risk for life.
  - Note that, even in the absence of clinically evident signs of hypoxia or respiratory distress, the poisoned subject can be severely hypoxic and may collapse during slight exertion.
  - Neuropsychiatric effects can be observed as delayed effects of poisoning, with the onset of symptoms occurring 1-3 weeks after the exposure event.
  - Long-term, low-level exposures to CO have been observed to lead to neuropathic effects.
- Examinations:
  - In severe intoxication, the colour of the venous blood is similar to the arterial blood (as haemoglobin acquires a bright red colour when converted into carboxyhaemoglobin).
  - Carboxyhaemoglobin concentration in blood and percent of HbCO out of total haemoglobin could help in guiding the diagnosis.
  - An electrocardiogram may show a picture of ischaemia.
  - Electroencephalogram may show various degrees of brain injury.

Exposure assessment

- History of occupational exposure: confirmed occupational exposure to high levels of carbon monoxide and, if available, detection of CO in the working environment and of carboxyhaemoglobin in the blood (end of shift collection). When occupational hygiene measurements are not available, it may prove difficult to attribute long-term neuro-psychiatric effects to CO exposure.
- Minimum duration of exposure: few minutes.
- Maximum latent period: 24 hours.

1.1.16 Diseases caused by asphyxiants like carbon monoxide, hydrogen sulfide, hydrogen cyanide or its derivatives ICD Code T58, T59.6, T57.3 +Z57

Toxic encephalopathy due to hydrogen sulfide (G92)

Short description of the disease

In the case of exposure to high levels of hydrogen sulfide, signs of central nervous system impairment can be observed.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms:
  - Headache, vertigo, dizziness, nausea, and vomiting.
  - A phenomenon referred to as "knockdown" was reported in oil field workers to describe a sudden, brief loss of consciousness associated with amnesia, followed by immediate full recovery. This phenomenon usually occurs after short-term exposure to very high doses of H_2S (>2000 ppm, after only one or two breaths), which can cause sudden death if emergency treatment is not promptly performed.
  - In the most severely poisoned subjects, nonspecific neurological sequelae may follow, such as hyper-susceptibility to gas smells, fatigue, lack of energy, reduction in memory and attention.
- Examinations:
  - Electrocardiogram may show a picture of ischaemia.
  - Electroencephalogram may show various degrees of brain injury.

Exposure assessment

- History of occupational exposure: confirmed occupational exposure to high levels of hydrogen sulfide and, when available, detection of blood and urinary thiosulphate, as well as workplace air monitoring.
- Minimum duration of exposure: few seconds.
- Maximum latent period: few minutes.

Toxic encephalopathy due to hydrogen cyanide (G92)

Short description of the disease

The toxicity of hydrogen cyanide depends on the affinity of cyanide ions for cytochrome oxidase and haemoglobin. Another mechanism involves its direct action on the respiratory centres. Concentrations around 18-36 ppm can cause irritation of the eyes and respiratory tract, nausea, weakness and headache. Exposures in the order of 100 ppm can cause loss of consciousness, apnoea and death after 30-60 minutes. Exposures up to 270 ppm are immediately fatal.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms:
  - Headache, dizziness and vertigo, bitter almonds taste, agitation and confusion, nausea and vomiting, tachypnoea, dyspnoea, tachycardia, angina pectoris, loss of consciousness, seizures, convulsions, cardiovascular shock, coma and death. In the poisoned subject, the pink colour of the skin is typically present, even with concurrent hypoxia.
  - Symptoms may take several weeks to resolve completely, but delayed neurological impairments following prolonged tissue hypoxia may occur.
  - A chronic toxic encephalopathy may be observed as a delayed consequence of severe acute poisoning.
- Examinations:
  - The pink colour of the skin may be noticed at objective evaluation, even in mild intoxication.
  - Electrocardiogram may show a picture of ischaemia.

Exposure assessment

- History of occupational exposure: confirmed occupational exposure to high levels of hydrogen cyanide and, when available, detection of urinary thiocyanate and blood thiocyanate/cyanide, as well as workplace air monitoring.
- Minimum duration of exposure: few minutes.
- Maximum latent period: 24 hours.

1.1.16 Diseases caused by asphyxiants like carbon monoxide, hydrogen sulfide, hydrogen cyanide or its derivatives ICD Code T58, T59.6, T57.3 +Z57

Hypoxic brain injury due to asphyxiants (G93.1)

Short description of the disease

In the presence of asphyxiant gases in ambient air, the quantity of inspirable oxygen is significantly reduced, with consequent hypoxic hypoxia. In the most severe cases, hypoxic hypoxia may cause ischaemic brain damage, often followed by long-term neurological sequelae, major neurological deficits and neurobehavioral changes. From a pathogenetic point of view, poisoning by these agents does not usually cause brain damage unless hypotension supervenes, when brain injury may arise in a distribution resembling that seen in global ischaemia after cardiac arrest. In this context, both hydrogen sulfide and cyanide are potent and immediate depressors of blood pressure. On the other hand, the action of carbon monoxide is more complex than the other two asphyxiant agents, but the mechanism is poorly understood.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: the severity of the clinical picture ranges from mild features, such as temporary memory loss, reduced ability to move body parts, and reduced concentration capacity, to more serious ones, i.e., seizures, coma and, eventually, brain death.
- Examinations: CT or MRI may show bilateral necrosis of the globus pallidus (common), but also of the basal ganglia, hippocampus and white matter.

Exposure assessment

- History of occupational exposure: confirmed occupational exposure to carbon monoxide, hydrogen sulfide, or hydrogen cyanide and, if available, detection of the compounds, their metabolites or indicators of early effect in biological fluids (e.g. HbCO, blood and urinary thiosulphate, blood thiocyanate/cyanide and urinary thiocyanate) as well as workplace air monitoring. When occupational hygiene measurements are not available, it may prove difficult to attribute long-term neuro-psychiatric effects to CO exposure.
- Minimum duration of exposure: few minutes.
- Maximum latent period: one year.

Obliterative bronchiolitis due to asphyxiants (J68.4)

Short description of the disease

Exposure to asphyxiant gases can result in patchy consolidation of the lungs. Obliterative bronchiolitis (or *bronchiolitis obliterans*) is a documented complication in gassing accidents involving fire smoke and hydrogen sulfide, characterized by granulation tissue shaped as polypoid tufts inside the airway lumen, involving predominantly the respiratory bronchioles, the alveolar ducts, and the alveoli. Inhalation of hydrogen sulfide, in particular, has been shown to cause inflammation or fibrosis, narrowing or blocking the airway, as well as scarring of the lungs, which can lead to obstruction of the small airways and ultimately impaired lung function. Chronic high exposure can lead to gradual worsening of symptoms over time, whilst acute exposure can result in lung damage that may be asymptomatic for a short period but can then lead to rapid death due to severe obstructive breathing impairment.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: dry cough, dyspnoea, wheezing.
- Examinations:
  - Lung function testing typically shows obstruction [low forced expiratory volume in one second (FEV_1) and reduced ratio between FEV_1 and forced vital capacity (FVC)] that does not improve with use of an inhaled bronchodilator. In moderate to severe disease, increased residual volume may occur.
  - The chest X-ray is usually normal, but high-resolution lung computed tomography (CT) with inspiratory and expiratory views may show heterogeneous aeration on the expiratory view.
  - The diagnosis can be confirmed by identifying bronchiolitis in an open (or thoracoscopic) lung biopsy specimen. Lung biopsy shows diffuse alveolar damage and epithelial injury of the bronchioles, and other signs including inflammation, a proliferation of granulating tissue tufts or plugs in the lumen of bronchioles, and fibrosis, narrowing or blocking the airway. However, the pathologic process in the lung is patchy in distribution, and it is only with great care, special stains, and the examination of many biopsy sections that the typical lesion can be identified. Since the process of obtaining the tissue is invasive and the yield is not certain, the need for a lung biopsy for a tissue diagnosis has to be evaluated with great care.

1.1.16 Diseases caused by asphyxiants like carbon monoxide, hydrogen sulfide, hydrogen cyanide or its derivatives ICD Code T58, T59.6, T57.3 +Z57

Exposure assessment

- History of occupational exposure: confirmed acute or prolonged occupational exposure to asphyxiant gases (hydrogen sulfide in particular) and, if available, detection of the compounds, their metabolites or indicators of early effect in biological fluids as well as workplace air monitoring.
- Minimum duration of exposure: few minutes for acute effects; some weeks for chronic effects.
- Maximum latent period: one month for acute effects; six months for chronic effects.

Exacerbation of ischaemic heart disease (I24.9) and of toxic encephalopathy (G92) due to carbon monoxide

Short description of the disease

A prolonged exposure to carbon monoxide causing an HbCO/Hb ratio higher than 5% can exacerbate pre-existing heart disease, up to angina and hence infarction.

In previously acutely poisoned subjects, as well as in subjects continuously exposed to high doses, cognitive and behavioural effects can be observed. Features of neuropsychiatric impairment may persist or subsequently improve.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms:
  - In those with existing heart disease, angina and infarction.
  - In subjects having already experienced acute or chronic poisoning by carbon monoxide, changes in personality, agitation, anxiety, depression, impulsiveness and moodiness, disorientation, impairment of memory, learning ability, attention span, coordination and abstract thinking, suicidal tendencies, and personality deterioration.
- Examinations:
  - Electrocardiogram may show the typical picture of ischaemia.
  - Electroencephalography (EEG) may show various degree of abnormalities.
  - CT or MRI may show bilateral necrosis of the globus pallidus, but also of the basal ganglia, hippocampus and white matter.
  - Neurobehavioral testing may show some of the above mentioned cognitive, emotional or behavioural alterations.

Exposure assessment

- History of occupational exposure: confirmed occupational exposure to high levels of carbon monoxide and, if available, detection of CO in the working environment and of carboxyhaemoglobin in the blood (end of shift collection).
- Minimum duration of exposure: few minutes.
- Maximum latent period: 18 months for cardiovascular or neurological effects.

Ototoxic hearing loss due to asphyxiants (H91.0)

Short description of the disease

Vestibular dysfunction as a chronic effect of asphyxiant gases poisoning may occur. Asphyxiant gases, especially carbon monoxide, with the potential to disrupt intrinsic antioxidant pathways or to enhance the generation of reactive oxygen species, can produce a permanent hearing loss, in particular in the presence of noise.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: evidence of tinnitus and mild hearing loss to profound deafness with difficulty in communicating in noisy environments.
- Examinations: pure-tone test shows a sensorineural hearing loss.

Exposure assessment

- History of occupational exposure: confirmed occupational exposure to carbon monoxide, hydrogen sulfide, or hydrogen cyanide and, if available, detection of the compounds, their metabolites or indicators of early effect in biological fluids as well as workplace air monitoring.
- Minimum duration of exposure: few minutes.
- Maximum latent period: six months.

1.1.16 Diseases caused by asphyxiants like carbon monoxide, hydrogen sulfide, hydrogen cyanide or its derivatives	ICD Code T58, T59.6, T57.3 +Z57
Key actions for prevention	Enclosure of sources of asphyxiants is the most effective preventive strategy, and the use of personal protective equipment, such as breathing apparatus, is mandatory whenever workers are in areas where a health-threatening concentration of those gases may be present. For carbon monoxide, several devices for the real-time measurement of airborne concentration are available as portable and wearable appliances. For hydrogen sulfide and hydrogen cyanide, passive monitors based on colorimetric reactions have long been used. As regards *carbon monoxide*, in modern chemical and metallurgical plants, the areas where hazardous concentrations of CO can build up are usually restricted in access, and personnel who needs to operate in those areas is always equipped with closed-circuit respirators, backed-up by well-trained staff, and provided with on-site real-time measurement of CO concentration performed with portable devices. In assessing the overall risk of exposure, both airborne concentration levels and exposure time need to be considered, as well as the potential role of effect modification by physical exercise. A limit of 25 ppm as an 8hr TWA of workplace atmospheric concentrations has been observed by the group of experts to provide a reasonable level of protection for workers' health and to be used in a number of countries. This limit is recommended for occupational exposure to carbon monoxide to maintain blood HbCO levels below 3.5%, to minimize the potential for adverse neurobehavioral changes, and to minimize cardiovascular work and exercise capacities. Workers suffering from ischaemic heart disease should avoid exposure to CO. Workers who smoke often have HbCO levels above 3.5%. Accordingly, exogenous carbon monoxide exposures place them at additional risk of adverse health effects. Pregnant workers and their unborn children may be at additional risk, especially under conditions of heavy labour, high temperatures, or at high elevations as the risk of adverse health effects related to CO exposure increases at high altitudes. Pregnant workers should thus avoid exposure to carbon monoxide because of a risk of foetal death, developmental disorders and cerebral anoxic lesions in the foetus. As regards *hydrogen sulfide*, limits corresponding to 1 ppm as 8hr TWA and 5 ppm as short-term exposure limit (STEL) of workplace atmospheric concentrations have been observed by the group of experts to provide a reasonable level of protection for workers' health and to be used in a number of countries. These limits are intended to protect against all the unwanted effects of hydrogen sulfide. Because hydrogen sulfide is extremely malodorous, it is necessary to control exposure below these limits to prevent complaints of odour. Personnel operating in areas where *hydrogen cyanide* can be present should always be equipped with closed-circuit respirators and backed-up by well-trained staff, including on-site real-time measurements and medical assistance. Specific antidotes must be available. A limit of 4.7 ppm of workplace atmospheric concentrations as STEL has been observed by the group of experts to provide a reasonable level of protection for workers' health and to be used in a number of countries. For all three gases, other specific limit values have been established by a number of countries and specialized agencies to ensure that workers can escape from a given contaminated environment in the event of failure of the respiratory protection equipment and to indicate a maximum level above which only a highly reliable breathing apparatus, providing maximum worker protection, is permitted. As a valuable example, below are the Immediately Dangerous for Life and Health (IDLH) values issued by the USA National Institute for Occupational Safety and Health (NIOSH): • 1,200 ppm for carbon monoxide. • 100 ppm for hydrogen sulfide. • 50 ppm for hydrogen cyanide.

1.1.16 Diseases caused by asphyxiants like carbon monoxide, hydrogen sulfide, hydrogen cyanide or its derivatives ICD Code T58, T59.6, T57.3 +Z57

Further reading

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For the chemical entities listed below an entry exists in the collection of International Chemical Safety Cards (ICSC) hosted in the ILO website

Name	Synonyms	ICSC
Carbon monoxide	Carbon oxide, Carbonic oxide	0023
Hydrogen sulfide	Sulfur hydride	0165
Hydrogen cyanide, liquefied	Hydrocyanic acid, Prussic acid, Formonitrile	0492

▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
1.1.16	Acute/chronic diseases caused by asphyxiants	T58, T59.6, T57.3	NE61, &XM1X11, &XM7FL0, &XM8WA4
1.1.16	Respiratory tract irritation	J68	CA81.Y
1.1.16	Acute chemical pneumonitis and bronchitis	J68.0	CA81.0
1.1.16	Pulmonary oedema	J68.1	CA81.1
1.1.16	Upper respiratory inflammation	J68.2	CA81.2
1.1.16	Reactive airways dysfunction syndrome (RADS), Irritant-induced occupational asthma	J68.3	CA81.Y
1.1.16	Burns and corrosions of eye and adnexa	T26.0-T26.1, T26.5-T26.6	NE00 & XA3RB1, XA9K79, XA0JV9, XA53T1, XA4AX5
1.1.16	Conjunctivitis	H10.2	9A60.Z
1.1.16	Keratoconjunctivitis	H16.2	9A7Z
1.1.16	Corneal erosion	H16.0	9A78.8
1.1.16	Retinal haemorrhage	H35.6	9B78.5
1.1.16	Irritant contact dermatitis	L24	EK02
1.1.16	Frostbite	T35	NE4Z
1.1.16	Chemical burns and corrosions of external body surface	T20-T25	ND9Z, NE10, ND9Y, NE2Z, ND99.1, NE11
1.1.16	Burns and corrosions of internal organs	T28.0-T28.2, T28.5-T28.7	NE02, NE0Z,
1.1.16	Toxic encephalopathy due to carbon monoxide	G92	8D43.0Y &XM1X11
1.1.16	Toxic encephalopathy due to hydrogen sulfide	G92	8D43.0Z &XM7FL0
1.1.16	Toxic encephalopathy due to hydrogen cyanide	G92	8D43.0Z &XM8WA4
1.1.16	Hypoxic brain injury due to asphyxiants	G93.1	8B24
1.1.16	Obliterative bronchiolitis due to asphyxiants	J68.4	CA81.Y
1.1.16	Exacerbation of ischaemic heart disease due to carbon monoxide	I24.9	BA4Z
1.1.16	Exacerbation of toxic encephalopathy due to carbon monoxide	G92	8D43.0Y
1.1.16	Ototoxic hearing loss due to asphyxiants	H91.0	&XM1X11

1.1.17 Diseases caused by acrylonitrile — ICD Code T65.8 +Z57

General characteristics of the causal agent	Acrylonitrile (C_3H_3N, also known as cyanoethylene or vinyl cyanide, CAS number 107-13-1, molecular mass 53.1) is a chemical compound that is liquid at room temperature, volatile, flammable, colourless or pale yellow, lighter-than-water, slightly water-soluble, and with a weakly pungent odour. The vapour is heavier than air and tends to migrate along the ground. Vapours can ignite, and explosion can be triggered by exothermic, spontaneous polymerization, particularly in the presence of oxygen, visible light or heat. Thermal decomposition yields toxic fumes, including hydrogen cyanide, ammonia, carbon monoxide and nitrogen oxides. Acrylonitrile polymers do not revert thermally to the monomer, but rather decompose to the above-mentioned compounds.
Occupational exposures	Occupational exposure to acrylonitrile can occur in chemical plants where the compound is produced, in the preparation of its derived products (mainly polymers), in the manufacture of synthetic fibres and plastic materials from the polymers, and in the transformation of polymers into goods. The largest use of this bulk chemical is in the production of acrylic and modacrylic textile fibres. Other large uses include acrylonitrile-butadiene-styrene (ABS) and styrene-acrylonitrile plastics, nitrile-butadiene rubber and other polymeric materials, as well as the production of acrylamide, acrylic acid, and adiponitrile. Thermoplastics, including ABS, are also used in the emerging field of three-dimensional printing, currently employed in a variety of industrial, consumer, and biomedical research applications.
Toxicological profile, main health effects and diagnostic criteria	
Short toxicological profile	Acrylonitrile does not accumulate in living organisms and is rapidly distributed throughout the body after exposure via inhalation. Elimination occurs mainly via the urine. Systemic effects of exposure to acrylonitrile are in part related to its oxidative biotransformation to much more toxic products, such as the respiratory poison free cyanide and the genotoxic and immunogenic 2-cyanoethylene oxide. Toxicity in the human shows considerable variability, related to the polymorphism of several enzymes involved in acrylonitrile metabolism, i.e., bio-transforming enzymes (such as CYP2E1 of the cytochrome P450 system), the target glutathione S-transferases and the cyanide-detoxifying rhodanese. Nonetheless, no comprehensive toxicity pathway has been established for health effects associated with acrylonitrile exposure.

Name of the diseases and ICD code: **Acute diseases caused by acrylonitrile** *(Specific disease code)* **+T65.8 +Z57**

Respiratory tract irritation (J68), Burns and corrosions of respiratory tract (T27), Burns and corrosions of external body surface (T20-T25), Burns and corrosions of mouth, pharynx and oesophagus (T28.0-T28.1, T28.5-T28.6), Burns and corrosions of eye and adnexa (T26.0-T26.1, T26.5-T26.6), Conjunctivitis (H10.2), Corneal ulcer (H16.0), Irritant contact dermatitis (L24)

Short description of the disease

Acute poisoning by acrylonitrile may cause a plethora of manifestations similar to the ones following exposure to most volatile organic compounds (i.e., solvents). Due to the large variability of human susceptibility, it is very hard to identify a safe level of exposure both for acute and chronic effects. Exposures to acrylonitrile at concentrations between 20 and 100 ppm (i.e., 44 to 220 mg/m^3) for 20 to 45 minutes can cause irritation of the nose and throat and a feeling of fullness in the chest.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: industrial workers who inhaled acrylonitrile at 16-100 ppm for 20 to 45 minutes experienced generic symptoms such as dull headache, fullness of chest, irritation of all mucous membranes, feeling of apprehension and irritability. Skin contact with acrylonitrile may cause severe and painful symptoms on the exposed skin (direct irritation, erythema, dermatitis) and on mucous membranes and corneal damage in the eye. Since acrylonitrile is readily absorbed into leather or clothing, blistering may appear unless the contaminated articles are removed promptly, and the underlying skin washed.
- Examinations: chest X-rays may show signs of bronchitis, with increased bronchovascular markings.

Exposure assessment

- History of occupational exposure: confirmed occupational exposure to airborne or liquid acrylonitrile via inhalation, skin or eye contact and, when available, workplace air monitoring data and determination of blood cyanide/acrylonitrile and urinary thiocyanates. For the latter, a possible contribution from tobacco smoking should also be taken into account.
- Minimum duration of exposure: few minutes.
- Maximum latent period: 24 hours.

1.1.17 Diseases caused by acrylonitrile — ICD Code T65.8 +Z57

Acute systemic poisoning (T65.8)

Short description of the disease

Symptoms and signs of acute acrylonitrile systemic poisoning follow the onset of tissue anoxia and resemble those of cyanide poisoning, although the onset is slower and symptoms are more persistent over time.

Initial symptoms of acrylonitrile poisoning occur after 20 to 45 minutes of exposure at air levels between 20 and 100 ppm (i.e., 44 to 220 mg/m^3) and include headache, irritation, anxiety, dizziness, disorientation, impaired judgment, salivation, nausea and vomiting.

At higher doses, symptoms include limb weakness, convulsions and respiratory failure, but these may be delayed by between 15 minutes and several hours after exposure. Liver failure has also been described.

In the later stages, collapse and cardiac arrest may occur without warning. When exposure is continued over time, the levels of blood cyanide may progressively increase well before the appearance of symptoms.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms:
  - *Central nervous system:* headache, bitter almonds taste, salivation, nausea, irritability, anxiety, weakness, ataxia, dizziness, impaired judgment, stupor, loss of consciousness, dyspnoea, burning sensation in the throat, respiratory depression, cyanosis, convulsions, coma and death. In some cases, hysterical or even violent behaviour has also been observed.
  - *Cardiovascular system:* tachycardia, angina pectoris and cardiac arrest can be observed.
  - *Liver:* liver dysfunction compounded by depletion of glutathione stores and characterized by jaundice, malaise, anorexia, and leucocytosis can be observed.
- Examinations:
  - Electrolyte profile examination may show acid-base imbalance, metabolic acidosis in particular.
  - Chest X-rays may show a picture of bronchitis with increased bronchovascular markings.
  - ECG may show arrhythmias and ischaemic changes.
  - Liver function tests may show an increase in liver enzymes.

Exposure assessment

- History of occupational exposure: confirmed occupational exposure to airborne or liquid acrylonitrile via inhalation, skin or eye contact and, when available, workplace air monitoring data and determination of blood cyanide/acrylonitrile and urinary thiocyanates. For the latter, a possible contribution from tobacco smoking should also be taken into account.
- Minimum duration of exposure: few minutes.
- Maximum latent period: 24 hours.

Name of the diseases and ICD code: **Chronic diseases caused by acrylonitrile** *(Specific disease code)* **+T65.8 +Z57**

Allergic contact dermatitis (L23)

The potential of acrylonitrile to cause skin sensitization following repeated or prolonged exposure has been reported. For further details on clinical manifestations and exposure assessment criteria of allergic contact dermatitis, refer to item 2.2.1.

Carcinogenic effects of acrylonitrile

Acrylonitrile is classed as a possible carcinogen (2B) by the IARC. It causes a range of tumours in animal experiments. The association between acrylonitrile exposure and lung cancer in humans is not considered strong enough to class it as a grade 1 carcinogen.

1.1.17 Diseases caused by acrylonitrile — ICD Code T65.8 +Z57

Key actions for prevention

Acrylonitrile may be released into ambient air during its manufacture and use. Since occupational exposure occurs most likely via inhalation, basic interventions are represented by total enclosure and appropriate local exhaust ventilation systems at workplaces, during use and manufacturing of synthetic fibres, ABS and other materials.

In the absence of total enclosure or in case of emergency, the use of a chemical respirator is the preferred method in controlling exposure. However, to avoid exposure of workers entering enclosures that have been previously sanitized by purgings with acrylonitrile, such as in tanks, a closed breathing apparatus and a suitably resistant hazmat suit are a better choice. Rubber protective clothing should be inspected and washed frequently because it will soften and swell over time, thus losing its protective purpose or, having absorbed acrylonitrile, will itself become a source of exposure.

An important hazard is fire and explosion. The low flashpoint (i.e., the lowest temperature at which vapours above a volatile combustible substance ignite in air when exposed to flame) indicates that sufficient vapour is evolved at normal temperatures to form a flammable mixture with air. Acrylonitrile has the ability to polymerize spontaneously under the action of light or heat, which may lead to an explosion even when it is kept in closed containers. It must therefore never be stored without some form of inhibition. The danger of fire and explosion is intensified by the lethal nature of the fumes and vapours evolved, such as ammonia and hydrogen cyanide.

The group of experts considered that a limit of exposure of workplace atmospheric concentrations of 2 ppm for acrylonitrile (as 8hr TWA) has been observed to provide a reasonable level of protection for workers' health and to be used in a number of countries.

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For the chemical entities listed below an entry exists in the collection of International Chemical Safety Cards (ICSC) hosted in the ILO website

Name	Synonyms	ICSC
Acrylonitrile	Cyanoethylene; 2-Propenenitrile; Vinyl cyanide	0092

▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
1.1.17	Acute diseases caused by acrylonitrile	T65.8	NE61&XM23N0
1.1.17	Respiratory tract irritation	J68	CA81
1.1.17	Burns and corrosions of respiratory tract	T27	NE01
1.1.17	Burns and corrosions of external body surface	T20-T25	ND9Z, NE10
1.1.17	Burn and corrosion of mouth, pharynx and oesophagus	T28.0-T28.1, T28.5-T28.6	NE02
1.1.17	Burns and corrosions of eye and adnexa	T26.0-T26.1, T26.5 -T26.6	NE00
1.1.17	Conjunctivitis	H10.2	9A60.Z
1.1.17	Corneal ulcer	H16.0	9A76
1.1.17	Irritant contact dermatitis	L24	EK02
1.1.17	Acute systemic poisoning	T65.8	NE61&XM23N0
1.1.17	Allergic contact dermatitis	L23	EK00

1.1.18 Diseases caused by oxides of nitrogen or its compounds	ICD Code T59.0 + Z57
General characteristics of the causal agent	Nitrogen oxides (NO_x) (or nitric oxides) are the binary compounds of nitrogen and oxygen, which are mainly formed at high temperature and pressure levels or under the action of electric sparks. Nitrogen oxide (NO) and nitrogen dioxide (NO_2) are airborne contaminants, which give rise to acidic compounds (nitrous and nitric acid) when dissolved in water. Nitric acid is formed in ambient air from nitrogen oxides, which are released as a by-product of fuel combustion, mainly in car engines, with other minor sources being the combustion of fossil fuels for power generation and biomass burning. Natural sources of nitrogen oxides with strong relevance in atmospheric chemistry and climate control are high-voltage electrical sparks in the atmosphere, such as lightning. *Nitric oxide* (NO, also known as nitrogen oxide, CAS number 10102-43-9, molecular mass 30.01) is a colourless and odourless gas with a density similar to air. It is quickly oxidized to brown nitrogen dioxide by air and other combustible and reducing materials. *Nitrogen dioxide* (NO_2, CAS number 10102-44-0, molecular mass 46.01) is liquid at room temperature and a reddish-brown gas above 21°C, which is heavier than air and has a strong irritating odour. It is a strong oxidant, which reacts violently with combustible and reducing materials, and decomposes in water forming nitric acid and nitric oxide. Under ambient conditions, nitrogen dioxide is in chemical equilibrium with its dimer (i.e., the colourless dinitrogen tetroxide, N_2O_4, commonly referred to as nitrogen tetroxide). *Nitrogen tetroxide* (N_2O_4, CAS number 10544-72-6, molecular mass 92.01) is a colourless powerful oxidizer and has a strong irritating odour. *Nitrous oxide* (N_2O, also known as laughing gas or nitrous, CAS number 10024-97-2, molecular mass 44.01) is a colourless gas, heavier than air, with a characteristic faint, sweet odour. The gas is a strong oxidant above 300°C and may form explosive mixtures with ammonia, carbon monoxide, hydrogen sulfide, oil, grease, and fuels.
Occupational exposures	Nitrogen oxides are released from the exhaust of motor vehicles, the burning of coal, oil, or natural gas, and during arc welding, electroplating, engraving, and dynamite blasting. Nitrogen oxides are intermediates in the production of nitric acid and are sometimes employed as chemical reagents in the synthesis of fine chemicals and in the nitration of organic compounds, especially in the manufacturing of civil explosives, rocket fuels, and military ordnance. Fumes of nitrogen oxides are generated in fires in the low-temperature aging of nitrate-containing materials, such as fertilizers (ammonium nitrate) and aged ammunition. *Nitric oxide* is produced by high-temperature catalysed reaction of oxygen-nitrogen mixtures, and is employed in situ to produce ammonia and nitric acid, which are major chemical commodities. *Nitrogen dioxide* is a common airborne pollutant generated by internal combustion engines, in fires, and in industrial and military explosions. *Nitrogen tetroxid*e is used as an oxidizer rocket propellant (often with the addition of a small percentage of nitric oxide) and can be stored as a liquid at room temperature. *Nitrous oxide* has limited industrial uses as an oxidant in high-temperature oxy-gas welding, as rocket propellant, and as a gasoline combustion booster in racing car engines. To avoid fire and explosions, care has to be taken that the gas stream does not come into contact with organic oil lubricants, which are therefore substituted by graphite or molybdenum sulphide. It is used as an aerosol spray propellant in consumer products, such as shaving foams and whipped cream. The inhalation of nitrous dioxide for the purpose of surgical anaesthesia has been a common practice for more than a century. Its use at levels lower than those necessary to induce surgical anaesthesia is currently increasing to assist obstetric delivery in minor surgery and in dentistry for slight sedation of the patient. As such, anaesthetists are particularly at risk because of their exposure to gas potentially leaking from the equipment and from the patients' exhaled breath. The main exposure route to all these compounds is through inhalation and contact with the skin and the mucosae of the eyes and upper respiratory tract.

1.1.18 Diseases caused by oxides of nitrogen or its compounds — ICD Code T59.0 + Z57

Toxicological profile, main health effects and diagnostic criteria

Short toxicological profile	Nitrogen oxides exert their action on human health mainly by means of their irritant and corrosive power and through their effect on the structures of the respiratory, central nervous, and haemopoietic systems. NO_2 is thought to damage lungs through its conversion to nitric and nitrous acids in the distal airways, which directly damage lung cells with functional and structural roles. It can initiate the generation of free radicals that eventually lead to damage of cell membranes, protein oxidation, and lipid peroxidation. Finally, alteration of macrophage and immune function by NO_2 reduces resistance to infections. Damage to the lower structures of the respiratory tract can lead to scarring of the bronchioles, which is the pathological basis for life-threatening episodes that may occur even several weeks following exposure to nitrogen gases.

Name of the diseases and ICD code: **Acute diseases caused by oxides of nitrogen**
(Specific disease code) **+T59.0 +Z57**

Mucous membrane irritation (J68), Bronchitis and pneumonitis (J68.0), Pulmonary oedema (J68.1), Upper respiratory inflammation (J68.2), Reactive airways dysfunction syndrome (RADS) (J68.3), Irritant-induced acute occupational asthma (J68.3), Acute irritant contact dermatitis (L24), Burns and corrosions of external body surface (T20-T25), Burns and corrosions of eye and adnexa (T26.0-T26.1, T26.5-T26.6), Conjunctivitis (H10.2), Corneal ulcer (H16.0), Blindness (H16.1)

Short description of the disease

Inhalation exposure to high concentrations of nitrogen oxides can irritate eyes, nose, throat, and lungs, causing cough and shortness of breath, tiredness, and nausea. Exposure to higher levels can cause rapid burning, spasms, swelling of tissues in the throat and upper respiratory tract, reduced oxygenation of body tissues, a build-up of fluid in the lungs, and can be fatal. Repeated exposure to nitrogen oxides can cause chronic inflammatory diseases of the airways, such as reactive airways dysfunction syndrome and asthma, up to lung oedema. The skin and eyes can experience serious burns when coming into contact with high concentrations of nitrogen oxide gases or nitrogen dioxide liquid.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms:
  - Immediate response to nitrogen oxides and their compounds may include coughing, rhinitis, fatigue, weakness, sweating, choking, nausea, vomiting, abdominal pain, headache, drowsiness, dizziness, euphoria (N_2O), confusion, unconsciousness (NO, N_2O), convulsion (NO) and difficulty in breathing. Initial irritant effects may be accompanied by evidence of blue lips, fingers, and nails.
  - NO and NO_2 are skin and eye irritants (pain, redness). Skin moisture in contact with liquid N_2O or high concentrations of its vapour can result in nitric acid formation, leading to second and third-degree skin burns. Nitric acid may cause yellowing of the skin and erosion of dental enamel.
  - Liquid nitrogen oxides cause severe eye burns even with brief contact. High concentrations of the gas after prolonged exposure may cause clouding of the cornea and blindness.
- Examinations:
  - Evidence of various degrees of irritation and burns of skin and mucous membranes at physical examination.
  - Pulmonary auscultation should document signs of respiratory impairment (e.g. crackles or wheezes).
  - Chest X-ray may show increased bronchovascular markings, diffuse bilateral alveolar infiltrates or severe bilateral pulmonary oedema.
  - Pulmonary function tests may show signs of obstruction, such as reduced FEV_1 and FVC.

Exposure assessment

- History of occupational exposure: confirmed high exposure to nitrogen oxides, also considering that:
  - Nitrogen dioxide and nitric oxides are usually present whenever nitric acid is used: in solutions at concentrations <30% are irritants, and at concentrations >30% are highly corrosive and can cause second or third-degree burns after short contact. Intense irritation of the respiratory tract usually occurs at workplace air concentration > 4 ppm (10 mg/m^3).
  - Exposure to 5-25 ppm of NO_2 usually results in severe cough, potentially accompanied by haemoptysis and chest pain. Exposure for less than an hour to 100-150 ppm can result in fatal pulmonary oedema arising between 3 and 72 hours after the onset of the initial irritant effects.
- Minimum duration of exposure: few minutes.
- Maximum latent period: few hours for irritation; 72 hours for pulmonary oedema.

1.1.18 Diseases caused by oxides of nitrogen or its compounds ICD Code T59.0 + Z57

Silo-filler's disease (J68.8)

Short description of the disease

Natural microbiological processes that occur in fermenting grass converted into animal fodder in the micro-aerophilic environment of the silo produce nitrogen dioxide. Exposure to high levels of gases released from the silo may give rise to severe respiratory effects and even to acute fatalities ("silo-filler's disease"). Clinical presentation of silo-filler's disease depends on the duration of exposure and the concentration of the gas. Without proper precautions, farm workers entering a silo or remaining near the open hatches during the first 10 days of filling may experience various degrees of exposure.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: coughing, breathlessness, expiratory wheezes, emission of a bloody foam from the mouth. Pulmonary infiltrates may be observed as delayed effects.
- Examinations:
  - Chest X-ray shows evidence of diffuse alveolar damage with hyaline membranes and pulmonary oedema.
  - Blood gas analysis documents hypoxaemia.
  - Respiratory function assessment (if possible) should document transient airway obstruction.

Exposure assessment

- History of occupational exposure: confirmed exposure to silo gases.
- Minimum duration of exposure: few minutes.
- Maximum latent period: few hours.

Methaemoglobinaemia (D74.8)

Short description of the disease

High-dose exposure to NO may convert haemoglobin-Fe^{+2} ion to Fe^{+3}, causing methaemoglobinaemia. The production of methaemoglobin starts at levels of exposure in the order of 40 ppm and becomes relevant over 100 ppm.

Diagnostic criteria

Clinical manifestations

- Methaemoglobinaemia is characterized by intense cyanosis accompanied by a wide variety of manifestations, ranging from headache, irritability, dizziness, drowsiness, numbness, vertigo, weakness, fatigue, nausea, vomiting, dyspnoea, chest and abdominal pain, aphonia, air hunger, up to unconsciousness, seizures, tachycardia, cardiac dysrhythmias, and potentially death.
- The severity of symptoms depends on the percentage of haemoglobin that has been oxidized to methaemoglobin; severe poisoning is usually present when methaemoglobin represents more than 40 -50% of total haemoglobin. Metabolic acidosis may be present.

Exposure assessment

- History of occupational exposure: confirmed occupational exposure to NO, at concentrations usually above 40 ppm.
- Minimum duration of exposure: minutes.
- Maximum latent period: hours.

1.1.18 Diseases caused by oxides of nitrogen or its compounds — ICD Code T59.0 + Z57

Acute effects on the central nervous system (T41.0)

Short description of the disease

N_2O is employed as an anaesthetic gas in hospitals, for both full narcosis and mild sedation. Exposure to the gas can cause various degrees of central nervous system impairment.

Diagnostic criteria

Clinical manifestations

They may vary widely according to the dose of gas that has been inhaled, ranging from dizziness and drowsiness, to analgesia and euphoria, up to unconsciousness.

Exposure assessment

- History of occupational exposure: confirmed occupational exposure to nitrogen oxides, N_2O in particular.
- Minimum duration of exposure: few minutes.
- Maximum latent period: few minutes.

Name of the diseases and ICD code: **Chronic diseases caused by oxides of nitrogen**
(Specific disease code) **+T59.0 +Z57**

Bronchiolitis obliterans (J68.4)

Short description of the disease

Bronchiolitis obliterans is a delayed and progressive obstructive disease of the airways that can progress into permanent respiratory disability. This rare and life-threatening form of fixed obstructive lung disease is due to damage to, and subsequent scarring of, the epithelium of the small airways. As diagnosis is not easy in the initial stages, particular attention has to be taken not to misdiagnose the clinical picture of bronchiolitis obliterans as asthma, bronchitis, emphysema or bronchiectasis.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: dry cough, shortness of breath, fatigue, and wheezing.
- Examinations:
  - Pulmonary function tests may show fixed airway obstruction with normal diffusing capacity.
  - Chest X-ray, CT, and high resolution CT may show a picture of centrilobular nodules with a linear branching pattern (so-called “tree-in-bud pattern”) and mosaic attenuation with areas of air trapping.

Exposure assessment

- History of occupational exposure: confirmed occupational exposure to high concentrations of nitrogen oxides.
- Minimum duration of exposure: some weeks.
- Maximum latent period: few weeks.

Chronic obstructive pulmonary disease (COPD) (J68.4)

Short description of the disease

Repeated exposure to nitrogen oxides resembles the common chronic inflammatory disease of the airways characterized by variable and recurring symptoms, reversible airflow obstruction, and bronchospasm. With prolonged or repeated exposures, the phenotype of COPD may evolve. For further details on COPD, refer to the dedicated item 2.1.9.

Diagnostic criteria

Clinical manifestations

- Symptoms include coughing, breathlessness, expiratory wheezes.
- Examinations:
  - Lung function testing may show evidence of airways obstruction (FEV_1/FVC ratio less than 0.7).
  - Radiographs of patients with chronic bronchitis typically show only nonspecific peribronchial and perivascular markings.

1.1.18 Diseases caused by oxides of nitrogen or its compounds ICD Code T59.0 + Z57

Exposure assessment

- History of occupational exposure: confirmed occupational exposure to high concentrations of nitric oxides, considering that first symptoms may appear for concentrations as low as 0.3 ppm of NO_2.
- Minimum duration of exposure: some weeks.
- Maximum latent period: few weeks.

B12 Deficiency caused by exposure to nitrous oxide (D51.9)

Short description of the disease

Nitrous oxide exposure, typically self-administered as a form of substance abuse, oxidises B12, causing a syndrome of B12 deficiency. In severe cases there is sub-acute combined degeneration of the spinal cord.

Diagnostic criteria

Clinical manifestations

- Symptoms include malaise and nervous system symptoms (e.g. headache, speech difficulty, paresthesia of the lower extremities, lower limb weakness, ataxia).
- Examinations:
  - Macrocytic anaemia, serum B12 levels are low.
  - MRI may show degeneration of the spinal cord (hyperintensity).

Key actions for prevention	Indoor exposure to nitrogen oxides can be minimized by increasing ventilation, avoiding or limiting tobacco smoke and switching from combustion to electric heating and cooking appliances. Nitrogen oxides adversely affect children, pregnant workers, and the elderly because of the greater susceptibility of these subjects due to phases of development or underlying vulnerable health conditions. In several countries, gasoline engines are obligatorily fitted with catalytic converters, which reduce nitrogen oxides. Stationary plants that emit NO_x are equipped with "de-NO_x" units that reduce nitrogen oxides in combustion exhausts to elemental nitrogen gas by reaction with gaseous ammonia or with urea. To minimize exposure of surgical staff and other healthcare workers to nitrous oxide, improved devices with exhaust of exhaled air are used in hospitals, as well as alternative anaesthetic pharmaceuticals and procedures. The group of experts considered that the following limits of exposure of workplace atmospheric concentrations have been observed to provide a reasonable level of protection for workers' health and to be used in a number of countries: • Nitric oxide: 25 ppm as 8hr TWA. • Nitrogen dioxide: 0.2 ppm as 8hr TWA. • Nitrous oxide: 50 ppm as 8hr TWA.

Further reading

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6. Cheng HM, Park JH, Hernstadt D. Subacute combined degeneration of the spinal cord following recreational nitrous oxide use. BMJ Case Rep 2013; 2013:bcr2012008509. doi: 10.1136/bcr-2012-008509.

For the chemical entities listed below an entry exists in the collection of International Chemical Safety Cards (ICSC) hosted in the ILO website

Name	Synonyms	ICSC
Nitric oxide	Nitrogen oxide, Mononitrogen monoxide (cylinder)	1311
Nitrogen dioxide	Nitrogen peroxide (cylinder)	0930
Nitrous oxide	Dinitrogen monoxide, Hyponitrous acid anhydride, Laughing gas, Dinitrogen oxide (cylinder)	0067

▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
1.1.18	Acute/chronic diseases caused by oxides of nitrogen	T59.0	NE61& XM69M3
1.1.18	Mucous membrane irritation	J68	CA81
1.1.18	Bronchitis and pneumonitis	J68.0	CA81.0
1.1.18	Pulmonary oedema	J68.1	CA81.1
1.1.18	Upper respiratory inflammation	J68.2	CA81.2
1.1.18	Reactive airways dysfunction syndrome (RADS)	J68.3	CA81.Y
1.1.18	Irritant-induced acute occupational asthma	J68.3	CA81.Y
1.1.18	Acute irritant contact dermatitis	L24	EK02
1.1.18	Burns and corrosions of external body surface	T20-T25	ND9Z, NE10
1.1.18	Burns and corrosions of eye and adnexa	T26.0-T26.1, T26.5-T26.6	NE00
1.1.18	Conjunctivitis	H10.2	9A60.Z
1.1.18	Corneal ulcer	H16.0	9A76
1.1.18	Blindness	H16.1	9D90.Y
1.1.18	Silo fillers' disease	J68.8	CA81.Z
1.1.18	Methaemoglobinaemia	D74.8	3A93
1.1.18	Acute effects on the central nervous system	T41.0	NE60&XM73B5
1.1.18	Chronic bronchiolitis obliterans	J68.4	CA26.Z
1.1.18	Chronic obstructive pulmonary disease (COPD)	J68.4	CA22.Z
1.1.18	B12 Deficiency caused by exposure to nitrous oxide	D51.9	3A01.Z&NE61& XM73B5
	Occupational exposure to risk factors	Z57	QD84.Y

1.1.19 Diseases caused by vanadium and its compounds	ICD Code T56.8 +Z57
General characteristics of the causal agent	Vanadium (V), CAS number 7440-62-2, is the chemical element with atomic number 23 in the periodic table of the elements, is essentially mono-isotopic (^{50}V 0.25%, ^{51}V 99.75%), and has an atomic mass of 50.94 Da. Naturally occurring ^{50}V is weakly radioactive, with a very long half-life of $5*10^{17}$ years. Vanadium is classified in Group 5 (3-B; Transition metals) and features all oxidation numbers between -I, 0 (elemental) and V (vanadate). The colours of the four contiguous oxidation states of vanadium in water are lilac [Vanadium (II)], green [Vanadium (III)], blue [Vanadium (IV)], and yellow [Vanadium (V)]. In water, Vanadium (II) compounds are reducing agents, and Vanadium (V) compounds are oxidizing agents. Vanadium is a silvery grey, ductile and malleable metal, which occurs in the environment only in the form of its compounds. Among these, the most common are vanadium pentoxide, dioxide, and trioxide, ammonium metavanadate, and vanadium tetrachloride. Commercially important vanadium ores include the uranium mineral carnotite, patronite, and vanadinite. From tailings of carnotite, uranium was extracted as a pottery and glass pigment after extraction of vanadium for metallurgical use. Elemental vanadium resists corrosion from alkali and sulphuric and hydrochloric acid. It oxidizes at about 660°C in air, although an oxide layer forms even at room temperature. Currently, the greatest proportion of the world's vanadium production occurs from vanadium-containing magnetite. Vanadium is obtained from these ores by reduction as a ferrovanadium alloy that is directly used in steel alloying. Oxygen treatment of molten ferrovanadium preferentially oxidizes vanadium to its volatile pentoxide; vanadium pentoxide accumulates in metallurgical slags, which thus represent the primary source of pure vanadium, while non-ferrous ores are a secondary source. Crude oil contains small amounts of vanadium, which derives from that naturally contained in the respiratory pigment of ancient and current deep-sea living tunicates and ascidians from which oil was generated. Crude oil and bitumen from Venezuela, Mexico and Canada are relatively rich in vanadium, and their combustion concentrates the metal in the residual fuel ash, from which it can be extracted. The yearly world production of vanadium is about 80 thousand metric tons, as of 2017. Vanadium is an essential trace metal in biochemistry and metabolism, especially of marine organisms and microorganisms, but it seems to be of minor importance for humans. The chemical form of vanadium of greatest concern for occupational safety is vanadium pentoxide.
Occupational exposures	Occupational exposure to vanadium is possible in several production activities. The main ones are metallurgy during extraction and refining, where exposure to vanadium dioxide and trioxide can occur; the manufacture of iron-vanadium alloys in production of special, highly elastic steels; high-speed steel-HSS; the production of several special alloys (vanadium-gallium for high field magnets; alloys with copper, cobalt, titanium, chromium); the manufacture of tools, especially of vibration resistant cutting blades and drills. Other uses include the production of pigments for ceramics (vanadium pentoxide) and as dyeing mordant in the textile industry (vanadium sulphate and tetrachloride); the production and use of catalysts (vanadium silicates) for oxidation processes in the chemical industry, such as the production of sulphuric acid, of maleic anhydride from benzene (now mostly discontinued), and of phthalic anhydride from *o*-xylene and naphthalene. Minor uses include that as a photographic developer (vanadium pentoxide, ammonium metavanadate) and as a reagent in analytical chemistry (ammonium metavanadate). Vanadyl sulphate has attracted interest as a glucose-lowering treatment in non-insulin-dependent type 2 diabetes. Since vanadium oxides, pentoxide in particular, are produced during combustion of oil and other fossil fuels, significant exposure to furnace residues from oil refineries or to ash and soot from oil-fired boilers can occur in conduction, reparation, maintenance and cleaning of industrial boilers and gas turbine heat exchangers in thermal, mainly thermoelectric plants. Another source of exposure is from slags of ferrovanadium in the steel industry and from ore mining and milling.

1.1.19 Diseases caused by vanadium and its compounds — ICD Code T56.8 +Z57

Toxicological profile, main health effects and diagnostic criteria

Short toxicological profile	The general population can be exposed to vanadium from environmental sources, mainly through ingestion of contaminated food and water. On the other hand, workplace exposure to vanadium primarily occurs by inhalation of compounds, most of which are soluble in biological fluids. The most significant compounds, from a toxicological point of view, are vanadium pentoxide, sodium metavanadate, sodium orthovanadate, vanadyl sulfate, and ammonium vanadate. The solubility of vanadium compounds and the dimensions of their particulates affect their absorption at a respiratory level. The less soluble compounds can accumulate in the lungs, while the fraction that transfers to blood circulation is mainly carried by transferrins. Vanadium is rapidly excreted through urine, primarily within the first 24 hours after exposure. Ingested vanadium is largely excreted unabsorbed in the faeces. Vanadium can thus be found unaltered in blood, plasma and urine. Due to the oxidizing characteristics of vanadium (V) compounds in water, the acute and chronic exposures result in mucous membrane irritation, asthma, conjunctivitis, and contact dermatitis.

Name of the diseases and ICD code: **Acute diseases caused by vanadium or its compounds**
(Specific disease code) **+T56.8 +Z57**

Mucous membrane irritation (J68), Chemical bronchitis and pneumonitis (J68.0), Burns and corrosions of mouth, pharynx and oesophagus (T28.0-T28.1, T28.5-T28.6), Burns and corrosions of eyes and adnexa (T26.0-T26.1, T26.5-T26.6), Upper respiratory tract inflammation (J68.2), Burns and corrosion of respiratory tract (T27), Chemical pulmonary oedema (J68.1), Reactive airways dysfunction syndrome (RADS) (J68.3), Irritant-induced occupational asthma (J68.3), Irritant contact dermatitis (L24)

Short description of the disease

Exposure to vanadium fumes, dusts and vapours can induce acute irritation of eyes, mucous membranes, skin and the respiratory tract and, in the most severe cases, acute lung injury. Exposure to vanadium, usually as vanadium pentoxide, has been reported as a possible cause of irritant-induced occupational asthma, described especially in workers engaged in maintenance of oil-fired boilers, as the fly ash produced by some types of fuel oil could be very rich in vanadium.

The severity of the effects depends on the airborne concentration of the vanadium compounds and the duration of exposure, which causes a characteristic green-black discolouration of the tongue at high doses. A typical metallic taste accompanies intoxication.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms:
  - Profuse lacrimation, ocular burning and conjunctivitis.
  - Productive cough, breathlessness, chest pain, crackles, wheeze and haemoptysis. In the most severe cases, pulmonary oedema can be observed.
  - For details on clinical features of irritant contact dermatitis, refer to item 2.2.2.
- Examinations:
  - High occupational exposure to fly ash is often accompanied by reductions of forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) at pulmonary function testing; recovery is usually observed in no more than 10 days after the end of the exposure.
  - Chest radiograph is usually normal, although it may show nonspecific signs associated with coexisting respiratory infection or bronchiolitis or evidence of hyperinflation.

Exposure assessment

- History of occupational exposure: confirmed occupational exposure to vanadium (pentoxide in particular) and, when available, workplace air monitoring and measurements of biological markers, such as total blood, plasma, and urinary vanadium. Collection of urine samples should be performed at the end of the last working day of the working week. Normal urinary vanadium concentrations in unexposed populations are in the order of 20-40 ng/L.
- Minimum duration of exposure: few hours.
- Maximum latent period: 48 hours for most irritant effects (even shorter for irritant-induced asthma).

1.1.19 Diseases caused by vanadium and its compounds ICD Code T56.8 +Z57

Name of the diseases and ICD code: **Chronic diseases caused by vanadium**
(Specific disease code) **+T56.9 +Z57**

Sensitizer-induced occupational asthma (J45.0), Allergic contact dermatitis (L23)

Exposure to sodium metavanadate vapours, ammonium vanadate powder and vanadium pentoxide fumes and dust has been associated with sensitization and occupational asthma. More rarely, vanadium has been observed to cause an allergic skin rash.

For more details on clinical features and exposure assessment criteria of sensitizer-induced occupational asthma and allergic contact dermatitis, refer to items 2.1.7 and 2.2.2, respectively.

Chronic bronchitis and emphysema (J68.4), Chronic rhinitis (J31.0), Chronic pharyngitis (J31.2)

Short description of the disease

Chronic exposure to vanadium and its compounds may produce chronic bronchitis with or without emphysema. Chronic rhinitis and pharyngitis have been reported after long-term exposure. In high exposure scenarios, the tongue of the exposed workers may show a typical greenish or black colour.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: chronic cough, dyspnoea, and sputum production; wheezes, decreased intensity of breath sounds, and prolonged expiration on physical examination.
- Examinations:
  - Airflow limitation on pulmonary function testing that is not fully reversible and is most often progressive.
  - Chest radiographs of patients with chronic bronchitis typically show only nonspecific peribronchial and perivascular markings. Plain radiographs are insensitive for the diagnosis of emphysema; they show hyperinflation with flattening of the diaphragm or peripheral arterial deficiency in about half of cases. CT of the chest, particularly using high-resolution CT, is more sensitive and specific than plain radiographs for its diagnosis. In advanced disease, pulmonary hypertension may be suggested by enlargement of central pulmonary arteries on radiographs, and Doppler echocardiography provides an estimate of pulmonary artery pressure. Enlargement of the hilar region and lymph nodes can be found in some cases with radiographic examination.
- For clinical manifestations of disorders affecting the upper airways, refer to item 2.1.11.

Exposure assessment

- History of occupational exposure: confirmed prolonged occupational exposure to vanadium fumes, dusts and vapours and, when available, workplace air monitoring and measurements of biological markers, such as total blood, plasma, and urinary vanadium. Collection of urine samples should be performed at the end of the last working day of the working week. Normal urinary vanadium concentrations in unexposed populations are in the order of 20-40 ng/L.
- Minimum duration of exposure: ten years.
- Maximum latent period: five years after cessation of exposure.

Key actions for prevention	Since occupational exposure to vanadium mainly occurs through inhalation, enclosure of sources and respiratory protection are the interventions of choice to protect workers from excess exposure. For use as a catalyst, vanadium pentoxide can be produced in an agglomerated or pelleted form, which is dust-free; however, vibration in the plant may, in time, reduce a certain proportion to dust. In the processes associated with the manufacture of metallic vanadium and in the sieving of used catalyst during maintenance operations, the escape of dust should be prevented by the enclosure of the process and by the provision of exhaust ventilation. In boiler cleaning in power stations and on ships, maintenance workers may have to enter the boilers to remove soot and to make repairs. These workers should wear adequate respiratory protective equipment with full-face mask and eye protection. Wherever possible, on-load cleaning should be improved to reduce the need for workers to enter furnaces; where off-load cleaning proves essential, methods such as water lancing, which do not necessitate physical entry, should be tried. The group of experts considered that a limit of exposure of 0.05 mg/m^3 for vanadium pentoxide (inhalable fraction) as 8hr TWA of workplace atmospheric concentration has been observed to provide a reasonable level of protection for workers' health and used in a number of countries.

1.1.19 Diseases caused by vanadium and its compounds ICD Code T56.8 +Z57

Further reading

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For the chemical entities listed below an entry exists in the collection of International Chemical Safety Cards (ICSC) hosted in the ILO website

Name	Synonyms	ICSC
Vanadium trioxide	Divanadium trioxide; Vanadium sesquioxide; Vanadic oxide; Vanadium (III) oxide	0455
Vanadium pentoxide	Divanadium pentoxide; Vanadic anhydride; Vanadium (V) oxide	0596
Ammonium vanadium oxide	Vanadic acid; ammonium salt	1522

▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
1.1.19	Vanadium toxicity (acute/chronic)	T56.8	NE61&XM0907
1.1.19	Respiratory tract irritation	J68	CA81
1.1.19	Acute chemical pneumonitis and bronchitis	J68.0	CA81.0
1.1.19	Pulmonary oedema	J68.1	CA81.1
1.1.19	Upper respiratory inflammation	J68.2	CA81.2
1.1.19	Reactive airways dysfunction syndrome (RADS)	J68.3	CA81.Y
1.1.19	Irritant-induced occupational asthma	J68.3	CA81.Y
1.1.19	Burn and corrosion confined to eye and adnexa	T26.0-T26.1, T26.5-T26.6	NE00
1.1.19	Conjunctivitis (acute/chronic)	H10.2	9A60.Z
1.1.19	Irritant contact dermatitis	L24	EK02
1.1.19	Chronic bronchitis and emphysema	J68.4	CA20.1Y
1.1.19	Chronic rhinitis	J31.0	CA09.0
1.1.19	Chronic pharyngitis	J31.2	CA09.2
1.1.19	Sensitizer-induced occupational asthma	J45.0	CA23.0
1.1.19	Allergic contact dermatitis	L23.0	EK00.6
	Occupational exposure to risk factors	Z57	QD84.Z

1.1.20 Diseases caused by antimony or its compounds	ICD Code T56.8 +Z57
General characteristics of the causal agent	Antimony (Sb, *Stibium*, CAS number 7440-36-0) is the chemical element with atomic number 51 in the periodic table of elements. It is classified in Group 15 (V-A), is naturally present as two stable isotopes (^{121}Sb and ^{123}Sb), and has an atomic weight of 121.76 Da. Antimony is a heavy, silver-white, lustrous, hard, brittle, bright metal or a dark grey powder with no significant use in its unalloyed state. Like arsenic, antimony features three oxidation states: (-III), (III) and (V). The main chemical forms of antimony of concern for occupational safety include elemental antimony and its inorganic compounds, such as antimony trioxide (Sb_2O_3), antimony (V) oxide (Sb_2O_5), antimony (III) chloride ($SbCl_3$), antimony pentachloride ($SbCl_5$), antimony trisulphide (Sb_2S_3), antimony (V) sulphide (Sb_2S_5), and the volatile antimony hydride (SbH_3), also known as stibine. *Antimony trioxide* is the most important of the antimony oxides. When airborne, it tends to remain suspended for an exceptionally long time. It is obtained from antimony ore by a roasting process or by oxidizing metallic antimony and subsequent sublimation. *Antimony pentoxide* is produced by the oxidation of the trioxide or the pure metal in nitric acid under heat. *Antimony trichloride* is produced by the interaction of chlorine and antimony or by dissolving antimony trisulphide in hydrochloric acid. *Antimony pentachloride* is produced by the action of chlorine on molten antimony trichloride. *Antimony trisulphide* is found as a natural mineral, antimonite, but can be synthesized from antimony and sulphur at temperatures of 500-900°C, while antimony pentasulfide can be produced by the reaction of the two elements at a temperature of 250-400°C. *Stibine* is a highly toxic and colourless gas, which is generated in the reaction of binary antimony compounds with metals (antimonides) present in ores with acids during processing, and in the charging of electric batteries. The complex of antimony pentafluoride (SbF_5) and hydrogen fluoride (HF), known as "*magic acid*" (H^+ SbF_6^-), is the strongest known Brönsted acid and finds use in organic catalysis.
Occupational exposures	Almost 90% of antimony production derives from China, followed by Tajikistan, Russia, and Australia. A total mine production of 150.000 tons was estimated in 2017. The metal is obtained by roasting its main commercially exploitable sulphide mineral (stibnite) and by using recyclable scrap iron to convert the sulphide into volatile antimony (III) oxide and carbon as a reducing agent. The main industrial application of antimony is as antimony trioxide, which is used as a fire retardant for plastics, textiles, rubber, adhesives, pigments, and paper in a mixture with halogen-containing compounds. High-purity antimony is employed in the manufacture of semiconductors. Normal-purity antimony is used widely in the production of alloys, to which it imparts increased hardness, mechanical strength, corrosion resistance and a low coefficient of friction; alloys combining tin, lead and antimony are used in the electrical industry. The largest application of metallic antimony is alloying of lead to make more mechanically robust elements for lead-acid batteries. Antimony alloys are used for bearing shells, storage battery plates, cable sheathing, solder, ornamental castings and ammunition. Other uses of antimony include the making of lead typing characters, lead bullets for firearms, and safety matches. Antimony compounds are used as catalysts and stabilizers in the production of the condensation polymer poly-ethylene-terephthalate, which is used for manufacturing containers for bottled water and soft drinks. During processing, the antimony ore, which is extremely brittle, is converted into fine dust more rapidly than the accompanying rock, leading to high atmospheric concentrations of antimony dust during operations such as reduction and screening. Dust produced during crushing is relatively coarse, and the remaining operations – classification, flotation, filtration, and so on – are usually wet processes and, consequently, relatively dust-free. Furnace workers who refine metallic antimony and produce antimony alloy and workers setting type in the printing industry are all exposed to antimony metal dust and fumes. A limited use of antimony is in the preparation of medical drugs active against parasites, such as antimony potassium tartrate and sodium antimony dimercaptosuccinate. These are still first-line therapy against leishmaniasis and are also employed against schistomiasis both in animals and in humans. Antimony trisulphide is used in the pyrotechnics, match and explosives industries, in ruby glass manufacture, and as a pigment and plasticizer in the rubber industry. Antimony pentasulphide has much the same uses.

1.1.20 Diseases caused by antimony or its compounds	ICD Code T56.8 +Z57
Occupational exposures	The antimony chlorides are used for blueing steel and colouring aluminium, pewter and zinc, and as catalysts in organic synthesis, especially in the rubber and pharmaceutical industries. In addition, antimony trichloride is used in the match and petroleum industries. Antimony hydride gas (stibine) is used in confined reactors as an n-type gas-phase dopant for silicon in semiconductors, under strictly controlled conditions, so that exposure of operators is unlikely.
Toxicological profile, main health effects and diagnostic criteria	
Short toxicological profile	Antimony may enter the body through the skin, but the principal route is through the lungs. From the lungs, antimony, and especially free antimony, is absorbed and taken up by the blood and tissues. Studies on workers and experiments with radioactive antimony have shown that the greatest part of the absorbed dose enters the metabolism within 48 hours and is eliminated in the faeces and, to a lesser extent, the urine. The remainder stays in the blood for some considerable time, with the erythrocytes containing several times more antimony than the serum. In workers exposed to pentavalent antimony, the urinary excretion of antimony is related to the intensity of exposure. In intoxicated workers, clearance of antimony from the lungs was essentially complete in less than 10 days. The bioavailability of non-soluble forms is low; soluble forms are transported in the body as labile conjugates of antimony (III) with glutathione and are subject to a strong enterohepatic recirculation. Unlike arsenic, antimony does not undergo biological methylation in mammals. The therapeutic use of antimonial drugs has made it possible to detect the cumulative myocardial toxicity of the trivalent derivatives of antimony which are excreted more slowly than pentavalent derivatives. Reduction in the amplitude of T waves, increase of QT interval, and arrhythmias have been observed in electrocardiograms. Exposure to antimony during its refining and use has been associated to respiratory tract irritation, gastrointestinal complaints, dermatitis and a benign form of pneumoconiosis. Exposure to stibine causes haemolysis.

Name of the diseases and ICD code: **Acute diseases caused by antimony or its compounds**
(Specific disease code) **+T56.8 +Z57**

Respiratory irritation (J68), Chemical bronchitis and pneumonitis (J68.0), Upper respiratory tract inflammation (J68.2), Chemical pulmonary oedema (J68.1), Burns and corrosions of: respiratory tract (T27), external body surface (T20-T25), internal organs (T28.0-T28.2, T28.5-T28.7), eye and adnexa (T26.0-T26.1, T26.5-T26.6), Conjunctivitis (H10.2), Keratitis (H16), Corneal ulcer (H16.0), Irritant contact dermatitis (L24)

Short description of the disease

Exposure to antimony or its compounds via inhalation, skin and mucosal contact, or ingestion causes irritation of respiratory tract, skin and mucous membranes. Systemic effects of exposure to antimony or its compounds include headache, weakness, and abdominal pain.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms:
  - Exposure to fine airborne dust can cause inflammation of upper and lower respiratory tracts (bronchitis and pneumonitis, up to pulmonary oedema) with sneezing, chest tightness, wheezing, shortness of breath, and cyanosis. Stibine gas can cause respiratory irritation with cough, shortness of breath, sore throat, burning sensation, wheezing, and laboured breath. Inhalation of antimony pentachloride can cause mucosal corrosion.
  - Exposure to dusts and fumes of antimony compounds can irritate skin and mucous membranes with redness, dry skin, blisters (antimony trioxide), and serious skin burns (antimony trichloride or pentachloride). Exposure to liquid stibine can cause frostbite.
  - Contact of the eyes with dusts and fumes of antimony compounds can result in pain, redness, blepharospasm, lacrimation, photophobia, conjunctivitis, keratitis, blurred vision, severe deep eye burns (antimony trichloride or pentachloride) and corrosion (antimony pentachloride).
  - Ingestion of antimony or its compounds although very unlikely at the workplace causes abdominal pain, nausea, vomiting and melaena, sore throat, burning sensation in the stomach, diarrhoea, gastrointestinal bleeding, and haematuria. Systemic effects are slow in onset and characterized by shallow respiration accompanied by cardiac arrhythmia; coma can occur, sometimes followed by death due to hepatic and renal complications.

1.1.20 Diseases caused by antimony or its compounds ICD Code T56.8 +Z57

- Examinations:
  - Lung function testing may show evidence of airways obstruction (FEV_1/FVC ratio less than 0.7).
  - Chest radiograph may be normal or show mild or diffuse infiltrate in case of chemical pneumonia.
  - Electrocardiogram can show arrhythmia, reduction of T wave amplitude, increase of QT interval (long-term exposure to antimony trioxide).

Exposure assessment

- History of occupational exposure: evidence of exposure to airborne dusts and fumes of antimony or its compounds (via inhalation, skin and eye contact or accidental ingestion) and, when available, workplace air and biological monitoring: urinary antimony concentration is related to the intensity of exposure (pentavalent antimony).
- Minimum duration of exposure: few minutes.
- Maximum latent period: few hours.

Acute toxic haemolytic anaemia (D59.4), Acute toxic renal failure with tubular necrosis (N17.0)

Short description of the disease

Inhalation of stibine (antimony hydride) causes rapid and severe Coombs-negative haemolytic anaemia. The poisoned subject may describe the perception of an extremely unpleasant odour.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: dyspnoea, abdominal and lumbar pain, jaundice, haematuria; in the most severe cases, stibine-related haemolytic anaemia can lead to acute renal failure due to acute tubular necrosis.
- Examinations:
  - Blood cell count can show anaemia and possibly reticulocytosis. Increased levels of lactate dehydrogenase (LDH) and indirect bilirubin are detected in the serum. Red blood cell morphological changes can be identified at peripheral blood smear. Coombs' test results negative.
  - Urinalysis can reveal haematuria, myoglobinuria, increased urobilinogen, and increased urinary excretion of β2-microglobulin and retinol-binding protein (RBP), which are usually reabsorbed by the proximal tubule and thought to be an indicator of early damage to the renal proximal tubule.
  - Renal biopsy shows acute tubular necrosis.

Exposure assessment

- History of occupational exposure: evidence of acute exposure to high concentrations of stibine and, when available, workplace air and biological monitoring (urinary antimony).
- Minimum duration of exposure: few minutes.
- Maximum latent period: two days.

Pustular dermatitis (antimony spots) (L30.8)

Short description of the disease

Pustular eruptions (called antimony spots) may appear on body areas where the skin is in contact with antimony salts. As these lesions often become manifest in association with sweating, high temperature and friction, they mainly occur in the summer season.

Diagnostic criteria

Clinical manifestations

Transient papular rash or pustular skin lesions, possibly around sweat and sebaceous glands and potentially associated with areas of eczema and lichenification.

Exposure assessment

- History of occupational exposure: evidence of contact exposure to antimony salts in the occupational setting.
- Minimum duration of exposure: repeated exposure is usually needed for antimony spots to develop.
- Maximum latent period: few days.

1.1.20 Diseases caused by antimony or its compounds — ICD Code T56.8 +Z57

Name of the diseases and ICD code: **Chronic diseases caused by antimony or its compounds**
(Specific disease code) **+T56.8 +Z57**

Nose septal ulceration (J34.8), Deposits on teeth (K03.6)

Short description of the disease

Prolonged or repeated exposure to antimony pentachloride can cause nose bleeding, ulcers or sores in the nose and nasal septum perforation. Orange staining of the teeth may result from repeated exposure to antimony oxides or antimony sulphides. Prolonged or repeated low dose exposure to antimony or its compounds can also result in chronic poisoning.

Diagnostic criteria

Clinical manifestations

- Evidence of an ulceration of nasal mucosae preceded by irritation, possibly evolving into septal perforation.
- Symptoms of chronic poisoning include dryness of the throat, nausea, headache, dizziness, loss of appetite, sleeplessness, and depression.

Exposure assessment

- History of occupational exposure: evidence of prolonged or repeated occupational exposure to airborne dusts and fumes of antimony or its compounds and, when available, workplace air and biological monitoring.
- Minimum duration of exposure: weeks.
- Maximum latent period: six months.

Antimoniosis (J63.8)

Several authors have obtained pneumoconiosis-like X-ray pictures from workers with long-term occupational exposure to antimony. In some of these instances, concomitant exposure to silica was likely. A study conducted on antimony process workers found a correlation between estimated lung antimony and period of employment. Some authors refer to antimoniosis, known as antimony pneumoconiosis or more rarely, stibiosis, as a benign disorder with no detrimental effect on health or life expectancy. X-ray changes indicating antimoniosis (diffuse, densely distributed 1 mm punctate opacities) were found among workers in an antimony smelter, exposed for several years to dusts of antimony trioxide and antimony pentoxide, but also to small amounts of free silica. Some workers showed alterations at pulmonary function tests and complained of chronic coughing. Although antimoniosis mostly appears as a relatively benign condition, chronic respiratory effects have been reported in many studies, and relevant exposure to antimony or its compounds cannot be considered harmless.

1.1.20 Diseases caused by antimony or its compounds — ICD Code T56.8 +Z57

Key actions for prevention

The essence of any safety programme for the prevention of antimony poisoning should be the control of dust and fume formation at all stages of processing.

In mining, dust prevention measures are similar to those for metal mining in general: during crushing, the ore should be sprayed (water suppression of dust) or the process completely enclosed and fitted with local exhaust ventilation, combined with adequate general ventilation. In antimony smelting, the hazards of charge preparation, furnace operation, fettling and electrolytic cell operation should be eliminated, where possible, by isolation and process automation. Furnace workers should be provided with water sprays and effective ventilation.

Antimony trioxide is largely used as a flame retardant in polymers and in textiles. Considering that other alternatives, such as poly-brominated organic compounds, are cause of concern for their long-term health effects, it is likely that this use as a flame retardant will continue. Since antimony trioxide is volatile at the temperature of the smelting process, prevention of exposure entails encapsulation of the smelting units to prevent operators' exposure and the use of personal protective devices only to supplement measures of secondary prevention for workers who need to operate close to the functioning units.

Where complete elimination of exposure is not possible, the hands, arms, and faces of workers should be protected by gloves, dustproof clothing, and goggles; where atmospheric exposure is high, respirators should be provided. Skin conditioning creams should be applied, especially when handling soluble antimony compounds, in which case they should be combined with the use of waterproof clothing and rubber gloves. Personal hygiene measures should be strictly observed; no food or beverages should be consumed in the workshops, and suitable sanitary facilities should be provided so that workers can wash before meals and before leaving work.

The group of experts considered that the following limits of exposure of workplace atmospheric concentrations have been observed to provide a reasonable level of protection for workers' health and to be used in a number of countries:

- Antimony and its compounds: 0.5 mg/m^3 as 8hr TWA.
- Stibine: 0.1 ppm as 8hr TWA.

Further reading

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For the chemical entities listed below an entry exists in the collection of International Chemical Safety Cards (ICSC) hosted in the ILO website

Name	Synonyms	ICSC
Antimony trioxide	Antimony sesquioxide; Antimony (III) oxide; Antimony white; Flowers of antimony	0012
Antimony pentafluoride	Antimony (V) fluoride	0220
Antimony	Antimony black; Antimony regulus; Stibium	0775
Stibine	Antimony hydride; Antimony trihydride; Hydrogen antimonide	0776
Antimony trichloride	Trichlorostibine; Antimonous chloride; Butter of antimony; Antimony (III) chloride	1224

▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
1.1.20	Diseases caused by antimony or its compounds	T56.8	NE61&XM5HW4
1.1.20	Respiratory irritation	J68	CA81
1.1.20	Chemical bronchitis and pneumonitis	J68.0	CA81.0
1.1.20	Upper respiratory tract inflammation	J68.2	CA81.2
1.1.20	Chemical pulmonary oedema	J68.1	CA81.1
1.1.20	Burn and corrosion of respiratory tract	T27	NE01
1.1.20	Chemical burns and corrosions of external body surface	T20-T25	ND9Z, NE10
1.1.20	Burn and corrosion of internal organs	T28.0-T28.2, T28.5-T28.7	NE0Z, NE10
1.1.20	Chemical burn and corrosion of eye and adnexa	T26.0-T26.1, T26.5-T26.6	NE00
1.1.20	Conjunctivitis	H10.2	9A60.Z
1.1.20	Keratitis	H16	9A78.Z
1.1.20	Corneal ulcer	H16.0	9A76
1.1.20	Irritant contact dermatitis	L24	EK02
1.1.20	Acute toxic haemolytic anaemia	D59.4	3A21
1.1.20	Acute toxic renal failure with tubular necrosis	N17.0	GB60.Z
1.1.20	Pustular dermatitis (antimony spots)	L30.8	EA8Z
1.1.20	Nose septal ulceration	J34.8	CA0Z
1.1.20	Deposits on teeth	K03.6	DA08.4
1.1.20	Antimoniosis	J63.8	CA60.Z
	Occupational exposure to risk factors	Z57	QD84.Y

1.1.21 Diseases caused by hexane	ICD Code T52.8, +Z57
General characteristics of the causal agent	Hexane (Hexyl hydride), CAS number 110-54-3, molecular mass 86.2, is a six-carbon saturated, straight-chain aliphatic hydrocarbon with chemical formula C_6H_{14}. It is a volatile colourless liquid at room temperature (boiling point 69°C) and insoluble in water, with a characteristic gasoline odour. The vapour is heavier than air and may travel along the ground, making distant ignition possible. It reacts with strong oxidants causing fire and explosion hazards. Hexane also attacks some plastics, rubber and coatings. Note that the term "hexane" stands for normal (straight-chained) hexane and may theoretically refer to any of the five structural isomers corresponding to the chemical formula C_6H_{14} or to a mixture of them. In the nomenclature of the International Union of Pure and Applied Chemistry (IUPAC), however, hexane is just the unbranched isomer (*n*-hexane). Studies have shown that six-carbon mixtures without *n*-hexane did not produce signs of neurotoxic functional disorders or histologically detectable differences from the controls in the tissues of the brain, spinal cord, sciatic or tibial nerves. Only pure *n*-hexane and *n*-hexane containing mixtures have been proven to be neurotoxic. Thus, the present item will essentially refer to *n*-hexane.
Occupational exposures	Isomers of hexane are present in organic solvents, adhesives, protective coatings and paints. They are components of gasoline (motor spirit, petrol) and can occur as intermediates in the refining of petroleum. In technical hydrocarbon mixtures, *n*-hexane seldom occurs in a pure form. It can be one major component of petroleum ether (used as solvent or thinner for adhesives and paints), where it replaced benzene. In many uses, heptane mostly replaced hexane because of its much lower toxicity. The main use of hexane is as a solvent to extract edible oils from seed and vegetable crops (e.g. soybeans, peanuts, corn). The presence of hexane is possible in several industrial and consumer products, such as in volatile solvents for paints, lacquers, varnishes and printing inks, in petroleum-derived grease removers; in glue solvents (rubber cement, adhesives) for the production of footwear, handbags, suitcases, wallpaper, and for assembling and finishing of furniture and cabinetry; in the rubber industry, in the laminating processes; in roofing; in textile manufacturing (especially for textile waterproofing in the manufacture of raincoats), in the re-treading of car tyres. Occupational exposure, sometimes at high levels, is possible in cleaning, cleansing, and degreasing a variety of items (such as electronic components and printing plates), from paints, cements and adhesives. Hexane is used as the liquid in low-temperature thermometers. Some occupational groups that may be exposed to *n*-hexane include refinery workers, shoe and footwear assembly workers, laboratory technicians, workers operating or repairing typesetting and printing machinery, construction workers, carpet layers, carpenters, auto mechanics and gas station employees, workers in plants manufacturing tires or inner tubes, and workers in air transport and air freight operations.
Toxicological profile, main health effects and diagnostic criteria	
Short toxicological profile	Hexane is a widely occurring atmospheric pollutant, quickly and completely absorbed by inhalation (the most probable route of human exposure) and very well absorbed through the skin. After absorption, it is distributed throughout the human body, especially to lipid-rich tissues and organs (such as the brain), and partially excreted un-modified in exhaled air and in the urine. Temporary accumulation of *n*-hexane in the brain causes narcotic effects similar to those caused by several other organic solvents and by inhalation of anaesthetics. Its biotransformation occurs in the liver by microsomal oxidation at the (n-1) methylene positions, leading to the systemically toxic metabolite 2,5-hexanedione. This product is still sufficiently lipophilic to partition into the lipid-rich myelin sheath of peripheral nerves and electrophilic enough to react with the primary amino group of the lysine-residues side-chain of the very basic myelin proteins. This reaction, well known in organic chemistry as Paal-Knorr synthesis, leads to the formation of 2,5-dimethyl-pyrrole groups which are very prone to one-electron oxidation and to cross-linking. At the pathophysiological level, this is the accepted mechanism through which *n*-hexane produces a specific neurological disease characterized by loss of sensation and motion of fingers and limbs.

1.1.21 Diseases caused by hexane — ICD Code T52.8, +Z57

Name of the diseases and ICD code: **Acute diseases caused by *n*-hexane** *(Specific disease code)* **+ T52.8, +Z57**

Respiratory tract irritation (J68), Upper respiratory inflammation (J68.2), Conjunctivitis (H10.2), Corneal scar and opacity (H17.8), Irritant contact dermatitis (L24)

Short description of the disease

n-Hexane is characterized by low acute toxicity. However, exposure to very high concentrations (especially by contact) may cause irritant effects on the skin, eyes and respiratory tract.

Diagnostic criteria

Clinical manifestations

- Hexane has low solubility in water; therefore, the respiratory effects can be delayed (6 to 24 or even up to 72 hours) but are often (although not always) preceded by upper respiratory tract symptoms, such as redness and itching of the throat, and coughing.
- Chest X-rays and pulmonary function tests may show a picture of inflammation.
- After 10-20 minutes of dermal exposure, a slight transient erythema with a stinging and burning sensation is observed. Subjects developed blisters 5 hours following dermal exposure to *n*-hexane. Pain may occur if there is direct contact with the liquid. For more details on clinical features of irritant contact dermatitis, refer to item 2.2.2.
- *n*-Hexane splashed into the eye may cause corneal opacification and lipolysis, and loss of epithelial cells.

Exposure assessment

- History of occupational exposure: confirmed occupational exposure to hexane by inhalation, skin and eye contact. The presence of *n*-hexane main metabolite (2,5-hexanedione) in urine confirms the exposure.
- Minimum duration of exposure: few minutes.
- Maximum latent period: 48 hours for skin and eyes disorders; 72 hours for respiratory disorders (recall that delayed symptoms are possible because of the poor solubility of hexane).

Narcotic syndrome (T52.8)

Short description of the disease

Despite its low acute toxicity, *n*-hexane is a mild anaesthetic (in common with other solvents with a narcotic action, *n*-hexane has been the subject of misuse). In industrial settings, exposures to levels exceeding 1,000 ppm have been reported to cause mild symptoms of narcosis. Exposure to 1,500 ppm results in headache and slight nausea; exposure to 5,000 ppm of *n*-hexane for 10 minutes causes marked vertigo.

Diagnostic criteria

Clinical manifestations

Acute high dose absorption causes narcotic syndrome with euphoria, headache, nausea, vertigo, unsteadiness, weakness, somnolence, drowsiness, confusion, loss of consciousness, evolving to coma in the most severe cases.

Exposure assessment

- History of occupational exposure: confirmed occupational exposure to hexane by inhalation, skin and eye contact. The presence of *n*-hexane main metabolite (2,5-hexanedione) in urine confirms the exposure.
- Minimum duration of exposure: few minutes.
- Maximum latent period: 24 hours.

1.1.21 Diseases caused by hexane — ICD Code T52.8, +Z57

Name of the diseases and ICD code: **Chronic diseases caused by *n*-hexane**
(Specific disease code) **+T52.8, +Z57**

Peripheral polyneuropathy (G62.2)

Short description of the disease

The disease is a distal, sensorimotor polyneuropathy, mainly affecting the lower limbs, characterized by an insidious onset and a slow progression, observed for exposures in the range between 250–2500 ppm, note that these higher values usually correspond to very poor occupational hygiene conditions, as can be found for example when using glues for shoe repairing without ventilation. Overt neuropathy can be observed after continuous occupational exposure to concentrations usually not lower than 500 ppm, whilst lower exposure may cause subclinical reductions in nerve conduction velocities. In some cases, visual impairment consequent to optic neuropathy or maculopathy can be observed. Muscle wasting and atrophy have been reported in occupationally exposed workers. The metabolite responsible for hexane neuropathy characterized by distal degeneration of the central axons and secondary demyelination is 2,5-hexanedione. Coldness, reddishness, or roughness of the skin in the distal extremities has been observed in workers with peripheral neuropathy after inhalation of hexane in occupational settings.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: numbness at hands and feet is the first symptom to appear, together with muscle weakness (in particular at the lower legs and feet) or a heavy feeling at the lower limbs. Tendon reflexes can be weakened or even disappear, with the Achilles reflex being the first one usually affected. Distal paraesthesia, sensory anomalies, and muscle atrophy are usually present.
- Examinations:
  - Electromyography shows axonal disorders; the motor conduction velocity and the sensory conduction velocity are reduced, the motor distal latency is modified, and the sensory potential amplitude is diminished, in addition to signs of denervation in affected muscles and small or absent sensory nerve action potentials.
  - Biopsies of peripheral nerves may show demyelination and infiltration of leucocytes.
  - Spinal fluid examination does not give characteristic findings, except for rare cases of increased protein content.
  - Electroencephalography is usually normal; in the most severe cases, however, it is possible to detect dysrhythmias, widespread or subcortical discomfort, and irritation.
- Differentiation from non-occupational peripheral polyneuropathies can be based on the following features, usually characterizing hexane poisoning:
  - the paralysis is symmetrical;
  - the motor dysfunction is more relevant than the sensory loss; and
  - changes in the cerebrospinal fluid are mostly absent.

Exposure assessment

- History of occupational exposure: confirmed occupational exposure (even through skin contact) to *n*-hexane. The presence of *n*-hexane main metabolite (2,5-hexanedione) in urine confirms the exposure.
- Minimum duration of exposure: one month.
- Maximum latent period: three years.

Chronic toxic encephalopathy (G92)

Short description of the disease

Exposure to organic solvents, and thus to *n*-hexane as well, may cause chronic adverse effects to the central nervous system. Solvent-induced encephalopathy, known as chronic toxic encephalopathy or organic brain syndrome due to chronic exposure to solvents, may develop insidiously after long-term exposure (often decades), even at not particularly high exposure levels. Chronic solvent encephalopathy is characterized by irreversible impairment of memory, concentration, and mood, accompanied by fatigue and loss of initiative. Attention, learning, psychomotor performance and verbal and non-verbal reasoning, as well as concept formation, can be affected. Loss of colour vision and alterations in visual perception may be part of the clinical picture.

1.1.21 Diseases caused by hexane — ICD Code T52.8, +Z57

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: if exposure is not avoided, the disease progresses through three levels of increasing severity:
  - from *organic affective syndrome* (characterized by depression, irritability, loss of interest in daily activities);
  - to *mild chronic toxic encephalopathy* (characterized by fatigue, mood disturbances, memory and attentional complaints, together with impairment of psychomotor functions such as speed and dexterity); and
  - up to *severe chronic toxic encephalopathy* (characterized by loss of intellectual ability interfering with occupational or social functioning as well as by impairment of memory, abstract thinking and judgment). Third-level lesions become permanent, although the exposure ceases, and the affected person usually remains severely disabled.
- Examinations:
  - Neuropsychological assessment may show neurobehavioral impairment and should be conducted through the use of tests addressed at exploring the following functions: verbal and visual memory, attention, psychomotor speed, visual analysis, construction, abstraction, and primary intellectual abilities (some examples of specialized behavioural tests to measure neurotoxicity are reported in Table 2 at the end of item 1.1.38).
  - Electroencephalography may show nonspecific abnormalities (such as diffuse slowing).
  - Neuroimaging investigations may show mild cerebral atrophy.

Differential diagnosis

Depression and other psychiatric disorders; sleep and neurodegenerative disorders; vascular disorders of the brain; neoplasms such as brain tumours; metabolic causes such as thyroid disorders and avitaminosis; or traumatic brain disorders.

Exposure assessment

- History of occupational exposure: confirmed occupational exposure to *n*-hexane via inhalation or skin contact. The presence of *n*-hexane main metabolite (2,5-hexanedione) in urine confirms the exposure.
- Minimum duration of exposure: ten years.
- Maximum latent period: not applicable.

Key actions for prevention	To overcome the toxic and leukaemogenic hazard posed by benzene, *n*-hexane was used as a substitute solvent for glues and paints. However, due to its neurological toxicity, *n*-hexane itself has been in turn replaced by other less or non-toxic hydrocarbons, such as *n*-heptane. Enclosure of the sources, local exhaust and ventilation to prevent and control the exposure should be firstly applied when *n*-hexane is still used. Technical interventions aimed at enclosing the source to avoid explosion and fire risk are effective as a second-tier prevention measure to mitigate exposure. Personal protective equipment (protective gloves, safety goggles, face shield or eye protection in combination with respiratory protection), should be worn where any residual risk of exposure remains. Attention should be given when breathing protection is required for a long time due to the possibility that filters of facemasks saturate under intense exposure conditions. Exposure criteria have been issued in most countries and should be adhered to. The group of experts considered that the limit of 50 ppm of workplace atmospheric concentration as 8hr TWA is used in a number of countries, provides a reasonable level of protection for workers' health, and should be observed.

1.1.21 Diseases caused by hexane ICD Code T52.8, +Z57

Further reading

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10. Recommendation from the Scientific Expert Group on Occupational Exposure Limits for n-hexane SEG/SUM/52 1995, EU OSHA.

For the chemical entities listed below an entry exists in the collection of International Chemical Safety Cards (ICSC) hosted in the ILO website

Name	Synonyms	ICSC
Cyclohexane	Hexahydrobenzene, Hexamethylene, Hexanaphthene	0242
n-HEXANE	Hexyl hydride	0279
2-Methylpentane	Isohexane, Dimethylpropylmethane	1262
3-Methylpentane	Diethylmethylmethane	1263

▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
1.1.21	Acute/chronic diseases caused by *n*-hexane	T52.8	NE61& XM5LH2
1.1.21	Respiratory tract irritation	J68	CA81.Z
1.1.21	Upper respiratory inflammation	J68.2	CA81.2
1.1.21	Conjunctivitis	H10.2	9A60.Z
1.1.21	Corneal scar and opacity	H17.8	9A77.Z
1.1.21	Irritant contact dermatitis	L24	EK02
1.1.21	Narcotic syndrome	T52.8	PB31& XM5LH2
1.1.21	Peripheral polyneuropathy	G62.2	8C0Z
1.1.21	Chronic toxic encephalopathy	G92	8D43.0Z
	Occupational exposure to risk factors	Z57	QD84.Y

1.1.22 Diseases caused by mineral acids	ICD Code T54.2 +Z57
General characteristics of the causal agent	The acids considered in this item are "*mineral*" inorganic acids and oxy-acids containing hydrogen and one or more elements except for carbon (i.e., boron, nitrogen, fluorine, silicon, phosphorus, sulphur, chlorine) and some of their derivatives (such as acid anhydrides, acid chlorides, and acid amides) but not their inorganic and organic salts. All acids have common chemical properties, such as the ability to neutralize alkalis and other chemical bases and to produce specific colour changes with chemical substances known as pH indicators. Mineral acids show a stronger or weaker reactivity towards several metals in their elemental form, which are dissolved with the evolution of flammable and explosive hydrogen gas. Among the hundreds of chemically known inorganic acids and derivatives, only those of major industrial interest and concern for occupational safety and health are considered. For further information, see the tables at the end of the present item.
Occupational exposures	Inorganic acids are used as chemical intermediates and catalysts in chemical reactions. They are found in a variety of industries, including metal and wood-working, textile, dyestuffs, petroleum and photography. In metal-working, they are often used as cleaning agents before welding, plating or painting. Sulphamic acid, sulphuric acid, and hydrochloric acid are used in electroplating; perchloric acid is used in metal plating. Hydrochloric acid, sulphuric acid, perchloric acid, and sulphamic acid are widely used in industry and as cleaning agents. *Hydrochloric acid* (hydrogen chloride in aqueous solution) is used for industrial acidizing and for refining ores of tin and tantalum, converting corn-starch to syrup, and removing scale from boilers and heat-exchange equipment. It is used as a tanning agent in the leather industry. *Hydrofluoric acid* is used in the production of organic and inorganic fluorine compounds, in fluorination processes and as an acid catalyst particularly in paraffin alkylation in the petroleum industry, in non-chemical technological processes, such as removing sand from metallic castings, polishing, frosting and etching of glass and enamel processing. Hydrofluoric acid is widely used as a derusting agent in household products and by plumbers, who most often operate in the informal sector. *Sulphuric acid* is used in parchment paper and in various processes, including purification of petroleum, refining vegetable oil, carbonization of wool fabrics, extraction of uranium from pitchblende, and in iron and steel pickling. Together with perchloric acid, it is used in the explosives industry. *Sulphamic acid* is a flame retardant in the wood and textile industries and a bleaching agent and bactericide in the pulp and paper industries; it is used for chlorine stabilization in swimming pools. *Nitric acid* is used in the manufacture of ammonium nitrate for fertilizer and explosives, in organic synthesis, metallurgy, ore flotation, jewellery production, pharmaceutical industry, and for reprocessing spent nuclear fuel. Other sources of exposure are the manufacture of isopropanol (isopropyl alcohol), synthetic ethanol (ethyl alcohol), sulphuric acid, nitric acid, phosphate fertilizer, soap, detergent, lead batteries, copper smelting, pickling, and other acid treatment of metals.
Toxicological profile, main health effects and diagnostic criteria	
Short toxicological profile	From a toxicological point of view, the "*mineral*" inorganic acids and oxy-acids considered here, share the property of being destructive towards organic matter of living tissues, in a more or less severe and rapid manner, depending on the chemical identity of the compound, its concentration, and on the mode and duration of exposure. Their effects are often limited to the part of the body that the acids contact and are mostly neutralized by the chemically neutral environment of the biological matter. Some acids exert specific systemic biological effects when they are absorbed and distributed in the living organism. The major routes of occupational exposure are inhalation and dermal or ocular direct contact. Ingestion is a less important route of exposure in occupational settings.

1.1.22 Diseases caused by mineral acids — ICD Code T54.2 +Z57

Short toxicological profile	The effect of strong, concentrated mineral acids on the skin is mainly due to their ability to extract water from the tissue and to disrupt its architecture and barrier capacity. Only very concentrated sulphuric acid can lead to tissue charring. In general, the skin relies on its high lipid content and keratinocytes to mechanically protect the underlying tissue from the action of the acid, which mainly occurs through coagulation of tissue proteins rather than by chemical hydrolysis. Macroscopically, this phenomenon leads to burns and scars, which are usually localized at the point of contact. Alkali burns, on the contrary, are much more extensive and severe because of saponification of skin lipids and destructive hydrolysis of proteins. The same phenomena occur on internal mucosae when an acid is ingested or inhaled, with the difference that the inner lining of the internal organs is much less resistant, and consequently, damage is more severe and extensive. The capacity of most tissues to chemically neutralize excess acid is generally poor, except for the mucosae of the stomach but not that of the oesophagus. Thin parenchyma, such as that of the lung, is particularly vulnerable.

Name of the diseases and ICD code: **Acute diseases caused by mineral acids** *(Specific disease code)* **+T54.2, +Z57**

Mucous membranes irritation (J68), Acute chemical pneumonitis and bronchitis (J68.0), Upper respiratory inflammation (J68.2), Pulmonary oedema (J68.1), Reactive airways dysfunction syndrome (RADS) (J68.3), Irritant-induced acute occupational asthma (J68.3), Burns and corrosions of eye and adnexa (T26.0-T26.1,T26.5-T26.6), Conjunctivitis (H10.2), Blepharoconjunctivitis (H10.5), Keratoconjunctivitis (H16.2), Corneal ulcer (H16.0), Burns and corrosions of gastrointestinal tract (T28.0-T28.2,T28.5-T28.7), Burns and corrosions of external body surface (T20-T25), Acute irritant contact dermatitis (L24)

Short description of the disease

Exposure and contact with these compounds (e.g. hydrogen chloride gas or hydrochloric acid) can cause severe mucous membrane and skin irritation, and in some cases, severe burns. Acute exposure by inhalation causes irritation and ulceration. Contact with the respiratory tract may lead to pulmonary oedema. Ingestion may cause burns to the lips, mouth, throat, oesophagus and stomach. Clinical features of irritant contact dermatitis have been thoroughly addressed in dedicated item 2.2.2, which should be referred to for further details.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms:
  - Symptoms of respiratory irritation such as coughing, chest tightness, shortness of breath, and choking. At higher concentrations, tachypnoea and a chemical-induced type of non-allergic asthma (reactive airways dysfunction syndrome, RADS) can be observed. In high exposure scenarios, bronchospasm, laryngospasm, and acute pneumonitis can be observed, up to pulmonary oedema.
  - Acute eye exposure causes stinging pain, photophobia, blurred vision, ulceration, and conjunctivae irritation.
  - Ingestion causes salivation, dysphagia, intense thirst, nausea, vomiting, haemorrhage, diarrhoea, and abdominal pain.
- Examinations:
  - Evidence of various degrees of irritation and burns of skin and mucous membranes at physical examination.
  - Pulmonary auscultation may document signs of respiratory impairment (e.g. crackles).
  - Chest X-ray may show a picture of bronchitis, pneumonitis or even pulmonary oedema.
  - Respiratory function tests (when feasible) may show an acute obstructive picture.

Exposure assessment

- History of occupational exposure: evidence of exposure (contact, inhalation, or ingestion) to liquid, vapours, or aerosols of inorganic acids.
- Minimum duration of exposure: few seconds.
- Maximum latent period: few hours. Pulmonary oedema due to nitric and sulphuric acids is typically observed with a latent period of 6 to 24 hours (in any case, less than 72 hours) after exposure.

1.1.22 Diseases caused by mineral acids — ICD Code T54.2 +Z57

Acute toxic renal failure with tubular necrosis (N17.0), Acute toxic liver disease (K71.9), Liver toxicity (impairment, functional) (K72.9)

Short description of the disease

High exposure to sulphamic acid, inhalation of hydrogen chloride, ingestion of concentrated hydrochloric acid at concentrations in the order of those sufficient to produce mucosal irritation can cause renal failure and liver injury.

Diagnostic criteria

Clinical manifestations

Kidney function tests may document acute renal failure and reduction of glomerular filtration rate. An increase in the concentrations of serum hepatic enzymes and liver enlargement may be observed.

Exposure assessment

- History of occupational exposure: evidence of exposure (contact, inhalation, or ingestion) to liquid, vapours, or aerosols of inorganic acids, especially sulphuric acid and hydrogen chloride.
- Minimum duration of exposure: few minutes.
- Maximum latent period: few days.

Name of the diseases and ICD code: **Chronic diseases caused by mineral acids**
(Specific disease code) **+T54.2, +Z57**

Chronic skin and mucous membranes irritation (L24)

Short description of the disease

Due to their irritant properties, mineral acids may cause chronic inflammation of the skin, including hyperkeratosis and mucous membrane irritations. Exposure to nitric acids may cause a typical yellowish skin pigmentation (xanthoproteic reaction).

Diagnostic criteria

Clinical manifestations

Redness and burning of skin and eyes, cough, dysphonia, and dyspnoea can be observed. Clinical features of irritant contact dermatitis have been thoroughly addressed in dedicated item 2.2.2, which should be referred to for further details.

Exposure assessment

- History of occupational exposure: evidence of prolonged skin contact with inorganic acids (liquid, dust, aerosol or vapours).
- Minimum duration of exposure: six months.
- Maximum latent period: one month.

Chronic obstructive pulmonary disease (COPD) (J68.4)

Prolonged occupational exposure to sulphuric acid can cause COPD: its clinical features have been thoroughly addressed in dedicated item 2.1.9, which should be referred to for further details.

Erosion of teeth (K03.2)

Short description of the disease

Exposure to inorganic acids (especially sulphuric acid) may cause damage to dental enamel affecting particularly the incisors.

Diagnostic criteria

Clinical manifestations

Evidence of loss of dental lustre, decalcification streaks and increased sensitivity to temperature.

Exposure assessment

- History of occupational exposure: evidence of prolonged exposure to inorganic acids (liquid, dust, aerosol or vapours), especially sulphuric acid, in the occupational setting.
- Minimum duration of exposure: six months.
- Maximum latent period: some months.

1.1.22 Diseases caused by mineral acids — ICD Code T54.2 +Z57

Nasal septum ulceration (J34.8)

Short description of the disease

Erosion and ulceration of the mucosal membrane or perforation of the nasal septum have been described in subjects chronically exposed to gas or mist of hydrogen chloride or sulphuric acid.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: nasal pain and bleeding, rhinorrhoea.
- Examinations: rhinoscopy may show nasal mucosae ulceration and perforation of the nasal septum.

Exposure assessment

- History of occupational exposure: history of repeated/continuous occupational exposure to gas or mist of hydrogen chloride or sulphuric acid.
- Minimum duration of exposure: few months.
- Maximum latent period: few months.

Name of the diseases and ICD code: **Carcinogenic effects of mineral acids**
(Specific disease code) **+T54.2, +Z57**

Laryngeal cancer (C32)

Short description of the disease

Mists from strong inorganic acids (e.g. sulphuric, hydrochloric, nitric, and phosphoric acids) have been classified as Group 1 carcinogens (i.e., carcinogenic to humans) by the IARC because of the increased risk of laryngeal cancer in occupationally exposed workers. The highest risk levels have been observed in association with pickling operations (i.e., removal of scale and oxides from the metal surface) within the steel industry.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: symptoms may vary depending on the structures involved by the tumour and the concomitant inflammatory reaction and may include: dysphagia , dysphonia, cough, dyspnoea, blood-stained sputum, together with fatigue and weakness, sore throat, and the presence of a neck mass. Otalgia should be carefully considered as a potential sign of laryngeal cancer.
- Examinations:
  - CT and MRI scans may show the extension of the tumour as well as its potential extension into the surrounding tissue.
  - Flexible laryngoscopy shows the presence of the tumour and provides opportunities for biopsies of the mass (most laryngeal cancers are squamous cell carcinomas).

Exposure assessment

- History of occupational exposure: evidence of chronic exposure to strong inorganic acid mists.
- Minimum duration of exposure: five years.
- Maximum latent period: not applicable.

Key actions for prevention	Due to their widespread and high-volume use in most industrial activities, it is unlikely that strong mineral acids can be substituted by less hazardous chemical agents. Wherever possible, highly corrosive acids should be replaced by acids that present less hazard; it is essential to use only the minimum concentration necessary for the process. Notable exceptions are found in some chemical processes, where acid catalysts prepared by simple impregnation of porous media, such as pumice, are substituted by natural or synthetic zeolites. The use of acid baths for cleaning of wrought-metal items, such as billets, wound wire, and pipes, before welding, soldering, and machining has been sided or substituted by other treatments, such as electro-polishing, which are more efficient, generate less chemical waste and allow better control of workers' exposure. Acid fumes generated in metal electroplating can be confined by covering the equipment, exhausting the effluents, and chemical treatment (e.g. by neutralization scrubbing). The use of personal protective equipment, such as face-masks and breathing protection, is required for workers who need to access machineries for unscheduled interventions and for maintenance. Protection must, in any case, prevent workers falling into tanks since the result is nearly always fatal.

1.1.22 Diseases caused by mineral acids	ICD Code T54.2 +Z57
Key actions for prevention	Especially in the informal sector, it is theoretically possible that workers unwittingly ingest acid (alkaline and oxidant) solutions, especially when such substances are stored, diluted and applied in or from improvised containers, such as unlabelled bottles. Wherever inorganic acids are used, appropriate measures should be instituted, such as the ones proposed below (which have been adapted from the ILO Encyclopaedia of occupational health and safety, 4th edition). *Storage*. Avoid contact with other acids and combustible or oxidizable materials. Electrical installations should be of the acid-resistant type. Storage areas should be separated from other premises, well ventilated, sheltered from sunlight and sources of heat; they should have a cement floor and contain no substances with which an acid might react. Large stocks should be surrounded by kerbs or sills to retain the acid in the event of leakage, and provisions for neutralization should be made. A fire hydrant and a supply of self-contained respiratory protective equipment for emergency or rescue purposes should be provided outside the storage premises. Spillages should be dealt with immediately by hosing down; in the event of a large leakage, personnel should vacate the premises and then, having donned emergency equipment, return to neutralize the acid with water or calcined sand. Electrical equipment should be waterproof and resistant to acid attack. Safety lighting is desirable. Containers should be kept tightly closed and should be clearly labelled to indicate the contents. Decompression measures should be taken where necessary. Piping, couplings, gaskets and valves should all be made of material resistant to nitric acid. Glass or plastic containers should be adequately protected against impact; they should be kept off the floor to facilitate flushing in the event of leakage. Drums should be stored on cradles or racks and chocked in position. Gas cylinders of gaseous anhydrous acid should be stored upright with the cap in place. Empty and full containers should preferably be stored apart. Maintenance and good housekeeping are essential. *Handling*. Wherever possible, acids should be pumped through sealed systems to prevent all danger of contact. Wherever individual containers have to be transported or decanted, the appropriate equipment should be employed and only experienced persons allowed to undertake the work. Decanting should be done by means of special siphons, transfer pumps, or drum or carboy tilting cradles and so on. Cylinders of anhydrous acid gas require special discharge valves and connections. Where acids are mixed with other chemicals or water, workers must be fully aware of any violent or dangerous reaction that may take place. For example, a concentrated acid should be slowly added to water, rather than vice versa, in order to avoid the generation of excessive heat and violent reactions, which can cause splashes and skin or eye contact. *Ventilation*. Where processes produce acid mists or vapours, such as in electroplating, exhaust ventilation should be installed. *Personal protection*. Persons exposed to dangerous splashes of inorganic acids should be required to wear acid-resistant personal protective equipment, including hand and arm protection, eye and face protection and aprons, overalls or coats. Provided safe working procedures are adopted, the use of respiratory protective equipment should not be necessary; however, it should be available for emergency use in the event of leakage or spillage. When workers are required to enter a tank that has contained inorganic acids in order to carry out maintenance or repairs, the tanks should first be purged, and all precautions for entry into enclosed spaces should be taken. *Training*. All workers required to handle acids should be instructed about their hazardous properties. Certain work activities, such as those involving enclosed spaces or handling large quantities of acids, should always be done by two persons, one being ready to come to the other's aid in case of need. *Sanitation*. Personal hygiene is of utmost importance where there is contact with inorganic acids. Adequate washing and sanitary facilities should be provided, and workers encouraged to wash thoroughly before meals and at the ends of shifts. *Medical supervision*. Workers should receive pre-placement and periodic medical examinations which might include a check on the condition of the teeth.

1.1.22 Diseases caused by mineral acids — ICD Code T54.2 +Z57

Some additional preventive actions for specific substances are detailed below.

Hydrochloric acid: In addition to the general measures described above, the acid should not be stored near flammable or oxidizing substances, such as nitric acid or chlorates, or near metals and metal hydrides which may be attacked by the acid with the formation of hydrogen. Electrical equipment should be flameproof and protected against the corrosive action of the vapours.

Nitric acid: Depending on the quantities and concentrations involved, nitric acid should be stored in stainless steel, aluminium or glass containers. Glass carboys or Winchesters should be protected by a metal envelope to provide resistance to impacts. However, nitric acid containing any fluorinated compounds should not be stored in glass. Organic materials such as wood, straw, sawdust and so on should be kept away from operations involving nitric acid. When nitric acid is to be diluted with water, the acid should be poured into the water, and localized heating should be avoided.

Sulphuric acid: The most effective measures are the total enclosure of processes and the mechanization of handling procedures to prevent all personal contact with sulphuric acid. Particular attention should be devoted to acid storage, handling and application procedures, the ventilation and lighting of workplaces, maintenance and good housekeeping, and personal protective equipment. In addition to the general precautions given above, sulphuric acid should not be stored near chromates, chlorates or similar substances in view of the fire and explosion hazard involved.

The group of experts considered that the following limits of exposure of workplace atmospheric concentrations have been observed to provide a reasonable level of protection for workers' health and have been used in a number of countries:

- Boric acid: 2 mg/m^3 as 8hr TWA 6 mg/m^3 as STEL.
- Hydrogen chloride: 2 ppm as STEL.
- Fluoroboric acid: 2.5 mg/m^3 (as F) as 8hr TWA.
- Nitric acid: 2 ppm as TWA; 4 ppm as STEL.
- Phosphoric acid: 1 mg/m^3 as 8hr TWA; 3 mg/m^3 as STEL.
- Sulphuric acid: 0.2 mg/m^3 as 8hr TWA.

Further reading

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Mineral acids: Summary tables
(adapted from the ILO Encyclopaedia of occupational health and safety, 4th edition)

Chemical information

Chemical name	CAS number	UN code	ICSC number	Synonyms
Boric acid	10043-35-3		0991	Boracic acid; Orthoboric acid
Chlorosulphuric acid	7790-94-5	UN1754	1039	Chlorosulphonic acid; Monochlorosulphuric acid; Sulphonic acid monochloride; Sulphuric chlorohydrin
Fluorosulphuric acid	7789-21-1	UN1777	0996	Fluorosulphonic acid; Fluosulphonic acid
Hydrochloric acid	7647-01-0	UN1050	0163	Anhydrous hydrochloric acid; Anhydrous hydrogen chloride; Chlorohydric acid; Hydrochloride; Hydrogen chloride
Hydrofluoboric acid	16872-11-0	UN1789	1040	Borofluoric acid; Fluoboric acid; Hydrogen tetrafluoroborate; Tetrafluoroboric acid
Nitric acid	7697-37-2	UN2186	0183	Agua fortis; Azotic acid
Perchloric acid	7601-90-3	UN1775	1006	Hydronium perchlorate
Phosphoric acid	7664-38-2	UN2032	1008	Orthophosphoric acid
Silicic acid	1344-09-8	UN1802	1137	Metasilicic acid; Precipitated silica; Silica gel; Sodium silicate; Sodium salt; Waterglass
Sulfamic acid	5329-14-6	UN1873	0328	Amidosulphonic acid; Amidosulphuric acid; Sulfamidic acid
Sulphuric acid	7664-93-9	UN1805	0362	Dihydrogen sulphate; Sulfuric acid 100%; Oil of vitriol

Health hazards

Chemical name	ICSC short-term exposure	ICSC long-term exposure	ICSC routes of exposure and symptoms
Boric acid			
Chlorosulphuric acid			
Fluorosulphuric acid			
Hydrochloric acid	eyes; skin; resp tract; lungs	lungs; teeth	Inhalation: corrosive, burning sensation, cough, laboured breathing, shortness of breath, sore throat, symptoms may be delayed Skin: corrosive, serious skin burns, pain Eyes: corrosive, pain, blurred vision, severe deep burns
Hydrofluoboric acid			
Nitric acid			Inhalation: corrosive, burning sensation, cough, laboured breathing, unconsciousness, symptoms may be delayed Skin: corrosive, serious skin burns, pain, yellow discolouration Eyes: corrosive, redness, pain, blurred vision, severe deep burns Ingestion: corrosive, abdominal pain, burning sensation, shock
Perchloric acid			
Phosphoric acid	eyes; skin; resp tract; lungs		Inhalation: burning sensation, cough, laboured breathing, shortness of breath, sore throat, unconsciousness Skin: redness, pain, blisters Eyes: redness, pain, blurred vision, severe deep burns Ingestion: abdominal cramps, burning sensation, confusion, laboured breathing, sore throat, unconsciousness, weakness
Silicic acid			
Sulfamic acid	eyes; skin; resp tract; lungs		
Sulphuric acid	eyes; skin; resp tract; lungs		Inhalation: corrosive, burning sensation, cough, laboured breathing, sore throat Skin: corrosive, redness, serious skin burns, pain, severe deep burns Ingestion: corrosive, abdominal pain, burning sensation, vomiting, collapse

Physical and chemical hazards

Chemical name	Physical	Chemical	UN class or division/ subsidiary risks
Boric acid			
Chlorosulphuric acid			8
Fluorosulphuric acid			8
Hydrochloric acid	The gas is heavier than air	The solution in water is a strong acid, it reacts violently with bases and is corrosive. Reacts violently with oxidants, forming toxic gas (chlorine). On contact with air it emits corrosive fumes (hydrochloric acid). Attacks many metals, forming combustible gas (hydrogen).	8
Hydrofluoboric acid			8
Nitric acid		The substance decomposes on warming producing nitrogen oxides. The substance is a strong oxidant and reacts violently with combustible and reducing materials, e.g. turpentine, charcoal, alcohol. The substance is a strong acid, it reacts violently with bases and is corrosive to metals. Reacts very violently with organic chemicals (e.g. acetone, acetic acid, acetic anhydride), causing fire and explosion hazard. Attacks some plastics.	8
Perchloric acid			5.1/8
Phosphoric acid		The substance violently polymerizes under the influence of azo compounds, epoxides and other polymerizable compounds. On combustion, forms toxic fumes (phosphorous oxides). The substance decomposes on contact with metals, alcohols, aldehydes, cyanides, ketones, phenols, esters, sulfides, halogenated organics, producing toxic fumes. The substance is a medium strong acid. Attacks metals to liberate flammable hydrogen gas.	8
Silicic acid			
Sulfamic acid			8
Sulphuric acid		On combustion, forms toxic fumes (sulphur oxides). The substance is a strong oxidant and reacts violently with combustible and reducing materials. The substance is a strong acid, it reacts violently with bases and is corrosive to most common metals, forming a flammable/explosive gas (hydrogen). Reacts violently with water and organic materials with evolution of heat. Upon heating, irritating or toxic fumes (or gases) (sulphur oxides) are formed.	8

Physical and chemical properties

Chemical name	Colour/form	Boiling point (°C)	Melting point (°C)	Molecular weight	Solubility in water	Relative density (water=1)	Relative vapour density (air=1)	Vapour pressure
Boric acid	colourless, transparent crystals or white granules or powder	300	169	61.84	1 g/18 ml	1.435 at 15°C		
Chlorosulphuric acid	colourless or slightly yellow liquid	151-152 at 755 mm Hg	-80	116.53		1.753	4.02	at 32 °C
Fluorosulphuric acid	colourless liquid; reddish-brown colour with acetone	163	-89	100.07		1.726 at 25°C/4°C		
Hydrochloric acid	colourless liquid	-85	-114	36.46	82.3 g/100 ml	1.05 at 15 °C/4 °C	1.3	
Hydrofluoboric acid	colourless liquid	130		87.82	misc	1.84		
Nitric acid	transparent colourless or yellowish liquid	83	-42	63.01	sol	1.5027 at 25°C/4°C	2-3	6.4
Perchloric acid	colourless, oily liquid	19 at 11 mm Hg	-112	100.47	misc	1.768 at 22 °C		
Phosphoric acid	unstable orthorhombic crystals or clear syrupy liquid; at 20 deg C, the 50 and 75% strengths are mobile liquids, the 85% is of a syrupy consistency, while the 100% acid is in the form of crystals; viscous, colourless, odorless liquid	213	42.4	98	v sol		3.4	4
Silicic acid	jelly-like precipitate obtained when sodium silicate solution is acidified during drying jelly is converted to a white amorphous powder.							
Sulfamic acid	orthorhombic crystals; white crystalline solid		205	97.1	sol	2.15		
Sulphuric acid	clear, colourless, oily liquid when pure but brownish in hue when impure	290	10.4	98.08	sol	1.841	3.4	0.13

▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
1.1.22	Acute/chronic diseases caused by mineral acids	T54.2	NE61&XM6PB5
1.1.22	Mucous membranes irritation	J68	CA81.Y
1.1.22	Acute chemical pneumonitis and bronchitis	J68.0	CA81.0
1.1.22	Upper respiratory inflammation	J68.2	CA81.2
1.1.22	Pulmonary oedema	J68.1	CA81.1
1.1.22	Reactive airways dysfunction syndrome (RADS)	J68.3	CA81.Y
1.1.22	Irritant-induced acute occupational asthma	J68.3	CA81.Y
1.1.22	Burns and corrosions of eye and adnexa	T26.0-T26.1, T26.5-T26.6	NE00
1.1.22	Conjunctivitis	H10.2	9A60.Z
1.1.22	Blepharoconjunctivitis	H10.5	9A60.4
1.1.22	Keratoconjunctivitis	H16.2	9A7Z
1.1.22	Corneal ulcer	H16.0	9A78.8
1.1.22	Burns and corrosions of gastrointestinal tract	T28.0-T28.2, T28.5-T28.7	NE02, NE0Z
1.1.22	Burns and corrosions of external body surface	T20-T25	ND9Z
1.1.22	Acute irritant contact dermatitis	L24	EK02
1.1.22	Acute toxic renal failure with tubular necrosis	N17.0	GB60.Z
1.1.22	Acute toxic liver disease	K71.9	DB95.Z
1.1.22	Liver toxicity (impairment, functional)	K72.9	DB99.7
1.1.22	Chronic obstructive pulmonary disease (COPD)	J68.4	CA22.Z
1.1.22	Chronic skin and mucous membranes irritation	L24	EK02
1.1.22	Erosion of teeth	K03.2	DA08.12
1.1.22	Nose septal ulceration	J34.8	CA0Z
1.1.22	Laryngeal cancer	C32	2C23.Z
	Occupational exposure to risk factors	Z57	QD84.Y

1.1.23 Diseases caused by pharmaceutical agents	ICD Code (T36-T50)+ Z57.5
General characteristics of the causal agent	Pharmaceutical agents comprise a variety of inorganic and organic chemical compounds that are used to prevent, diagnose or treat diseases in humans and animals. In the pharmaceutical industry, most drugs (active principles) are obtained by batch chemical synthesis in a way similar to several other speciality chemicals, such as dyes and pesticides. Production volumes vary widely: for some compounds, such as antibiotics, which can easily reach several thousand tons per year. In a few cases, drugs are extracted and purified from natural sources (mostly vegetable plants). The extraction of drugs from animal sources, such as from slaughterhouse offal (liver, pancreas, brain, adrenal capsules), has been greatly reduced and superseded by biotechnological processes due to the biological hazard posed by viral and prion diseases. The only exception is the production of human blood and of plasma-derived products. In all cases, stringent precautions are adopted throughout the industrial production, formulation and compounding, packaging and storing process to ensure identity, purity, stability, homogeneity, safety, and tracing of the final product. Nowadays, commercial formulations of drugs are often prepared from active drug substances produced in other chemical plants. It is worth mentioning that the World Health Organization classifies pharmaceutical agents according to the Anatomical Therapeutic Chemical (ATC) classification system, which divides drugs into different groups according to the organ or system on which they act and their therapeutic and chemical characteristics.
Occupational exposures	Chemical workers in pharmaceutical production plants and health and veterinary workers are those most likely to be exposed to pharmaceutical drugs. Farmers and farm-workers might be exposed to concentrated veterinary drugs, especially during top dressing (i.e., application) and mixing into water or feed of ready-to-use veterinary medical products. In addition, workers in academic and industrial research and development institutions can also be exposed to existing and new drugs that are being developed. In the pharmaceutical industry, exposure occurs in the production of active drug substances by chemical synthesis or during extraction processes, and in the formulation phase, when active substances are delivered, dried, milled, blended, and transformed into the final packaged products for distribution and marketing. Exposure to pharmaceutical products is a particular concern when mixtures containing high proportions of active substances are handled or processed. Wet granulation, compounding, and coating operations may cause workers' exposure to solvent vapours. Activities at higher risk of exposure are weighing, assembly, granulation, compression and packaging operations. Skin absorption may occur, particularly during the wet phases of granulation, since alcohol solutions are used. Quality-control and laboratory personnel are at risk of exposure while sampling, assaying or otherwise handling substances. Maintenance personnel can be exposed while cleaning, repairing or inspecting mixers, hoppers, mills, vacuum lines and ventilation systems, or changing filters. In the healthcare settings, nurses, pharmacy technicians, and (to a much lesser extent) surgeons and medical doctors prepare and administer therapies to patients. Administration of drugs via aerosol can lead to measurable air concentrations in the breathing zone of workers providing treatment. A major health concern regards the very toxic and potentially carcinogenic active agents, such as some anti-cancer drugs. Contact with hazardous drugs can take place via contact with treated patients and their biological fluids by cleaning staff, personal care workers, hospital laundry workers, and waste handlers. There is increasing use of veterinary drugs in cattle farming and in the care of pet animals, and this often carries a higher chance of exposure for veterinarians. There is a chance (albeit limited) of exposure to pharmaceutical drugs both as raw chemicals and as packaged products in logistics (shipping and land transportation, receiving and storage, custody).
Toxicological profile, main health effects and diagnostic criteria	
Short toxicological profile	Pharmaceutical drugs (somewhat like pesticides, see item 1.1.36) show several specific differences in their occupational hazards, compared to dyes, plasticizers, resins, lubricants and other utility chemicals. First, the amounts used are far less than those of production chemicals and of chemical auxiliaries in manufacturing (e.g. solvents). Moreover, the circumstances that can lead to occupational exposure and the number of possibly exposed workers are often far less concerning; nonetheless, exposure during manufacturing is not limited to the active substances but may include reagents, intermediates, and solvents used in the (usually batch and multistep) processes of synthesis and purification.

1.1.23 Diseases caused by pharmaceutical agents	ICD Code (T36-T50)+ Z57.5
Short toxicological profile	Second, while the effects of most production chemicals and chemical auxiliaries are broadly generic on body tissues and organs, biologically active chemicals, such as pharmaceutical drugs (and pesticides), have a much higher built-in degree of specific interaction with tissues, which in turn leads to pathways for toxicity that are more specific than with most other chemicals. Moreover, the properties of pharmaceutical drugs (and pesticides) are much better known before they enter the market when compared with other speciality chemicals such as organic dyes, industrial auxiliaries, and additives of comparable chemical complexity. The toxic effects of pharmaceutical drugs are mostly related to the pharmacological and side effects of the drugs purposely administered to the patients. As for the safety side, it is worth mentioning that the doses of pharmaceutical drugs the workers might be exposed to are usually lower than the therapeutic ones by orders of magnitude. In addition, pharmaceutical drugs used to treat chronic conditions are specifically evaluated for lack of toxic or side effects, even after a lifetime of use. In some cases, the toxicity to humans is relevant, but the necessity of use is based on a cost-benefit analysis, as might be the case with antineoplastic drugs. In some instances, the health effects of the active ingredients of pharmaceutical drugs are a consequence of their expected biological properties. Typical cases of unwanted effects in pharmaceutical workers are the hormonal effects of active steroids, such as birth control products and hormone replacement drugs. Effects such as menses dysregulation in females, and gynaecomastia in men, were first observed in compounding facilities where contraceptives were prepared as the first high-volume, highly active hormonal drugs that could be administered orally and thus that can be absorbed through occupationally relevant routes, especially by inhalation of dusts. Another side effect of pharmaceutical drugs that can occur because of occupational exposure is allergic sensitization, as first observed in the case of beta-lactam antibiotics such as natural and semi-synthetic penicillins and cephalosporins. Occupational exposure to therapeutic antibiotics may not only cause potentially fatal allergies in sensitized individuals but also foster the development of antibiotic-resistant fungal and bacterial species. As regard anti-cancer drugs, most of them are explicitly designed to kill diseased human cells; however, their selectivity is often poor, and other types of proliferating cells are targeted. In some cases, such as the alkylating antineoplastic drugs, the pharmaceutical agents target directly the cell's DNA (which renders these drugs inherently carcinogenic), or present other occupationally unacceptable risk, such as teratogenicity. Other classes of anti-cancer drugs present less threatening but still serious health risks for occupationally exposed workers, such as neurotoxicity (*Vinca* alkaloids), cumulative cardiotoxicity (anthracycline antibiotics), or immunotoxicity (some nucleoside analogues).

Name of the diseases and ICD code: **Diseases caused by pharmaceutical agents**
(Specific disease code) **(T36-T50)+ Z57.5**

Respiratory tract irritation (J68), Irritant-induced occupational asthma (J68.3), Irritant contact dermatitis (L24)

Short description of the disease

Workers who are involved in the aerosol administration of medications may suffer symptoms of respiratory tract irritation. Direct contact of the drugs with skin and mucous membranes may cause irritation and even, in case of contact with antineoplastic drugs, chemical burns of skin and mucous membranes.

Diagnostic criteria

Clinical manifestations

- Symptoms of respiratory tract irritation include cough, wheezing, and symptoms of 'bronchial irritability'. Chest tightness and breathlessness may be present. The onset of symptoms occurs within 24 hours after a single specific exposure.
- Signs and symptoms of irritant contact dermatitis range from simple irritation (redness, itching, scaling, minor erythema) to severe (third-degree) chemical burns (corrosion), including erythema, swelling, blisters, oozing and crusting. If the disease evolves into chronic dermatitis, its main features are desquamation, thickening and lichenification of the skin with painful fissures. Lesions are confined to the areas exposed to the irritants (mainly the hands and arms). Volatile irritants may cause airborne lesions in uncovered skin areas, like the face and neck. Signs are usually accompanied by pain and burning sensations.
- As both irritant-induced occupational asthma and irritant contact dermatitis have been thoroughly addressed elsewhere, refer to dedicated items 2.1.7 and 2.2.2, respectively, for further details.

1.1.23 Diseases caused by pharmaceutical agents ICD Code (T36-T50)+ Z57.5

Exposure assessment

- History of occupational exposure: confirmed occupational exposure to irritant pharmaceutical agents through inhalation or contact of skin and mucous membranes.
- Minimum duration of exposure: extremely variable, depending on the intensity of the exposure and the characteristics of the compound but may be as short as seconds, especially for irritation of the respiratory tract.
- Maximum latent period: no more than some days, usually no more than a few hours.

Sensitizer-induced occupational asthma (J45.0), Allergic rhinitis (J30.3), Contact urticaria (L50.0), Allergic contact dermatitis (L23)

Short description of the disease

Allergy to antibiotics and non-steroidal anti-inflammatory drugs has been reported in workers who are exposed to these pharmaceutical agents. Exposure in susceptible individuals can lead to asthma or allergic contact dermatitis. Occupational exposure to antineoplastic drugs can cause allergic-type reactions in workers. Beta-lactam antibiotics are well known as particularly effective sensitizers.

Diagnostic criteria for sensitizer-induced occupational asthma and allergic rhinitis

Clinical manifestations

- Signs and symptoms:
  - Episodic wheezing, difficulty in breathing, chest tightness and cough. Excess sputum production is common. Pre-existing asthma does not exclude the development of occupational asthma.
  - Allergic rhinitis manifests itself with rhinorrhoea, sneezing, lacrimation, red eyes, itchy eyes, nose and throat, nasal cavity obstruction, watery and pale nasal mucosae, congested conjunctivae.
- Examinations:
  - Eosinophils can be found in the nasal secretions of the affected subjects.
  - Lung function testing may show evidence of airway obstruction.
  - Recording serial peak flow measurements (sPEF) is the initial method of either confirming or refuting a possible occupational cause for asthma.
  - Serum specific IgE to the hypothesized sensitising agent may be present and may assist in making a diagnosis, together with more sophisticated exams such as the basophil activation test (BAT) that return positive results in case of sensitization.
  - Non-specific bronchial reactivity to challenge with a variety of agents (including histamine, methacholine, mannitol) may be increased in occupational asthma. Additionally, sequential measures of airway reactivity, including periods at work and away from work, may assist in making a diagnosis.
  - Specific bronchial challenge to the agent (in a specialist facility under carefully controlled conditions) may assist in making a diagnosis. It can generally be interpreted in a similar way to specific IgE testing. Note that a negative test does not exclude this diagnosis.

Exposure assessment

- History of occupational exposure: confirmed occupational exposure to the sensitizing pharmaceutical agent.
- Minimum duration of exposure: usually from weeks to years, but, in some cases, this period may be as short as a few days.
- Maximum latent period: usually between 3 to 24 months but may be shorter in atopic subjects, and in exceptional cases, it may be as short as a few days. In sensitized subjects, the latency between exposure and onset of symptoms is usually no longer than 48 hours.

Diagnostic criteria for allergic contact dermatitis (ACD)

Clinical manifestations

- Signs and symptoms: redness, swelling, vesicles, oozing and crusting (acute eczematous reaction) of the skin. The development of the skin lesions is in direct relationship to the work activities, with a pattern of recurrence of the disease on re-exposure to the same agent. Through a cumulative effect, repeated contact with the allergen can cause a sub-acute form of contact dermatitis characterized by dry, and red plaques. If the exposure continues, dermatitis will become chronic. Features of chronic ACD are dry, thickened and scaly skin, cracking and fissuring of the fingers and palms, chronic nail dystrophy (chronic eczematous reaction). Itch (pruritus) is usually present.

1.1.23 Diseases caused by pharmaceutical agents ICD Code (T36-T50)+ Z57.5

- Examinations:
  - Lesions are localized at allergen contact sites but often spread in the surrounding area or even to other body sites. Occupational ACD is mainly found on the hands. Upon exposure to volatile allergens or by transference from the hands, it may occur at the face, neck, arms.
  - Patch tests should be performed by a specialized physician. This diagnostic approach might bring about sensitization, and the testing concentration should be defined according to specific recommendations.

Exposure assessment

- History of occupational exposure: confirmed previous occupational exposure (at least one episode) to the allergenic substance and onset of signs and symptoms as a consequence of subsequent exposures. A dose-effect relationship in the onset of allergic contact dermatitis can usually be shown. In general, induction of sensitization needs higher levels of exposure than elicitation.
- Minimum duration of exposure: usually several instances of exposure are required over long periods for sensitization, but in exceptional cases even a single contact might be sufficient. For elicitation of ACD in sensitized individuals, a skin contact with the allergen of a few minutes to several hours may give rise to skin reactions.
- Maximum latent period: in sensitized subjects any further exposure to the agent causes the onset of clinical signs usually within 12-72 hours, or even later (up to 1-2 weeks).

Diagnostic criteria for contact urticaria

Clinical manifestations

- Signs and symptoms: acute wheals and flare skin reactions (urticaria) and itch within minutes after contact with the allergenic substance. Contact urticaria has a duration of minutes to 24 hours. Occasionally, it may develop into generalized urticaria and in anaphylaxis affecting internal organs (contact urticaria syndrome, grade 2 onward). The pathology of urticaria is characterized by oedema of the superficial dermis. Particular care is needed in the investigation of subjects with systemic symptoms.
- Examinations: serum specific IgE to the hypothesized sensitising agent may be present and may assist in making a diagnosis, together with more sophisticated exams such as the basophil activation test (BAT) that return positive results in case of sensitization.

Exposure assessment

- History of occupational exposure: confirmed previous occupational exposure (at least one episode) to the allergenic substance and onset of signs and symptoms as a consequence of subsequent exposures.
- Minimum duration of exposure: the sensitization period is generally 10 to 15 days. After sensitization, any further exposure causes the onset of clinical signs in allergic subjects within 15 to 30 min.
- Maximum latent period: in sensitized subjects, any further exposure to the agent causes the onset of clinical signs usually within hours, not longer than 1 day.

Hyperoestrogenic syndrome (E28.0), Gynaecomastia (N62), Menstrual disorders (N92.6)

Short description of the disease

High occupational exposures to endocrine modulators can result in the hyper-oestrogenic syndrome. The syndrome in both male and female workers has often been associated with exposures to diethylstilbestrol (DES, a synthetic oestrogen) and its derivatives, natural or conjugated oestrogens hexoestrol and its derivatives and steroidal synthetics such as ethynyloestradiol and mestranol. There have been reports of toxicity associated with some progestogenic compounds, including acetoxy-progesterone and vinyl-estrenolone in combination with ethynyl-estradiol.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms:
  - Among the reported effects are: nipple sensitivity (tingling or tenderness of the nipple); a feeling of pressure in the breast area and gynaecomastia; a decreased libido and impotence among male workers; menstrual disorders (increased flow or inter-menstrual spotting, abnormal over-growth of the endometrium and excessive bleeding during menopause), with nausea, headaches, breast pain, leucorrhoea and ankle oedema among female workers.
  - Exposure of male workers to progestogen may cause a lack of libido and testicular pain. On the other hand, exposure of female workers to androgens is known to cause menstrual and ovarian function disorders, diminished fertility, increased frequency of spontaneous abortions, and symptoms consequent to hyperandrogenicity.

1.1.23 Diseases caused by pharmaceutical agents ICD Code (T36-T50)+ Z57.5

- Examinations:
  - Specific hormone blood tests to verify variation from physiological levels.
  - Serum ethynyloestradiol levels appeared to show possible oestrogen exposure and absorption despite the use of respirators.

Exposure assessment

- History of occupational exposure: evidence of occupational exposure to the pure active oestrogenic compound through inhalation (and to some extent oral ingestion) and, when available, detection of the compound or its metabolites in biological fluids.
- Minimum duration of exposure: depending on the substance and the levels of exposure.
- Maximum latent period: weeks.

Prolongation of bleeding, coagulation or prothrombin time (D68.9), Epistaxis (R04.0)

Short description of the disease

Alteration of coagulation and bleeding from prolonged occupational exposure to coumarin and its derivatives via inhalation, ingestion, and dermal absorption among employees in pharmaceutical industries has been reported. The drugs act by blocking liver prothrombin production and by causing vascular injury at the capillary level.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: petechial rashes, epistaxis, gum bleeding, ecchymosis and haematoma. Theoretically, more severe effects such as haematuria, hematemesis, melena, and intracerebral haemorrhage may occur.
- Examinations: increased clotting, prothrombin, and partial thromboplastin time; some subjects may have decreased haemoglobin levels, as well as haematuria.

Exposure assessment

- History of occupational exposure: evidence of chronic occupational exposure to warfarin or its derivatives (e.g. manufacture of Coumadin drugs) and, when available, detection of the compounds or their metabolites in biological fluids.
- Minimum duration of exposure: depending on the intensity of exposure (theoretically, even a single high dose can cause the diseases).
- Maximum latent period: few weeks.

Bacterial infection (A49) resistant to antibiotics +(U80-U89), Vitamins B deficiency (E53.9), Opportunistic/fungus skin infections (B36.9), Opportunistic/fungus nail infections (B35.1), Vaginal candidiasis (B37.3)

Short description of the disease

Exposure to antibiotics, even at low doses, may cause development of bacterial resistance, as well as modification of the microbiological flora. In workers exposed to antibiotics, changes in the bacterial population present in the gastrointestinal tract may lead to a drop in the body's vitamin content, especially of the B vitamins. The condition of antibiotic resistance becomes manifest when an infection demonstrates a lack of response to antibiotic therapy. Opportunistic fungal infections of the skin, genital tract and nails can be observed in workers exposed to antibiotics. Cases of vaginal yeast infections resistant to therapy have been reported in exposed workers. Microbiological testing of bacteria and fungi collected from infections in skin, nails, genital tract and other parts of the body should be performed, with assessment of resistance to antibiotics of the collected microorganisms.

Exposure assessment

- History of occupational exposure: confirmed chronic occupational exposures to specific antibiotics and, when available, detection of the antibiotics or their metabolites in biological fluids.
- Minimum duration of exposure: some months.
- Maximum latent period: some months.

1.1.23 Diseases caused by pharmaceutical agents — ICD Code (T36-T50)+ Z57.5

Accidental poisoning by and exposure to tranquilizers, antidepressants, and anaesthetic gases (X44)

Occupational exposure to particularly high concentrations of tranquilizers, antidepressants, and anaesthetic gases in workers of pharmaceutical industries and operating rooms (respectively) might, at least theoretically, cause toxic syndromes characterized by neurological and neurobehavioral effects. The main symptom of overexposure to tranquilizer drugs, sleep inducers, and anaesthetic gases is sedation, with degree of severity varying with the dose. Inhaled nitrous oxide used as an analgesic is sometimes abused for its central nervous system effects.

Exposure assessment

- History of occupational exposure: evidence of occupational exposure to tranquilizers, antidepressants, and anaesthetic gases and, when available, detection of the compounds or metabolites in biological fluids.
- Minimum duration of exposure: depending on the intensity of exposure.
- Maximum latent period: some days.

Liver toxicity (impairment, failure) (K72.9), Infertility (N46, N97.0), Congenital malformation syndromes (Q86.8), Alopecia (L65.9)

In theory, exposure to cytotoxic drugs may cause hepatic injury, as well as symptoms such as lightheadedness, dizziness, nausea, headache, and allergic reactions. These agents are known to be toxic to the skin and mucous membranes, including the cornea, and can cause skin rashes, allergic-type reactions and hair loss. Workplace exposure to antineoplastic drugs has been associated in the past with adverse reproductive outcomes and increased foetal loss (antineoplastic drugs may reduce fertility and increase poor neonatal outcomes among occupationally exposed oncology nurses). These effects have not been confirmed by more recent studies, but might occur when occupational exposures are poorly controlled, because of the intrinsic toxicity of these compounds.

Exposure assessment

- History of occupational exposure: evidence of occupational exposures to antineoplastic drugs by inhalation, ingestion and skin contact or absorption and, when available, detection of the antineoplastic drugs or their metabolites in biological fluids.
- Minimum duration of exposure: one single exposure for acute effects; weeks for the others.
- Maximum latent period: minutes for the acute effects; weeks for the others.

Carcinogenic effects of antineoplastic drugs (T45.1)

Several antineoplastic agents have carcinogenic properties (to the point that the International Agency for Research on Cancer classified some as Group 1 carcinogens), but there is no firm epidemiological evidence of an increased cancer risk in exposed workers. Working in an oncology pharmacy or ward might theoretically entail prolonged exposures over time; as such, according to the precautionary principle, all preventive measures (see below) must always be implemented. Particularly at-risk situations include preparation of drug mixtures, administration of therapy, or assistance to cancer patients, when accidental spillage of antineoplastic drugs may occur. The main route of exposure is dermal contact and absorption from the skin, inhalation of dusts or aerosols is much less likely, and ingestion should be the least likely.

Key actions for prevention	Considering the necessity to treat and cure diseases, and the expanding number of people who receive sanitary and medical services, the pharmaceutical field is ever-expanding, as is the working population that is involved in manufacturing and use of pharmaceutical drugs. The chemical manufacturing of pharmaceutical drugs is an increasingly global enterprise, and the production of active ingredients is progressively expanding, and out-sourced to industrially developing countries. Stringent requirements of certified quality and full traceability of active substances and of formulated drugs are necessary for the global marketing of these products, due to the requirements of the national authorities of the most developed countries and of international organizations. Therefore, the “Big Pharma” market players adopt the highest degree of manufacturing and compounding good practice in their own and in the licensed facilities worldwide. In these large-scale production units contamination is kept to a minimum and occupational exposure to active substances is usually below levels causing health effects.

1.1.23 Diseases caused by pharmaceutical agents	ICD Code (T36-T50)+ Z57.5
Key actions for prevention	For the occupational safety of healthcare providers, especially in the handling of anticancer drugs, many of the same concepts apply. In developed countries, not only are there guidelines aimed at minimizing the risk of undue exposure of pharmacy technicians and oncology nurses, but also state-of-the-art devices that limit or reduce exposure are available. These single-use devices allow health care workers to mix, dilute and administer by intravenous infusion personalized mixtures of anti-cancer drugs, with minimal to no exposure of personnel. The main tenets for the management of the preparation and administration of chemotherapy to cancer patients and of risk management of hospital workers are: (a) Preparation in isolated, labelled, restricted-access, fully equipped units within the hospital pharmacy, with independent ventilation and equipped with biological safety cabinets for drug manipulation. Very large units can use preparation robots that exclude pharmacy technicians from direct contact with drugs; very small scale preparation, such as directly at patient's home or hospice can be performed with single-use, closed-circuit devices. (b) Involvement of the lowest number of highly trained workers, who wear full body protection with specially designed items (aprons, gloves, facemasks) that are checked for resistance to the penetration of drug solutions. (c) Safe storage of drugs and safe transportation of formulated therapies in controlled paths and in isolated containers. (d) Administration of therapies to patients in dedicated hospital facilities by specialized and trained nurses, who wear appropriate full body protection and use closed-loop infusion devices. (e) Safe disposal of hospital wastes derived from cancer pharmacies and wards. (f) Continuous availability at the pharmacy and administration units of single-use equipment to manage accidental spills and to collect patient body fluids in the case of adverse effect that occur during therapy. (g) Scheduled and as-needed medical surveillance of the hospital operators, including withdrawal from duty of pregnant and of breastfeeding workers, of workers with specific diseases and disabilities, or recovering from specific diseases. (h) Scheduled surveillance of the levels of contamination in the preparation pharmacy, in the patient's ward and of the operators themselves, mainly with the use of surface wipe sampling, rather than of workplace air monitoring. (i) In case of a suspected exposure of the pharmacist or nurse, post-accident medical surveillance with possible inclusion of biological monitoring to assess the level, if any, of absorption of antineoplastic drugs.

Further reading

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2. Occupational Safety and Health Administration. Technical manual, Section VI, Chapter 2 – Controlling occupational exposures to hazardous drugs. Available at: https://www.osha.gov/dts/osta/otm/otm_vi/otm_vi_2.html. Last accessed: December 2020.
3. ILO Encyclopaedia of occupational health and safety, 4th edition; available at: https://iloencyclopaedia.org/. Last accessed: December 2020.
4. Heron RJL, Pickering FC. Health effects of exposure to active pharmaceutical ingredients (APIs). Occup Med (Lond). 2003;53(6):357-62. doi: 10.1093/occmed/kqg115.
5. International Agency of Research on Cancer (IARC). Pharmaceuticals. Volume 100A. A review of human carcinogens. Monographs on the Evaluation of Carcinogenic Risks to Humans. 2012.
6. Hausmann OV, Gentinetta T, Bridts CH, Ebo DG. The basophil activation test in immediate-type drug allergy. Immunol Allergy Clin North Am. 2009;29(3):555-66. doi: 10.1016/j.iac.2009.04.011.

For the chemical entities listed below an entry exists in the collection of International Chemical Safety Cards (ICSC) hosted in the ILO website

Name	Synonyms	ICSC
Nitrous oxide	Dinitrogen monoxide; Hyponitrous acid anhydride; Laughing gas; Dinitrogen oxide	0067
Ozone		0068
Oxygen		0138
Picric acid	2,4,6-Trinitrophenol	0316
Polydimethylsiloxane	Dimethyl polysiloxane	0318
Titanium dioxide	Rutile	0338
Rosin	Colophony; Gum rosin	0358
Aluminum hydroxide	Alumina hydrate; Aluminum oxide trihydrate; Trihydroxyaluminum	0373
Antipyrine	1,2-Dihydro-1,5-dimethyl-2-phenyl-3H-pyrazol-3-one; 2,3-Dimethyl-1-phenyl-3-pyrazolin-3-one; Phenazone	0376
Caffeine	1,3,7-Trimethylxanthine; 3,7-Dihydro-1,3,7-trimethyl-1H-purine-2,6-dione; Methyltheobromine; Methyltheophylline	0405
Sodium lauryl sulfate	Dodecyl sodium sulfate; Lauryl sodium sulfate; Sodium dodecyl sulfate	0502
Salicylic acid	2-Hydroxybenzoic acid; o-Hydroxybenzoic acid	0563
Sodium borate	Disodium tetraborate decahydrate, Sodium tetraborate decahydrate; Sodium pyroborate decahydrate; Borax	0567
Creosote	Wash oil; Creosote oil; Coal tar creosote	0572
Potassium permanganate	Permanganic acid potassium salt	0672
Theophylline	3,7-Dihydro-1,3-dimethyl-1H-purine-2,6-dione; 1,3-Dimethylxanthine	0678
Cyclophosphamide (anhydrous)	2-Bis (2-chloroethyl) amino tetrahydro-2H-1,3,2-oxazaphosphorin-2-amine 2-oxide; N,N-Bis (2-chloroethyl)tetrahydro-2H-1,3,2-oxazaphosphorin-2-amine 2-oxide; 2-H-1,3,2-Oxazaphosphorinane	0689
Potassium perchlorate	Potassium hyperchlorate; Perchloric acid; potassium salt; Peroidin	0714
Silver	Argentium; C.I. 77820	0810
Oxygen difluoride	Oxygen fluoride; Fluorine monoxide; Difluoride monoxide	0818
Warfarin	3-(alpha-Acetonylbenzyl)-4-hydroxycoumarin; 4-Hydroxy-3-(3-oxo-1-phenylbutyl)-2H-1-benzopyran-2-one	0821
Enflurane	2-Chloro-1-(difluoromethoxy)-1,1,2-trifluoroethane; Ethrane; Ether, 2-chloro-1,1,2-trifluoroethyl difluoromethyl; 2-Chloro-1,1,2-trifluoroethyl difluoromethyl ether	0887
D-sorbitol	D-glucitol; Hexahydric alcohol; Glucitol	0892
Tetrapotassium pyrophosphate	Potassium pyrophosphate; Pyrophosphoric acid; tetrapotassium salt	0983
Oleic acid	9-Octadecenoic acid; 9,10-Octadecenoic acid; Oleinic acid cis-9-Octadecenoic acid	1005
Isoniazid	Isonicotinic hydrazide; 4-pyridinecarboxylic acid	1258
Paracetamol	Acetaminophen; 4-Hydroxyacetanilide; p-Acetylaminophenol; N-(4-Hydroxyphenyl) acetamide	1330
Propylene glycol dinitrate	1,2-Propanediol dinitrate; PGDN	1392
Coal-tar pitch	Pitch	1415
Isoflurane	Ether, 1-chloro-2,2,2-trifluoroethyl difluoromethyl; 2-Chloro-2-(difluoromethoxy)-1,1,1-trifluoroethane	1435
Sevoflurane	1,1,1,3,3,3-Hexafluoro-2-(fluoromethoxy)propane; Ether, fluoromethyl 2,2,2-trifluoro-1-(trifluoromethyl)ethyl-	1436
Desflurane	1,2,2,2-tetrafluoroethyl difluoromethyl ether	1437
Disulfiram	Tetraethylthiuramdisulfide; 1,1'-Dithiobis(N,N-diethylthioformamide); bis-(N,N-Diethylthiocarbamoyl)disulfide; TETD	1438
Petrolatum (white)	Vaseline; Petroleum jelly; Paraffin jelly	1440

Name	Synonyms	ICSC
Castor oil	Ricinus oil	1452
Riboflavin	Lactoflavine; Vitamin B2	1454
Povidone-iodine	1-Vinyl-2-pyrrolidinone polymers, iodine complex; 1-Ethenyl-2-pyrrolidinone homopolymer compound with iodine; Poly(1-(2-oxo-1-pyrrolidinyl)ethylene)iodine complex	1471
Polyethylene glycol	PEG; Oxyethylene polymer; Poly(oxy-1,2-ethynediyl); alpha-hydro-omega-hydroxy	1517
Nonoxynol-9	Nonoxynol-9; Nonyl phenoxypolyethoxyethanol	1558
White mineral oil	Paraffinum liquidum; Paraffin oil	1597
Methoxyflurane	2,2-Dichloro-1,1-difluoroethyl methyl ether; 2,2-Dichloro-1,1-difluoro-1-methoxyethane; Methoflurane; Penthrane	1636

▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
1.1.23	Poisoning by drugs, medicaments and biological substances	(T36-T50)	NE60
1.1.23	Respiratory tract irritation	J68	CA81.Z
1.1.23	Irritant-induced occupational asthma	J68.3	CA81.Y
1.1.23	Irritant contact dermatitis	L24	EK02
1.1.23	Sensitizer-induced occupational asthma	J45.0	CA23.0
1.1.23	Allergic rhinitis	J30.3	CA08.03
1.1.23	Contact urticaria	L50.0	EB01.3
1.1.23	Allergic contact dermatitis	L23	EK00
1.1.23	Hyperoestrogenic syndrome	E28.0	5A80.Z
1.1.23	Gynaecomastia	N62	GB22
1.1.23	Menstrual disorders	N92.6	GA20.3
1.1.23	Prolongation of bleeding, coagulation or prothrombin time	D68.9	3B4Z
1.1.23	Epistaxis	R04.0	MD20
1.1.23	Bacterial infection resistant to antibiotics	(A49)+U80-U89	1C41& MG5Z
1.1.23	Vitamins B deficiency	E53.9	5B7Z
1.1.23	Opportunistic/fungus skin infections	B36.9	1F2D
1.1.23	Opportunistic/fungus nail infections	B35.1	1F28.1
1.1.23	Vaginitis candidiasis	B37.3	1F23.10
1.1.23	Accidental poisoning by and exposure to tranquilizers, antidepressants, and anaesthetic gases	X44	PB28
1.1.23	Liver toxicity (impairment, failure)	K72.9	DB99.7
1.1.23	Infertility	N46, N97.0	GA31.Z, GB04.Z
1.1.23	Congenital malformation syndromes	Q86.8	LD2F.Z
1.1.23	Alopecia	L65.9	ED70.Z
1.1.23	Carcinogenic effects of antineoplastic drugs	T45.1	NE60
	Occupational exposure to toxic agents in other industries (solids, liquids, gases or vapours)	Z57.5	QD84.2

1.1.24 Diseases caused by nickel or its compounds	ICD Code T56.8 +Z57
General characteristics of the causal agent	*Nickel* [Ni (powder), CAS number 7440-02-0] is a silvery white metal, whose dust or granular form is pyrophoric and explosive. It is the chemical element with atomic number 28 in the periodic table of elements. It is classified in Group 10 (VIII-B) and is naturally present as two main stable isotopes (^{58}Ni. 68% and ^{60}Ni. 26%), three minor isotopes (^{61}Ni, ^{62}Ni, ^{64}Ni) and one natural radioactive isotope (^{59}Ni with a half-life of 76,000 yr). Nickel is a medium-density, highmelting (1,455°C) metal, ferromagnetic at ambient temperature. Chemically it is a transition metal close to iron. Elemental nickel dissolves in acids in water solution and shows oxidation numbers II and III; the latter is unstable in water solution but stabilizes by the formation of coordination compounds with thiols. Nickel occurs in the environment mostly in the form of its inorganic nickel (II) compounds. Nickel compounds of industrial relevance include nickel oxide, nickel hydroxide, nickel subsulphide, nickel sulphate, nickel chloride, and nickel tetracarbonyl. *Nickel oxide* [NiO (powder), CAS number 1313-99-1] is a green to black crystalline powder, mainly used as an intermediate in the production of nickel alloys. *Nickel hydroxide* [$Ni(OH)_2$, CAS number 12054-48-7] is an apple-green electroactive solid that finds widespread applications in rechargeable batteries. *Nickel subsulphide* [Ni_3S_2, CAS number 12035-72-2] appears as pale yellowish bronze lumps with metallic lustre; it decomposes on heating to high temperatures producing sulphur oxides. *Nickel sulphate* [$NiSO_4$, CAS number 7786-81-4] is a green, yellow or blue solid, mainly used in electroplating and as a chemical intermediate to produce other nickel compounds. *Nickel chloride* [$NiCl_2$, CAS number 7718-54-9] is a yellow or green solid mainly used in electroplating, in nickel catalysts, and to absorb ammonia in industrial gas masks. *Nickel tetracarbonyl* [$Ni(CO)_4$, CAS number 13463-39-3] is a member of the family of metal carbonyl coordination compounds. It is a low-boiling (43°C) liquid with a threshold for odour perception at 1-3 ppm. It is prepared by flowing carbon monoxide over finely divided nickel metal at temperature > 50°C; the mixture heated at temperatures of 180°C or higher decomposes back to high purity nickel and carbon monoxide. This process (Mond process, sometimes known as the carbonyl process) is used industrially to isolate nickel from its ore.
Occupational exposures	Nickel is widely present in the earth's surface. Mineral forms of nickel of commercial interest are mainly the mixed nickeliron oxides and sulphides such as laterite and pentlandite ores. The nickel-iron alloy that results from reduction of the mixed oxide mineral is used in metallurgical applications, such as the manufacture of steel. Recovery of pure nickel from its richest ores is obtained through mineral purification by flotation, followed by reduction with coal to obtain a high-titre alloy. Nickel is recovered in its high-purity form by electrochemical deposition on nickel ingots, or as spheres with the Mond carbonyl process. Most nickel is employed in the production of steel and of other metal alloys, in electroplating and in the manufacture of coins and of other metal items with a shiny finish, such as cutlery and silverware. Stainless steel and other nickel-chromium-iron alloys are widely used for corrosionresistant equipment, architectural applications and cooking utensils. Monel metal and other nickel-copper alloys are used in coinage, food processing machinery and dairy equipment. Nickel-aluminium alloys are used for magnets and catalyst production; a very pure, pyrophoric form of nickel-aluminium alloy (Raney nickel) is used as a hydrogenation catalyst in the hardening of unsaturated vegetable oils to obtain solid fats (e.g. margarine) and in the industrial synthesis of fine chemicals. Nickel-chromium alloys are used for heating elements, gas turbines and jet engines. Alloys of nickel with precious metals are used in jewellery, although because of its allergenic properties, the use of nickel in the plating of objects that touch the skin has been greatly reduced. For example, bijoux jewellery, clothing accessories (especially bra strap clips and belt buckles), wristwatches and cutlery, and mechanical tools (such as plated wrenches, screwdrivers, and pincers). Nickel metal, its compounds and alloys have (or had) many other uses, including magnetic tapes and computer components, arcwelding rods, surgical and dental prostheses, nickel-cadmium batteries, paint pigments (e.g. yellow nickel titanate), moulds for ceramic and glass containers, and catalysts for hydrogenation reactions, organic syntheses, and the final methanation step of coal gasification. Nickel (III) oxide hydroxide is used as the cathode in nickel-cadmium and nickel-metal hydride electric batteries.

1.1.24 Diseases caused by nickel or its compounds	ICD Code T56.8 +Z57
Occupational exposures	Nickel carbonyl is employed in the Mond process for purification and for the thermal deposition of ultrathin layers of the metal on non-conducting substrates such as mirror glass. Exposure to airborne fumes, dusts and mists containing nickel and its compounds occurs for several million workers worldwide. Occupational exposure occurs both in nickel producing industries (e.g. mining, milling, smelting, and refining) and in nickel using industries and operations (e.g. alloy and stainless steel manufacture; electro-plating and electroextraction; welding, grinding and cutting). Exposure is possible in the manufacture of nickel-cadmium batteries, coins, and kitchen utensils. Occupational exposure can occur in recycling operations since nickel-bearing materials (especially from the steel industry) are commonly melted, refined and used to prepare alloys similar in composition to those that enter the recycling process. Exposure routes in the occupational setting are mainly inhalation and skin contact, while exposure through ingestion rarely occurs.
Toxicological profile, main health effects and diagnostic criteria	
Short toxicological profile	Inhalation absorption of the metal from inhaled nickel-containing particulate matter, such as from welding and metalworking fumes, depends on the solubility of the species in the alveolar fluid in the lung. Nickel from less soluble compounds, such as green nickel oxide, is removed by a macrophage-mediated mechanism and cleared only in faeces. On the contrary, nickel subsulphide is removed by dissolution-absorption and excreted mostly in the urine. Soluble inorganic nickel (II) salts absorbed through the lungs clear in the urine within 36 hours. They can even penetrate through the skin, and the potential role of humid environments in favouring the release of the nickel ion from metallic nickel and nickel alloys has to be taken into consideration, especially for their sensitising potential (see below). Absorption rates through the skin also depends on the nature of the corresponding counterion, chloride being the most efficient. Nickel carbonyl is one of the most toxic industrial chemicals. Inhalation at concentrations above 3-30 ppm leads to acute fatal intoxication. Initial symptoms of acute exposure include headache, nausea, chest tightness, and dizziness and can be followed by delayed symptoms of shortness of breath, cyanosis, and pulmonary oedema. Human health hazards (other than nickel carbonyl poisoning) from occupational exposures to nickel compounds fall into three major categories: 1. allergy; 2. rhinitis and sinusitis; and 3. cancers of the lung and of the nasal cavity and paranasal sinuses. Some evidence of asthma (especially during welding of nickel-containing alloys) and, less consistently, pulmonary fibrosis documented with X-ray abnormalities (associated with refinery activities) has been reported in nickel workers. The mechanisms responsible for the somatic and carcinogenic toxic effects of nickel are likely based on its ability to produce oxidative stress by acting as a catalyst of the Fenton reaction (production of endogenous hydrogen peroxide and reactive oxygen species). Serum and urine nickel levels are useful biomarkers of nickel exposure, as they may reflect the recent exposures of workers to metallic nickel and soluble nickel compounds. When interpreting biomonitoring data, environmental exposure to nickel (especially from food or cigarette smoke) has to be taken into consideration; reference values for non-occupationally exposed healthy adults have been estimated at about 0.2 µg/L in serum and 1-3 µg/L in urine.

Name of the diseases and ICD code: **Acute diseases caused by nickel or its compounds**
(Specific disease code) **+T56.8, +Z57**

Nickel tetracarbonyl poisoning (T56.8), Chemical pneumonitis (J68.0), Pulmonary oedema (J68.1)

Short description of the disease

Acute inhalation of nickel tetracarbonyl tends to produce mild, nonspecific, immediate symptoms (see below). These initial symptoms usually disappear within a few hours. After 12 to 36 hours (and occasionally as long as 5 days after exposure), severe pulmonary symptoms develop. Cases of myocarditis have been reported. Acute inhalation of vapours of nickel carbonyl at very high concentrations may directly cause haemorrhagic pulmonary oedema. Exposure to 30 ppm for 30 minutes should be considered potentially lethal to humans.

Neurological symptoms (e.g. insomnia, headache, dizziness, memory loss) and other manifestations (e.g. chest tightness, excessive sweating, alopecia) have been reported for chronic exposure to low atmospheric concentrations of nickel carbonyl (up to about 0.5 mg/m^3); however, evidence of health effects of longterm low level exposure to nickel carbonyl is less consistent.

1.1.24 Diseases caused by nickel or its compounds — ICD Code T56.8 +Z57

Name of the diseases and ICD code: **Acute diseases caused by nickel or its compounds**
(Specific disease code) **+T56.8, +Z57**

Diagnostic criteria

Clinical manifestations

- Signs and symptoms:
  - Initial stage: nausea, vertigo, headache, dyspnoea and chest pain.
  - Delayed stage: tachycardia, cyanosis, profound weakness, cough, dyspnoea, and respiratory impairment up to pulmonary oedema.
- Examinations:
  - Blood cells counts may reveal leucocytosis.
  - Chest X-ray may demonstrate various abnormalities such as irregular linear shadows, diffuse irregular nodular mottling or patchy shadows, expansion and increased density of the hilum.

Exposure assessment

- History of occupational exposure: evidence of exposure to nickel carbonyl through inhalation and, when available, workplace and biological monitoring measurements.
- Minimum duration of exposure: few minutes.
- Maximum latent period: 48 hours (but pulmonary symptoms have been occasionally observed as long as five days after exposure).

Name of the diseases and ICD code: **Chronic diseases caused by nickel or its compounds**
(Specific disease code) **+T56.8, +Z57**

Allergic contact dermatitis (L23)

Short description of the disease

Nickel and nickel compounds are among the most common causes of allergic contact dermatitis (ACD). Dermal sensitization can occur either at the workplace or outside of it, from exposures to nickel-containing coins, jewellery, watchcases and clothing fasteners (although the use of nickel in the plating of objects that touch the skin has been greatly reduced). Nickel sensitized subjects can then react to further contact with nickel, either at the workplace or in any non-occupational setting. Occupational nickel contact dermatitis, also known as '*nickel itch*', was frequently found in the past in workers who handled nickelplated instruments or tools but is nowadays less common.

In nickel exposed persons, nickel dermatitis usually begins as papular erythema of the hands. The skin gradually becomes eczematous, and, in the chronic stage, lichenification frequently develops. Nickel sensitization sometimes causes (or used to cause) conjunctivitis, eosinophilic pneumonitis, and local or systemic reactions to nickel-containing implants (e.g. intraosseous pins, dental inlays, cardiac valve prostheses and pacemaker wires). Nickel may be responsible for allergic reactions and pseudo-tumour formation to metalalloy hip prostheses.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: redness, swelling, vesicles, oozing and crusting (acute eczematous reaction) of the skin. The development of the skin lesions is directly related to the work activities, with a pattern of recurrence of the disease on re-exposure to nickel or its compounds. If the exposure continues, dermatitis will become chronic. Features of chronic ACD are diverse and can range from dry, thickened and scaly skin (i.e., lichenification) to cracking and fissuring of the fingers and palms up to chronic nail dystrophy (chronic eczematous reaction). Itch (pruritus) is usually present.
- Examinations:
  - Lesions are localized at nickel contact sites but often spread in the surrounding area or to other body sites. Occupational ACD is mainly found on the hands.
  - Patch tests should be performed by a specialized physician, according to relevant guidelines (such as those listed among the 'further reading'). This diagnostic approach might bring about sensitization, and the testing concentration should be defined according to specific recommendations.

Exposure assessment

- History of occupational exposure: confirmed previous occupational exposure (at least one episode) to nickel or its compounds and onset of signs and symptoms as a consequence of subsequent exposures.
- Minimum duration of exposure: usually, several instances of exposure are required over long periods for sensitization, but in exceptional cases even a single contact might be sufficient. For elicitation of ACD in sensitized individuals, skin contact with nickel or its compounds of a few minutes to several hours may give rise to skin reactions.
- Maximum latent period: in sensitized subjects, any further exposure to nickel or its compounds causes the onset of clinical signs, usually within 12-72 hours or even later (up to 1-2 weeks).

1.1.24 Diseases caused by nickel or its compounds — ICD Code T56.8 +Z57

Sensitizer-induced occupational asthma (J45.0)

Short description of the disease

There is some evidence that inhalation of soluble nickel and of nickel oxide fumes in the welding of nickel-containing alloys can cause asthma. Following sensitization to nickel, some cases of eosinophilic pneumonitis have been observed. Nickel asthma is often associated with urticarial (acute wheals and flare skin reactions) and allergic contact dermatitis.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: cough, dyspnoea, wheezing.
- Examinations:
  - Lung function testing may show evidence of airway obstruction; bronchodilator response may be seen in certain workers with occupational asthma when given ß2 agonists.
  - Recording serial peak flow measurements (sPEF) is the initial method of confirming a possible occupational cause for asthma. sPEF recording over three weeks with at least 4 recordings a day has very high specificity and moderately good sensitivity for making a diagnosis of occupational asthma. A comparison of measures collected in conditions of exposure vs. absence of exposure to the suspected causal agent is very useful for reaching a diagnosis.
  - Non-specific bronchial reactivity to challenge with a variety of agents (including histamine, methacholine, mannitol) may be increased in occupational asthma. Additionally, sequential measures of airway reactivity, including periods at work and away from work, may assist in making a diagnosis.
  - Changes in sputum eosinophilia may be helpful in the diagnosis.

Exposure assessment

- History of occupational exposure: confirmed occupational exposure to nickel or its compounds and, when available, workplace and biological monitoring measurements.
- Minimum duration of exposure: usually from weeks to years, but, in some cases, this period may be as short as a few days.
- Maximum latent period: usually between 3 to 24 months, but it may be shorter in atopic subjects and in exceptional cases, it may be as short as a few days. In sensitized subjects, the latency between exposure and onset of symptoms is usually no longer than 48 hours.

Name of the diseases and ICD code: **Carcinogenic effects caused by nickel or its compounds**
(Specific disease code) **+T56.8, +Z57**

Cancers of the lung (C34) and of the nasal cavity (C30.0) and paranasal sinuses (C31)

Short description of the disease

Nickel compounds have been classified as carcinogenic for humans by the International Agency for Research on Cancer (Group 1): there is sufficient evidence in humans for the carcinogenicity of mixtures that include nickel compounds and nickel metal, especially for their potential of causing cancers of the lung and of the nasal cavity and paranasal sinuses. For further details on cancers caused by nickel compounds, refer to item 3.1.13.

Key actions for prevention	The metallurgical use of nickel for the preparation of steel and copper alloys is likely to continue as high-volume production. On the contrary, the use of nickel for electroplating and for the manufacturing of consumer goods is fading due to its sensitizing and carcinogenic properties. The prevention of exposure in the metallurgical industry is based on the enclosure of crucibles and ovens. In metalworking, such as welding, cutting and machining, the enclosure of the sources of metal dusts and the use of personal protection devices by the workers is strongly advised. Pre-placement assessment of nickel exposed workers should identify pre-existing medical conditions that may help in job placement and provide baseline data for subsequent functional, physiological or pathological changes. The assessment includes (i) detailed medical and occupational history, focusing on lung problems, exposures to lung toxins, past or present allergies (particularly to nickel), asthma and personal habits (e.g. smoking), (ii) complete physical examination, with attention to respiratory and skin problems and (iii) determination of the respiratory protective equipment that may be worn. Chest X-ray and pulmonary function tests may be included. Skin patch testing for nickel sensitivity should not be routinely performed because such tests could possibly sensitize the subject. If the organization conducts a biological monitoring programme for nickel exposed workers (see below), baseline nickel concentrations in urine or serum can be obtained during the pre-placement assessment (keeping in mind that urinary nickel levels mostly reflect recent exposures.

1.1.24 Diseases caused by nickel or its compounds	ICD Code T56.8 +Z57
Key actions for prevention	Periodic assessment, typically performed annually, of nickel-exposed workers should monitor the worker's general health and to address nickel-associated concerns. The examination includes the history of recent illnesses, symptom review, physical examination and re-evaluation of the worker's ability to use the respiratory protective equipment required for particular tasks. Pulmonary symptoms might be assessed by means of standardized questionnaires. Chest X-ray may be legally required in some countries, while pulmonary function tests [e.g. forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV_1)] are generally left to the physician's discretion. In workers with high risk exposures in nickel refining, periodic procedures aimed to detect early neoplastic lesions (e.g. rhinoscopy, nasal sinus X-rays, nasal mucosal biopsy, exfoliative cytology studies) may be indicated. Measurements of nickel concentrations in urine and serum samples should not be used as a surrogate for environmental exposure measurements since they do not furnish reliable measures of the total body nickel burden but just reflect the recent exposures of workers to metallic nickel and soluble nickel compounds. If a biological monitoring programme is implemented, it should be coupled with an environmental monitoring programme. The manufacture and use of nickel carbonyl is a specialized activity, and very stringent safety measures need to be put into operation, including the use of supplied-air respirators. Nickel carbonyl can under certain circumstances form in steel pipes that carry carbon monoxide in chemical plants. Apart from its toxicity, the generation of nickel and iron carbonyls can over time corrode pipes and other metalware (especially at the margins of the metalwork) such as pipe threads and give rise to corrosion leaks. Because of its flammability and tendency to explode, nickel carbonyl should be stored in tightly closed containers in a cool, well-ventilated area, away from heat and oxidizers such as nitric acid and chlorine. Flames and sources of ignition should be prohibited wherever nickel carbonyl is handled, used or stored. Nickel carbonyl should be transported in steel cylinders. Foam, dry chemical, or carbon dioxide fire extinguishers should be used to extinguish burning nickel carbonyl, rather than a stream of water, which might scatter and spread the fire. In addition to the medical surveillance measures recommended for all nickel exposed workers, persons with occupational exposures to nickel carbonyl should have biological monitoring of nickel concentration in urine specimens on a regular basis, typically monthly. Persons, who enter confined spaces where they might possibly be exposed to nickel carbonyl, should have self-contained breathing apparatus and a suitable harness with a lifeline tended by another employee outside the space. Several scientific bodies and regulatory agencies suggest or enforce exposure limits for occupational exposure to nickel or its compounds. The group of experts considered that the following limits of exposure of workplace atmospheric concentrations have been observed to provide a reasonable level of protection for workers' health and to be used in a number of countries: • Nickel (inhalable fraction): 1.5 mg/m^3 as 8hr TWA. • Nickel subsulphide/sulphate/oxide/carbonate (inhalable fraction): 0.1 mg/m^3 as 8hr TWA. • Nickel tetracarbonyl: 0.05 ppm as short-term exposure limit.

Further reading

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1.1.24 Diseases caused by nickel or its compounds ICD Code T56.8 +Z57

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For the chemical entities listed below an entry exists in the collection of International Chemical Safety Cards (ICSC) hosted in the ILO website

Name	Synonyms	ICSC
Nickel		0062
Nickel (II) sulphate	Nickelous sulphate; Nickel(2+) sulfate	0063
Nickel carbonyl	Nickel tetracarbonyl	0064
Nickel (II) oxide	Nickel monoxide; Nickelous oxide	0926
Nickel carbonate	Nickelous carbonate; Nickel (II) carbonate	0927
Nickel sulphide	Heazlewoodite; Nickel subsulphide; Trinickel disulfide	0928

▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
1.1.24	Acute and chronic diseases and carcinogenic effects caused by nickel or its compounds	T56.8	NE61&XM4E11
1.1.24	Nickel tetracarbonyl poisoning	T56.8	NE61&XM9P91
1.1.24	Chemical pneumonitis	J68.0	CA81.0
1.1.24	Pulmonary oedema	J68.1	CB01, CA81.1
1.1.24	Allergic contact dermatitis	L23	EK00
1.1.24	Sensitizer-induced occupational asthma	J45.0	CA23.0
1.1.24	Chronic rhinitis	J31.0	CA09.0
1.1.24	Chronic sinusitis	J32	CA0A.Z
1.1.24	Anosmia	R43.0	MB41.0
1.1.24	Nasal ulceration	J34.8	CA0Z
1.1.24	Nasal cavity cancer	C30.0	2C20.Z
1.1.24	Paranasal sinuses cancer	C31	2C22.Z
1.1.24	Lung cancer	C34	2C25.Z
	Occupational exposure to risk factors	Z57	QD84.Y

1.1.25 Diseases caused by thallium or its compounds	ICD Code T56.8 +Z57
General characteristics of the causal agent	Thallium (Tl), CAS number 7440-28-0, is the chemical element with atomic number 81 in the periodic table of the elements naturally present as two stable isotopes and with atomic weight 204.38 Da. It is classified in Group 13 (III-A) (boron group) in the element families. The artificial radioisotope ^{201}TI (half-life of 73hrs) is used as contrast medium for cardiac imaging (scintigraphy). Thallium is a heavy (specific gravity 11.85 g/cm^3), soft, malleable, bluish-white metal. In its pure form, thallium has no odour or taste. Thallium occurs in the environment only in the form of its compounds where the element is present as Tl(I), the stable chemical form in water, or as Tl(III) if coordinated by ligands that prevent its reduction to Tl(I). Metallic thallium reacts with strong acids but yields a poorly soluble chloride and insoluble sulphide and selenide. The main chemical forms of thallium of concern for occupational safety include thallium (I) sulphate and thallium (I) and (III) oxides.
Occupational exposures	Thallium is obtained as a metal from the by-products of sulphuric acid production, from the roasting of pyrites (mostly a process residual), and in the smelting of lead and zinc ores. Thallium forms salts used in photoelectric cells, lamps and electronics (semiconductors), thallium sulphide and thallium selenide crystals for detection of infrared radiation, in special glass productions (glass colouring, optical fibres, optical lenses), in the production of fireworks (bright green flame), and as a catalyst in organic synthesis. A mercury-thallium alloy is used in thermometers and low temperature switches and the use of thallium for high temperature superconductors is increasing. Given its high toxicity, as it interferes with the function of numerous vital enzymes, thallium has seen use as a pesticide. In some countries thallium sulphate is still used as a rodenticide. Occupational exposure is thus possible in metal extraction, in flue dusts and dusts from pyrite roasting, in the preparation of thallium salts and of thallium-mercury alloys and in their manufacture uses.
Toxicological profile, main health effects and diagnostic criteria	
Short toxicological profile	Soluble thallium (I) salts are readily absorbed through the gastrointestinal and respiratory tracts, and through the skin. After absorption, thallium is rapidly distributed to all the organs of the body. It can also permeate the placenta and blood-brain barriers. It strongly binds the thiol group of cysteine thus potentially exerting an impairment at several key points in cellular biochemistry and physiology, so that only approximately 20-30% of the absorbed dose is cleared from the body (mainly into the urine). This makes thallium a cumulative poison. Elimination from the body takes place through the gastrointestinal tract, sweat, saliva, and breast milk. Using a wholebody counter, the biological half-life for thallium has been found to be 9.8 days (range = 7.4-12.4 days). The distribution of absorbed thallium (I) in the body is mainly due to its similarity to potassium (K^+) in ionic radius and electrical charge, a property which contributes to its toxic nature. The high systemic toxicity of thallium (lethal dose in the order of 1 gram of absorbed chemical) is due to its interference in K^+/Na^+ ion channels (10-fold higher affinity for rabbit kidney Na^+/K^+-ATPase than K^+) and to uncoupling of oxidative phosphorylation in mitochondria.

Name of the diseases and ICD code: **Acute diseases caused by thallium** *(Specific disease code)* **+T56.8 +Z57**

Gastrointestinal toxicity (K52.1), Hypertension (I10), Heart arrhythmia (R00), Polyneuropathy (Neurotoxicity) (G62.2), Nephrotoxicity (N14.3), Alopecia (L65.9)

Short description of the disease

The presentation of gastroenteritis, polyneuropathy and alopecia is regarded as the classic syndrome of thallium poisoning.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms:
  - Acute thallium poisoning primarily affects the gastrointestinal tract, with nausea, vomiting and abdominal pain, in some cases associated with diarrhoea or constipation unresponsive to laxatives. These symptoms appear usually within the first 3-4 hours.
  - Tachycardia and hypertension may result from autonomic (vagus nerve) function impairment. Neurologic symptoms usually appear 2-5 days post exposure (though some reports are for <24 h): these include severe dysaesthesia, and ascending peripheral neuropathies with cranial nerve involvement. Peripheral nervous symptoms may include paraesthesia, pain and weakness. Paraesthesia (both hyperaesthesia and hypoaesthesia) develops usually in severe poisoning, often affecting the hands and lower extremities (especially the soles of the feet). A distal motor weakness occurs, that affects the lower limbs more than the upper limbs. Cranial nerves can be affected, with optic neuritis, dysphagia and dysarthria.

1.1.25 Diseases caused by thallium or its compounds ICD Code T56.8 +Z57

- Central nervous system involvement leads to palsies, headache, seizures, unconsciousness, ataxia and athetosis, increased thirst, sleep disturbances. Neuropsychological manifestations are reported as anxiety, depression, acute agitation, aggression, confusional states, hallucinations, and psychosis. The sequelae can include, personality changes, cognitive impairment and psychosis.
- Neurological signs and symptoms appear 2-3 weeks before alopecia.
- Alopecia is a cardinal feature occurring in weeks 2-3, characterized by sudden hair loss. It primarily affects the scalp, temporal parts of the eyebrows, the eyelashes, and the limbs but may cause widespread depilation. Less often, the axillary regions are affected. Hair discolouration, brown or black bands, may also occur. Alopecia is generally reversible once serum thallium levels decrease.
- Ocular symptoms include diplopia, abnormal colour vision, and impairment of visual acuity. Non-inflammatory keratitis, lens opacities, and toxic optic neuropathy may occur.
- Dermatologic symptoms are nonspecific and include scaling of the palms and soles and acneiform or pustular eruptions of the face, maculopapular rashes progressed to scabbing. One month after the poisoning, Mee's lines (transverse white lines on the nails) appear in the nail plate. Other dermatologic findings include severe acne, crusted eczematous lesions, hypohidrosis, anhidrosis, hyperkeratosis or an eczematous eruption, palmar erythema, stomatitis, and painful glossitis with redness of the tip of the tongue. Sunlight hypersensitivity has been reported.
- Occupational poisoning may be more likely to be of chronic onset resulting from a long term moderate exposure. Hair loss may then be a late symptom arising after the appearance of polyneuritis; in mild poisoning, alopecia may not occur.
- The lethal dose of thallium varies from 6 to 40 mg/kg, but on average is between 10 and 15 mg/kg.
- In particularly severe poisonings, death occurs within hours from cardiac or respiratory failure. In less severe situations when the exposure doses are still significant, death occurs within 10–12 days if the patient is not treated.
- The prognosis for acute thallium toxicity is serious, having a mortality rate of 6-15%; among survivors, 33-50% will have neurological or ocular sequelae.

• Examinations:
  - Mee's lines.
  - In cases of oral ingestion, a bluish line on gums may appear 3 to 4 weeks after poisoning.
  - Detection of thallium in urine is the most reliable biomarker of exposure, with urinary excretion of thallium in excess of 10 to 20 mg in 24 hours considered diagnostic. Thallium is excreted in the urine for many weeks following ingestion or dermal absorption. Although less reliable for diagnosis than 24 hour urinary thallium excretion, whole blood thallium exceeding 100 µg/dL indicates potential poisoning.
  - Electrocardiography: bradycardia, ST segment, and T wave changes may be present.
  - Electroneurography: impairment of motor and sensory nerve conduction velocity.
  - Prolonged latency at visual evoked potential.
  - Microscopic examination of the hair root by polarized light may show black discolouration at the base, four days after ingestion of thallium.
  - In fatal cases, autopsy has shown high thallium concentrations in the kidneys, but moderate concentrations may also be present in the liver, other internal organs, muscles and bones.

Exposure assessment

- History of occupational exposure: confirmed history of accidental exposure to extremely high airborne doses (possible only in particularly bad occupational hygiene conditions) or oral intake of high doses of the metal (e.g. through transference) and, if available, monitoring of air concentration of thallium in the workplace. Thallium concentration in urine can be used to confirm exposure and to obtain an estimate of the severity of the poisoning: urine thallium concentrations above 500 µg/L have been associated with clinical poisoning.
- Minimum duration of exposure: minutes.
- Maximum latent period:
  - Gastrointestinal and neurologic effects: few days.
  - Alopecia: 2-3 weeks.
  - Nephrotoxicity: one month.

1.1.25 Diseases caused by thallium or its compounds — ICD Code T56.8 +Z57

Name of the diseases and ICD code: **Chronic diseases caused by thallium** *(Specific disease code)* **+T56.8 +Z57**

Polyneuropathy (neurotoxicity) (G62.2), Nephrotoxicity (N14.3), Alopecia (L65.9)

Short description of the disease

In chronic thallium poisoning the most striking clinical feature is loss of hair. Cases are described where other earlier nonspecific features were not attributed to thallium toxicity until alopecia occurred. Peripheral neuropathy is a feature of chronic toxicity. Chronic poisoning may cause anorexia, neurodegenerative changes, behavioural effects with headache, irritability, depression, tiredness, and insomnia.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: loss of appetite, headache, irritability, insomnia, loss of body weight, hair loss.
- Examinations:
  - Mee's lines.
  - Electrocardiogram may show evidence to arrhythmia.
  - Electroneurography: impairment of motor and sensory nerve conduction velocity.
  - Prolonged latency at visual evoked potential.
  - In fatal cases, autopsy has shown high thallium concentrations in the kidneys, but moderate concentrations may also be present in the liver, other internal organs, muscles and bones.

Exposure assessment

- History of occupational exposure: confirmed prolonged occupational exposure to thallium, at levels lower than those able to cause acute effects.
- Minimum duration of exposure: few months.
- Maximum latent period: few months.

Key actions for prevention	The standard precautions of industrial hygiene, i.e., source segregation, enhanced localized ventilation and the use of personal protective equipment (PPE) are mostly deemed sufficient to avoid overexposure of workers. Persons involved in work with thallium and its compounds should wear appropriate personal protective equipment. Respiratory protective equipment is essential where there is the possibility of dangerous inhalation of airborne dust. Work clothes should be washed regularly, and kept separate from ordinary clothes. Hand washing and personal shower facilities should be provided at the workplace with scrupulous personal hygiene encouraged. Close attention to the cleanliness of workplace is essential. Eating, drinking and smoking in working areas should be prohibited because of the risk of contamination by transference, ingestion or accidental consumption. A TLV-TWA of 0.02 mg/m^3, measured as thallium (Tl), is recommended for occupational exposure to elemental thallium and its soluble compounds (International Chemical Safety Cards database). This value should minimize the potential for a variety of central nervous system, cardiovascular and dermatologic effects, and alopecia. Urine biological exposure monitoring may be a useful measure to inform the efficacy of controls. A urine thallium concentration of 100 µg/L corresponds to a 40-hour/week exposure of 0.1 mg/m^3. Oral administration of Prussian blue and mannitol is used for treating thallium poisoning.

1.1.25 Diseases caused by thallium or its compounds ICD Code T56.8 +Z57

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1.1.25 Diseases caused by thallium or its compounds ICD Code T56.8 +Z57

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For the chemical entities listed below an entry exists in the collection of International Chemical Safety Cards (ICSC) hosted in the ILO website

Name	Synonyms	ICSC
Thallium	Ramor; Thallium (metal)	0077
Thallium sulphate	Thallium (I) sulphate; Dithallium sulphate; Thallous sulfate	0336
Thallium carbonate	Carbonic acid, dithallium (1+) salt; Dithallium carbonate; Thallous carbonate	1221

▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
1.1.25	Thallium toxicity (acute and chronic)	T56.8	PB36&XM63C5
1.1.25	Gastrointestinal toxicity	K52.1	DE2Z
1.1.25	Hypertension	I10	BA00.Z
1.1.25	Heart arrhythmia	R00	BC9Z
1.1.25	Polyneuropathy (neurotoxicity)	G62.2	8D43.2Y
1.1.25	Nephrotoxicity	N14.3	GB55.1
1.1.25	Alopecia	L65.9	ED70.Z
	Occupational exposure to risk factors	Z57	QD84

1.1.26 Diseases caused by osmium or its compounds	ICD Code T56.8 +Z57
General characteristics of the causal agent	Osmium (Os), CAS number 20816-12-0, is the chemical element with atomic number 76 in the periodic table of elements. It is classified in Group 8 (VIII-B), is naturally present as several isotopes, the most abundant ones being ^{192}Os (41%), ^{190}Os (26%), ^{189}Os (16%), and has mean atomic mass of 190.23 Da. Osmium is among the highest density elements (22.61 g/cm^3) and is a silvery blue, very high melting (3033°C), and very hard metal. It is found in nature in platinum ores as osmiridium, an alloy consisting of osmium and iridium, as well as in mixed sulphides of copper and nickel, where small amounts of the platinoid metals (i.e., palladium, iridium, osmium, rhodium, and ruthenium) can occur. Thermal refining of copper (smelting) releases osmium tetroxide into the air as a fine grey powder, which can be recovered for use as such, or as a source of the element. Osmium not only forms alloys with the platinum group metals but also with iron, cobalt and nickel, and forms brittle intermetallic compounds with tin and zinc as well. Osmium shows several negative and positive oxidation states, with VIII being the highest positive one: osmium tetroxide (O_4Os, CAS number 20816-12-0, also known as osmic acid anhydride, osmium oxide, or osmium tetraoxide) is a volatile colourless to pale yellow solid with strong oxidizing properties.
Occupational exposures	The manufacture of special alloys represents the main industrial use of osmium. Osmiridium, the best-known osmium alloy, is the material traditionally used for fountain pen tips and for the manufacture of wear resistant electrical contacts and mechanical pivots. Osmium dusts oxidize in air even at ambient temperature and yield vapours of toxic osmium tetroxide. Occupational exposure can thus occur in the manufacture of alloy-containing objects and as a by-product of copper smelting. Osmium tetroxide is used in electron microscopy and histology for staining fat or neural tissue (in biological laboratories) and as a catalyst in specialty organic chemical syntheses (Sharpless oxidation). Osmium tetroxide has been used in the treatment of arthritic joints (i.e., chemical synovectomy).
Toxicological profile, main health effects and diagnostic criteria	
Short toxicological profile	Like all rare elements, elemental osmium has a limited reactivity, and it is thus deemed to be biologically inert. On the contrary, osmium tetroxide is highly reactive; its peculiar reaction with unsaturated lipids accounts for its use as a lipid-selective staining reagent in electron microscopy and, possibly, for its toxic effects. Inhalation of vapours of osmium tetroxide causes lung congestion, while contact with skin and eyes causes burn damage.

Name of the diseases and ICD code: **Diseases caused by osmium or its compounds**
(Specific disease code) **+T56.8 +Z57**

Chemical bronchitis and pneumonitis (J68.0), Upper respiratory tract inflammation (J68.2), Reactive airways dysfunction syndrome (RADS) (J68.3), Burns and corrosion of respiratory tract (T27), Burns and corrosions of eyes and adnexa (T26.0-T26.1, T26.5-T26.6), Acute toxic conjunctivitis (H10.2), Corneal ulceration (H16.0), Keratoconjunctivitis (H16.2), Irritant contact dermatitis (L24)

Short description of the disease

Osmium tetroxide vapours are poisonous and extremely irritating to the eyes and respiratory tract even at low concentrations. The initial symptom is irritation, often accompanied by lacrimation, a feeling of dust in the eyes, and the appearance of rings around lights. Contact of the eyes with solutions containing osmium tetroxide can cause severe damage, up to blindness. Inhalation can cause headache, coughing, dizziness, and direct lung damage with breathing difficulties. Osmium tetroxide vapours can have insidious cumulative effects so that symptoms may remain unnoticed until several hours after exposure.

Contact of the skin with either the substance vapours or its solid form can cause dermatitis, severe irritation and burns. Some investigations reported systemic toxic effects involving liver and kidney damage. Diagnosis is mostly based on signs and symptoms, together with a confirmed history of exposure to osmium tetroxide.

1.1.26 Diseases caused by osmium or its compounds — ICD Code T56.8 +Z57

Diagnostic criteria

Clinical manifestations

- *Eyes:* lacrimation, photophobia, blepharospasm, conjunctival oedema; in most severe cases, corneal destruction and blindness may occur.
- *Respiratory tract:* burning sensation at the mucosae of the nose, throat, and bronchial tree, coryza, cough, wheezing, chest tightness, dyspnoea, and lung injury up to pulmonary oedema in most severe cases.
- *Skin:* discolouration (the skin tends to turn green or black), severe pain, burns, ulceration, and necrosis. Skin lesions can become permanent (prolonged contact can lead to dermatitis).

Exposure assessment

- History of occupational exposure: evidence of exposure to high levels of osmium tetroxide during metal smelting operations, or even to lower levels in electron microscopy and histology laboratories and, when available, workplace air monitoring of osmium tetroxide concentrations.
- Minimum duration of exposure: seconds for direct contact, few minutes for inhalation.
- Maximum latent period: hours.

Key actions for prevention	During the production of osmium, local exhaust ventilation should be provided. An enclosed ventilated area or hood is necessary in order to control the release of osmium tetroxide vapours into the work environment and prevent eye and respiratory irritation. This is particularly relevant in biological staining procedures in laboratories. Exposed workers should wear protective clothing (e.g. a coat with chemically resistant wrist guards), hand protection (e.g. double nitrile gloves), gas tight chemical safety eye protection, and full face respirators when enclosure is no possible or incomplete. When used for laboratory purposes, osmium tetroxide should be purchased as a liquid to avoid particulate exposure from the powdered form. The solutions should be stored in labelled tightly sealed containers, which should be placed in secondary containment. Secondary containment should be used whenever the material is transported across the laboratory. The group of experts considered that the following limits of exposure of workplace atmospheric concentrations of osmium tetroxide have been observed to provide a reasonable level of protection for workers' health and to be used in a number of countries: • 0.0002 ppm (0.0016 mg/m^3, as Os) as 8hr TWA. • 0.0006 ppm (0.0047 mg/m^3, as Os) as short-term exposure limit.

Further reading

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For the chemical entities listed below an entry exists in the collection of International Chemical Safety Cards (ICSC) hosted in the ILO website

Name	Synonyms	ICSC
Osmium tetroxide	Osmic acid anhydride; Osmium oxide; Osmium tetraoxide	0528

▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
1.1.26	Diseases caused by osmium or its compounds	T56.8	NE61&XM1UC6
1.1.26	Chemical bronchitis and pneumonitis	J68.0	CA81.0
1.1.26	Upper respiratory tract inflammation	J68.2	CA07.0
1.1.26	Reactive airways dysfunction syndrome (RADS)	J68.3	CA81.Y
1.1.26	Burns and corrosion of respiratory tract	T27	NE01
1.1.26	Burns and corrosions of eyes and adnexa	T26.0-T26.1, T26.5-T26.6	NE00
1.1.26	Acute toxic conjunctivitis	H10.2	9A60.2
1.1.26	Corneal ulceration	H16.0	9A76
1.1.26	Keratoconjunctivitis	H16.2	9A7Y
1.1.26	Burns and corrosions	T20-T25	ND9Z
1.1.26	Irritant contact dermatitis	L24	EK02
	Occupational exposure to risk factors	Z57	QD84.Y

1.1.27 Diseases caused by selenium or its compounds	ICD Code T56.8 +Z57
General characteristics of the causal agent	Selenium (Se) is the chemical element with atomic number 34 in the periodic table of the elements and belongs to Group 16 (VI-A; Chalcogens). Selenium is poly-isotopic (with an average atomic mass of 78.96 Da) and occurs as a pure element in two allotrope forms: one as an amorphous red powder (Red Selenium, cyclo-Se_8) and one with a bluish, metallic appearance. Selenium is rarely found in its elemental state in nature, and is usually present compounded with other elements, in one of three oxidation or valence states: -II (selenide), IV (selenous) and V (selenic). The chemical forms of selenium found in the environment often accompany those of the similar elements sulphur and tellurium and may be classified in three groups: 1. Soluble inorganic compounds (selenium (IV) and selenium (V) oxidation states). 2. Poorly soluble inorganic compounds (selenium (-II) oxidation state). 3. Biologically essential organic selenium compounds in living organisms. Elemental selenium reacts easily with hydrogen, fluorine, chlorine, and bromine, with nitric and sulphuric acids, and with several metals to form binary selenides. It reacts with oxygen, burning with a bright blue flame to form selenium dioxide (SeO_2), a compound with a characteristic odour of rotten horseradish and a major concern for occupational safety.
Occupational exposures	Selenium is extracted from the sludges (anode muds) of electrolytic copper refining and sulphuric acid plants. The largest industrial use of elemental selenium and of its compounds is in glass manufacturing, in deep red to light orange pigments for paints, plastics, ceramics, and glazes and as a chemical reagent for the preparation of specialty chemicals. Its use in electrical and electronic devices is declining, but it is used in plain paper photocopiers and laser printers, as well as in photovoltaic (solar) cells. The end of life disposal and recycling of electronic waste can entail exposure to selenium fumes, especially when performed in the informal sector. Among the important compounds, selenium sulphide (SeS_2) finds a pharmaceutical use as a topical antifungal agent and in shampoos for dandruff. Selenium diethyldithiocarbonate is used as a vulcanizing (i.e., "toughening") agent for rubber products. Selenate salts or biological forms of selenium (i.e., mixtures of selenoproteins) are sometimes present in nutritional products for human and veterinary use.
Toxicological profile, main health effects and diagnostic criteria	
Short toxicological profile	Selenium is an essential trace element of living matter and is an active component or cofactor of anti-oxidizing enzymes, such as glutathione peroxidase. Depending on the level of intake, selenium can have nutritional or potentially toxic effects. Selenium from the environment mainly enters the body through food that naturally contains the element. Beyond what the body needs, selenium is eliminated mainly in the urine but also in faeces and through exhaled breath. Selenium can, however, accumulate in the human body if exposure levels are very high or in case of prolonged exposure periods. It accumulates mostly in the liver and kidneys but also in the blood, lungs, heart, and testes. Selenium can be found in the nails and in the hair. The characteristic sign of absorption of selenium is a garlic odour of the breath and of the skin, which is due to its elimination from the body as volatile compounds in exhaled air and sweat. One such compound being dimethyl-selenium, which is produced in the liver via the same detoxifying methylation pathway as mercury. A similar garlic smell can be perceived in subjects who take excessive nutritional supplements containing selenium. Little is known about the specific biochemical mechanism by which selenium and its compounds exert their toxic effects. Acute exposure by inhalation to hydrogen selenide, and to fumes of elemental selenium or selenium dioxide primarily results in respiratory tract irritation, with the main effects being bronchitis, pneumonitis, and pulmonary oedema. Selenium fumes, especially those from selenium dioxide, are irritating to the eyes: one characteristic sign is conjunctivitis of the palpebral conjunctivae. Chronic exposure to selenium compounds through contact produces dermatitis, inflammation of the skin around the nail (paronychia), and loss of the nails. Selenium oxychloride can cause third-degree burns on skin contact. Chronic exposure to selenium compounds, both through occupational causes and in specific environments where the concentration of selenium is naturally elevated in the soil and water, gives rise to specific signs of intoxication, among which are red staining of teeth and nails and nail erosion. Hepatotoxic effects have been reported in subjects exposed to high levels of selenium.

1.1.27 Diseases caused by selenium or its compounds ICD Code T56.8 +Z57

Name of the diseases and ICD code: **Acute diseases caused by selenium or its compounds**
(Specific disease code) **+T56.8 +Z57**

Respiratory tract irritation (J68), Chemical bronchitis and pneumonitis (J68.0), Upper respiratory tract inflammation (J68.2), Chemical pulmonary oedema (J68.1), Burns and corrosion of respiratory tract (T27), Burns of eyes and adnexa (T26.0-T26.1), Acute toxic conjunctivitis (H10.2), Irritant contact dermatitis (L24), Burns and corrosions of external body surface (T20-T25)

Short description of the disease

Acute exposure to selenium fumes, as well as to selenium oxide or to hydrogen selenide gas, is irritating to mucous membranes of the respiratory tract, skin, and eyes. The main effects are bronchitis, pneumonitis, and pulmonary oedema due to local irritant effects on the alveoli. Selenium oxychloride readily destroys skin on contact, causing burns unless immediately removed with water. Contact with fumes or splashes of selenium oxide on the eye may cause conjunctivitis.

Diagnostic criteria

Clinical manifestations

- Symptoms of asphyxiation, cough, chest pain, dyspnoea, and cyanosis may appear. The first and most characteristic sign of selenium absorption is a garlic odour of the breath, caused by the production of dimethyl selenium. Affected subjects usually report a metallic taste in the mouth.
- Dermatitis due to exposure to airborne selenium oxide dust usually starts at the points of contact of the dust with the skin (most likely at the wrists or neck) and may extend to contiguous areas of the body. It usually consists of discrete, red, itchy papules, which may become confluent on the wrists, where selenium dioxide has penetrated the gap between the glove and sleeve of the coverall. Painful paronychia and, in some cases, loss of nails can be observed.
- Splashes of selenium oxide which enter the eye may cause conjunctivitis. Persons who work in atmospheres containing selenium dioxide dust may develop a particular allergic reaction known as “rose eye”, characterized by puffy eyelids. There is usually conjunctivitis of the palpebral conjunctivae but rarely of the bulbar conjunctivae.

Exposure assessment

- History of occupational exposure: confirmed occupational acute exposure to selenium or selenium compounds and, when available, workplace air and biological monitoring, such as selenium concentration in blood and urine.
- Minimum duration of exposure: the onset of manifestations occurs either during or immediately after exposure.
- Maximum latent period: few minutes.

Name of the diseases and ICD code: **Chronic diseases caused by selenium or its compounds**
(Specific disease code) **+T56.8 +Z57**

Chronic effects following occupational exposure to selenium and its compounds are uncommon, and only a few reports are available. In general, they consist of diarrhoea, abdominal pain, garlicky breath, a bitter metallic taste in the mouth associated with nail alterations. Ingestion of the metal, quite uncommon at the workplace, causes fingernail changes, alopecia, skin alterations, and peripheral nervous system disorders, mainly consisting of hyporeflexia and paraesthesia. This set of symptoms can be referred to as “selenosis”, a term mostly used to describe clinical pictures deriving from exposure to selenium from environmental sources.

Diagnostic criteria

Clinical manifestations

Teeth, nail and hair discolouration with alopecia, metallic taste in the mouth, garlic breath odour are specific for diagnosis, accompanied by vague gastrointestinal symptoms and giddiness, pallor, lassitude, irritability and nervous system impairment (dizziness, fatigue, emotional lability, nausea and vomiting, seizures, and signs of peripheral neuropathy).

Exposure assessment

- History of occupational exposure: confirmed prolonged or repeated occupational exposure to selenium and selenium compounds and, when available, workplace air and biological monitoring, such as selenium concentration in blood and urine.
- Minimum duration of exposure: few days.
- Maximum latent period: few months.

1.1.27 Diseases caused by selenium or its compounds	ICD Code T56.8 +Z57
Key actions for prevention	Whenever selenium is heated in the presence of air, selenium oxide is formed. All sources of selenium oxide or fumes should be fitted with exhaust ventilation systems with a velocity of at least 30 m/min. Workers should be provided with hand protection, coveralls, eye and face protection, and appropriate respiratory protection. Supplied-air respiratory protective equipment is necessary in cases where good extraction is not possible, such as in the cleaning of ventilation ducts. Smoking, eating and drinking at the workplace should be prohibited, and dining and sanitary facilities, including showers and locker rooms, should be provided at a point distant from exposure areas. Wherever possible, operations should be mechanized, automated or provided with remote controls. The group of experts considered that the following limits of exposure of workplace atmospheric concentrations have been observed to provide a reasonable level of protection for workers' health and to be used in a number of countries: • 0.2 mg/m^3 as 8hr TWA for selenium, selenium dioxide, selenium oxychloride, selenium trioxide, sodium selenite, and selenious acid. • 0.05 ppm as 8hr TWA for hydrogen selenide and selenium hexafluoride.

Further reading

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For the chemical entities listed below an entry exists in the collection of International Chemical Safety Cards (ICSC) hosted in the ILO website

Name	Synonyms	ICSC
Selenium		0072
Hydrogen selenide	Selenium hydride	0284
Sodium selenite	Disodium selenite; Selenious acid, disodium salt; Disodium selenium trioxide	0698
Selenious acid	Monohydrated selenium dioxide; Selenous acid	0945
Selenium dioxide	Selenious anhydride; Selenium oxide	0946
Selenium hexafluoride	Selenium fluoride	0947
Selenium oxychloride	Selenium chloride oxide; Seleninyl chloride	0948
Selenium trioxide	Selenic anhydride	0949

▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
1.1.27	Selenium toxicity (acute/chronic)	T56.8	NE61& XM47M7
1.1.27	Respiratory irritation	J68	CA81.Z
1.1.27	Chemical bronchitis and pneumonitis	J68.0	CA81.0
1.1.27	Upper respiratory tract inflammation	J68.2	CA07.0
1.1.27	Chemical pulmonary oedema	J68.1	CA81.1
1.1.27	Burns and corrosion of respiratory tract	T27	NE01
1.1.27	Burns of eyes and adnexa	T26.0-T26.1	NE00
1.1.27	Acute toxic conjunctivitis	H10.2	9A60.2
1.1.27	Irritant contact dermatitis	L24	EK02
1.1.27	Burns and corrosions of external body surface	T20-T25	ND9Z
	Occupational exposure to risk factors	Z57	QD84.Y

1.1.28 Diseases caused by copper or its compounds	ICD Code T56.4 +Z57
General characteristics of the causal agent	Copper (Cu), CAS number 7440-50-8, is the chemical element with atomic number 29 in the periodic table of elements. It is classified in Group 11 (I-B; Transition metals), has two main stable isotopes, and an average atomic mass of 63.55 Da. Copper seldom occurs in nature as a pure element: it most often occurs as minerals where it is present mainly in the II (cupric) and, occasionally, the I (cuprous) oxidation or valence state. The main minerals are the sulphides (such as chalcopyrite, bornite, covellite and chalcocite), the carbonates azurite and malachite, chalcanthite, and the copper (I) oxide cuprite. Large copper mines exist in relatively few countries, such as Chile, Peru, China, the USA, Australia, Mexico, Indonesia, Zambia, Congo, and Canada (all above 500.000 tons/year as of 2016). Elemental copper is red in colour (both as powder and as melted ingots), is malleable and ductile, conducts heat and electricity very well, and is resistant to acid corrosion. On exposure to moist air, it turns green through the formation of a mechanically resistant layer of copper carbonate. This property allows the use of copper pipes for domestic water supplies. In contrast, copper is slowly released from cooking pots, especially in the presence of acidic foods, unless the inner surface is protected by a layer of tin. Copper metal dissolves in oxidizing acids (such as nitric acid) and in chlorates, bromates, and iodates.
Occupational exposures	*Copper* is the third most widely used metal after iron and aluminium, either in its purest form for electrical applications or as alloys such as brass (copper-zinc alloys), bronze (copper-tin alloys) and weather resistant copper-nickel (cupronickel). Copper surfaces are very effective germicides, and thus bronze and brass can be used in appliances in which microbiological contamination needs to be kept low. Occupational exposure to copper and its compounds can occur in several activities including copper ore mining, extraction, thermal and electrochemical metallurgy and refining, alloying, machining, soldering, decommissioning and recycling, and in the synthesis and use of copper compounds. Electrical wires, cables and conductors represent a substantial proportion of the industrial use of copper, followed by bronze and brass alloying and manufacturing, and by plumbing and roofing in the building industry. Copper kitchenware is still traditional in several countries, although it has been mostly superseded by aluminium (cheaper and lighter) and stainless steel in many countries. *Copper sulphate* is used as an algicide and molluscicide in water; with lime, as a plant fungicide; as a mordant; in electroplating; as a froth flotation agent for the separation of zinc sulphide ore; and as an agent for leather tanning and hide preservation. Copper sulphate neutralized with hydrated lime, known as Bordeaux mixture, is used as a pesticide for the prevention of mildew in vineyards. Mixtures of copper sulphate, ammonia or alkyl amines and alkali are able to dissolve raw cellulose into a viscous paste from which a textile fibre (viscose, cuprammonium rayon, or Bemberg silk) is obtained, with applications mainly in the inner lining of garments and in the manufacturing of underwear. *Cupric oxide* has been used as a component of paint for ship bottoms and as a pigment in glass, ceramics, enamels, porcelain glazes and artificial gems. It is also used in the manufacture of rayon and other copper compounds and as an optical glass polishing agent and a solvent for chromic iron ores. Cupric oxide is a component of flux in copper metallurgy, pyrotechnic compositions, welding fluxes for bronze and agricultural products such as insecticides and fungicides. Black cupric oxide was (and sometimes still is) used for correcting copper-deficient soils and is added to food supplements for nutritional purposes. *Cupric hydroxide* is used in the manufacture of battery electrodes and for treating and staining paper. It is also a pigment, a feed additive, a mordant in dyeing and an ingredient in fungicides and insecticides. *Copper chromates* are pigments, catalysts for liquid-phase hydrogenation and potato fungicides. *Copper phthalocyanine* is extensively used as an 'absolute blue' pigment. Copper arsenates (Paris green, Scheele's green) and silicates (Egyptian blue) are still produced as paint pigments, although their use is mostly restricted to artistic items. Other applications of copper with possible occupational exposure are coinage and jewellery, electroplating, the preparation of copper catalysts for the chemical industry and other speciality chemical uses. In addition, recycling waste copper materials is a source of occupational exposure.

1.1.28 Diseases caused by copper or its compounds ICD Code T56.4 +Z57

Toxicological profile, main health effects and diagnostic criteria

Short toxicological profile

Copper is an essential element for human physiology, as it is the catalytic metal core of enzymes with specific oxidoreductive activity, such as the respiratory enzyme complex cytochrome c oxidase and the copper-zinc superoxide dismutase. These exploit the activity of the copper (II)/copper (I) redox couple. The regulation of copper concentration in the human body is tightly regulated: the physiological reservoir of copper (II) is held by the protein caeruloplasmin (more than 80% of the copper pool), while minor fractions are bound to albumin and soluble natural ligands (mainly amino acids). Excess of unbound copper in tissues is toxic since the copper (II)/copper (I) redox couple is able to chemically convert physiologically produced hydrogen peroxide to the cytotoxic hydroxyl radical. This occurs, for example, in congenital disorders such as Wilson's disease, characterized by the body's inability to clear excess dietary copper through the liver, the bile and the faeces.

Exogenous copper may be absorbed through ingestion (unlikely in the occupational setting) or inhalation of airborne fumes and fogs containing soluble or leachable copper. A common reaction to ingestion of copper is gastrointestinal distress, with a sensation of metallic taste in the mouth, nausea, vomiting sometimes together with melaena, and abdominal pain: these symptoms can occur, for example, after accidental ingestion of beverages or foods kept or prepared in unlined copper vessels.

Workers exposed to copper dust and fumes have shown irritation of the skin, and the respiratory mucosae, with congestion of the nasal and mucous membranes and ulceration with perforation of the nasal septum. Fumes from the heating of metallic copper can cause metal fume fever, although concurrent exposure to other metals may contribute to symptoms. Copper has a low potential for sensitization; nonetheless, contact urticaria and allergic, as well as irritant, contact dermatitis have been reported. Clinical pictures of severe pulmonary impairment, sometimes accompanied by hepatic toxicity, have been observed, especially in workers involved in vineyard spraying of pesticides containing copper compounds. Finally, ocular lesions have been observed after corneal penetration of copper-containing foreign bodies.

Name of the diseases and ICD code: **Acute diseases caused by copper or its compounds**
(Specific disease code) **+T56.4 +Z57**

Metal fume fever (T56.4)

Short description of the disease

Metal fume fever presents as a flu-like syndrome, and the diagnosis can be difficult, as symptoms are nonspecific: they generally appear a few hours after exposure and are reversible 1-4 days after cessation of exposure.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms:
  - Fever, chills, nausea, headache, fatigue, malaise, muscle aches, and joint pains appearing some hours after exposure.
  - A sweet or metallic taste in the mouth, which distorts the taste of food and cigarettes, is normally reported, along with a dry or irritated throat that may lead to hoarseness.
  - Symptoms may include a burning sensation in the body, shortness of breath, chest pain, cough, dyspnoea, rash, vomiting, watery or bloody diarrhoea and low blood pressure.
- Examinations:
  - Pulmonary function is commonly unaffected, but tests may show reduced lung volumes.
  - Chest X-ray findings are generally unremarkable.
  - There is an increase of white blood cell count (leucocytosis), although not in all cases.

Exposure assessment

- History of occupational exposure: confirmed acute exposure to copper or its compounds and, when available, workplace air monitoring.
- Minimum duration of exposure: few minutes.
- Maximum latent period: few hours.

1.1.28 Diseases caused by copper or its compounds ICD Code T56.4 +Z57

Respiratory tract irritation (J68), Upper respiratory inflammation (J68.2), Nose septal ulceration (J34.8)

Short description of the disease

The inhalation of dusts, fumes and mists of copper salts can cause congestion of the nasal and mucous membranes and septal ulceration, which can progress to perforation of the nasal septum. Irritation of the respiratory tract (coughing, sneezing, runny nose) is often present.

Diagnostic criteria

Clinical manifestations

- Sneezing, rhinorrhoea, chest tightness, wheezing, shortness of breath, cyanosis.
- Nasal mucous membranes and septal ulceration may progress to perforation of the nasal septum.

Exposure assessment

- History of occupational exposure: evidence of exposure to high levels of copper fumes, mists and dusts.
- Minimum duration of exposure: few hours.
- Maximum latent period: few days.

Name of the diseases and ICD code: **Chronic diseases caused by copper or its compounds**
(Specific disease code) **+T56.4 +Z57**

Chronic pulmonary fibrosis (J68.4), Hepatic granulomas (K71.8)

Short description of the disease

"Bordeaux mixture" is a pesticide traditionally used in vineyards, consisting of a 1%-2.5% solution of copper sulphate neutralized by hydrated lime. Workers spraying this product have been reported to suffer from pulmonary lesions (sometimes called "vineyard sprayer's lung") and copper-laden hepatic granulomas. These phenomena were often observed in workers with other disorders (e.g. tuberculosis, alcohol addiction): other factors might thus be at least partly responsible for the observed pulmonary and hepatic lesions. Prolonged exposure may cause an asymptomatic superficial discolouration of the exposed skin (yellow), hair (green), tongue, and teeth.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: cough, chest constriction, and dyspnoea.
- Examinations:
  - Lung function testing may reveal ventilation disorders with restrictive changes dominant.
  - The radiographic picture resembles that of silicosis, with micronodular infiltrates in the early stage of the disease and progressive massive fibrosis in its later stages.
  - Liver imaging, through either ultrasonography, computed tomography (CT), or magnetic resonance imaging (MRI), may show liver granulomatosis with calcification (if granulomas are long-standing), or filling defects, often with confluent lesions.

Exposure assessment

- History of occupational exposure: history of prolonged occupational exposure to copper fumes, mists and dusts (especially during vineyard spraying operations) and, when available, air monitoring measures.
- Minimum duration of exposure: one year.
- Maximum latent period: three years.

Chalcosis (H44.3)

Short description of the disease

Fragments of metallic copper or copper alloys that lodge in the eye (a condition known as chalcosis), may lead to uveitis, abscess and loss of the eye. Clinical pictures following penetration of foreign bodies into the cornea are diverse, ranging from an almost complete absence of reactions to a localised purulent inflammation with necrosis of surrounding tissue. The different manifestations depend mainly on the copper content of the foreign body, together with its size and host response. If the fragment is alloyed or is low in copper content, it may remain inactive for some years before diffusion and infiltration of material into the surrounding structures.

1.1.28 Diseases caused by copper or its compounds ICD Code T56.4 +Z57

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: affected subjects may complain of eye irritation, blurred vision, or a decreased visual acuity. In the most serious cases, uveitis (which may be recurrent), abscess, blindness, and phthisis bulbi (i.e., a shrunken, non-functional eye) may occur.
- Examinations: various alterations have been reported at slit lamp examinations, including:
  - Copper deposition in Descemet's membrane of the cornea, known as Kayser-Fleischer ring.
  - Sunflower cataract (mostly anterior subcapsular).
  - Fibrillar degeneration of the vitreous.

Exposure assessment

- History of occupational exposure: evidence of a traumatic event involving fragments of copper or its compounds occurring at the workplace.
- Minimum duration of exposure: a single traumatic event is sufficient for the foreign body to be retained within the cornea.
- Maximum latency period: given the plethora of clinical manifestations, the definition of a latency period is not straightforward. Most symptoms have been reported to occur within two years of the traumatic event.

Irritant contact dermatitis (L24), Allergic contact dermatitis (L23)

Copper has a low potential for sensitization; nonetheless, contact urticaria and allergic, as well as irritant, contact dermatitis have been reported. For further details on diagnostic and exposure assessment criteria, refer to items 2.2.1 and 2.2.2.

Key actions for prevention	Workers exposed to copper dusts or mists should be provided with adequate protective clothing to prevent repeated or prolonged skin contact. Where dust/mist conditions cannot be sufficiently controlled, as in the case of pesticide spraying, appropriate respirators and eye protection are necessary. Housekeeping and the provision of adequate sanitary facilities is essential since eating, drinking, and smoking should be prohibited at the worksite. In mines where there are water-soluble ores such as chalcanthite, workers should be particularly careful to wash their hands with water before eating. The employment of local exhaust ventilation is a necessary measure to collect copper fumes at the source. This might be particularly relevant for copper dusts generated in close-range work, such as by artisans and artists. Subjects who suffer from Wilson's disease should avoid any occupational task with a risk of significant exposure to copper. The group of experts considered that the following limits of exposure of workplace atmospheric concentrations have been observed to provide a reasonable level of protection for workers' health and have been used in a number of countries: • Copper fumes: 0.2 mg/m^3 as 8hr TWA. • Copper dusts and mists: 1 mg/m^3 as 8hr TWA.

1.1.28 Diseases caused by copper or its compounds ICD Code T56.4 +Z57

Further reading

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For the chemical entities listed below an entry exists in the collection of International Chemical Safety Cards (ICSC) hosted in the ILO website

Name	Synonyms	ICSC
Copper		0240
Copper naphthenate	Naphthenic acid, copper salt; Copper naphthenates	0303
Copper (I) oxide	Dicopper oxide; Cuprous oxide; Red copper oxide	0421
Copper (II) orthoarsenate	Arsenic acid, copper salt; Copper arsenate	0648
Copper sulfate (anhydrous)	Cupric sulphate; Sulfuric acid, copper(2+) salt(1:1)	0751
Copper 8-quinolate	Copper-8-hydroxyquinoline; Oxine-copper; 8-Quinolinol, copper (II) chelate; Bis(8-oxyquinoline) copper	0756
Copper (II) arsenite	Copper orthoarsenite; Acid copper arsenite; Arsenious acid, copper (II) salt; Cupric arsenite	1211
Copper (II) sulfate	Sulfuric acid, copper(2+) salt, pentahydrate	1416
Copper phthalocyanine	29H,31H-Phthalocyaninato(2-)-N29,N30,N31,N32 copper; Copper, (29H,31H-phthalocyaninato(2-)-N29,N30,N31,N32)-, (SP-4-1); Tetrabenzo-5,10,15,20-diazaporphyrinephthalocyanine; C.I. Pigment blue 15	1638

▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
1.1.28	Copper toxicity	T56.4	NE61&XM5KH2
1.1.28	Metal fume fever	T56.4	NE61&XM5KH2
1.1.28	Respiratory tract irritation	J68	CA81.Z
1.1.28	Upper respiratory inflammation	J68.2	CA81.2
1.1.28	Nose septal ulceration	J34.8	CA0Z
1.1.28	Chronic pulmonary fibrosis	J68.4	CA81.Y
1.1.28	Hepatic granulomas	K71.8	5C90.5/5C64.0Y
1.1.28	Chalcosis	H44.3	9E1Z
1.1.28	Irritant contact dermatitis	L24	EK02
1.1.28	Allergic contact dermatitis	L23	EK00
1.1.28	Contact urticaria	L50.0	EM0Z
	Occupational exposure to risk factors	Z57	QD84.Y

1.1.29 Diseases caused by platinum or its compounds	ICD Code T56.8 +Z57
General characteristics of the causal agent	Platinum (Pt), CAS number 7440-06-4, is the chemical element with atomic number 78 in the periodic table of the elements. It is classified in Group 10 (VIII-B), has an atomic weight of 195.09 Da, and is naturally present mainly as the stable isotopes ^{194}Pt (32.9%), ^{195}Pt (33.8%), and ^{196}Pt (25.3%). Platinum is a very heavy, malleable, silvery-white, noble metal, widely but sparingly distributed over the earth's crust. Its compounds mainly feature the oxidation states (II) and (IV); nonetheless, platinum yields molecular compounds where it binds neutral molecules and anions, keeping a formal oxidation state of (0). Elemental platinum in bulk form is in general unreactive but in finely divided forms (platinum sponge, platinum black powder) has exceptionally high and diverse catalytic properties, which are industrially exploited in many applications. Some chemicals, such as cyanides, sulphur, and elemental halogens, can corrode bulk platinum. In nature, platinum occurs mostly in the elemental form of its alloys with minor amounts of other elements such as iridium, osmium, palladium, ruthenium, and rhodium, which all belong to the same group of metals called the platinum group elements (PGE), platinum group metals (PGM), or platinoids. Some naturally occurring mineral forms of platinum are sperrylite and mixed sulphides of copper and nickel such as cooperite and braggite, which mostly occur in South Africa. As of 2016, South Africa accounts for about 70% of platinum world production, followed by Russia, Zimbabwe, and Canada. Platinum forms a large number of chemical compounds and of coordination complexes. Among those of practical interest are chloroplatinic acid, ammonium hexachloroplatinate, potassium hexachloroplatinate, potassium tetrachloroplatinate, platinum tetrachloride, and platinum hexafluoride. Platinum is used in anticancer drugs cis-dichloro-diamine-platinum (cisplatin), carboplatin and oxalylplatin (for further details, refer to item 1.1.23).
Occupational exposures	Occupational exposure to platinum mainly occurs in the extraction of the metal from its minerals, in the preparation of its compounds, and in the manufacture of platinum catalysts, speciality chemicals and industrial items. Compounding, preparation, clean-up, and administration to cancer patients of platinum-containing anticancer drugs can cause significant occupational exposure. Occupational exposure to platinum or its compounds can thus occur in the following sectors and jobs: platinum mining facilities and refineries, catalyst manufacturers and recyclers, jewellers, chemical and electronic manufacturers, the pharmaceutical industry, hospitals and healthcare facilities, and dental offices. The platinum production process entails very drastic reaction conditions to selectively solubilize and purify the element from the other platinoid metals, which have very similar physical and chemical properties. An important use of platinum is in the manufacture of catalytic converters for the control of emissions from automotive engines. Other applications of platinum as a component of chemical catalysts in the chemical process industry are: (a) the synthesis of nitric acid from ammonia, these catalysts are known to slowly release their platinum content as volatile coordination compounds to the atmosphere during plant operation; (b) the catalytic reforming of the aliphatic naphtha to alkyl-aromatic hydrocarbons; and (c) the hydrogenation ("hardening") of vegetable oil. Another major use is in jewellery manufacture, where occupational exposure can occur in high-temperature casting, in machining, and in manual carving with high-speed tools which produce finely divided particles of inhalable size. A related use, with similar potential for occupational exposure, is in the manufacture of medical and dental prostheses. The characteristics of chemical inertia and excellent thermal and electrical conductivity of platinum make this metal essential in technological applications such as the manufacture of electrical contacts, electrodes and thermocouples, coating of turbine blades, and tips for spark plugs spinnerets for fibrous glass and rayon spinning. *Chloroplatinic acid*, formed when platinum is dissolved in *aqua regia*, is useful in the manufacture of catalysts. *Ammonium hexachloroplatinate* (yellow salt) is used in platinum plating. *Potassium hexachloroplatinate* is used in the photographic industry. *Potassium tetrachloroplatinate* is used as a reagent for the preparation of other platinum coordination complexes. *Platinum tetrachloride* is used as a catalyst in the chemical industry. *Platinum hexafluoride* is an extremely powerful oxidizing agent, the first substance found to oxidize an inert gas (xenon).

1.1.29 Diseases caused by platinum or its compounds — ICD Code T56.8 +Z57

Toxicological profile, main health effects and diagnostic criteria

Short toxicological profile	Metallic platinum in bulk form is toxicologically inert and poorly soluble. Soluble halogeno-complex platinum salts especially hexachloroplatinic acid and ammonium hexachloroplatinate, cause allergic sensitization, which appears to be a type I, IgE-mediated response: platinum salts of low relative molecular mass may act as haptens, which combine with serum proteins to form the complete antigen resulting in sensitization. Platinum metal may occasionally provoke allergic contact dermatitis, but positive patch-test reactions for type IV platinum allergy are considered quite rare. Neutral compounds, such as cisplatin and non-halogenated amino- and nitro-platinum complexes, are not considered to be allergenic, nor is the metal itself. Studies carried out on the anti-cancer platinum drugs, as models of human exposure to soluble platinum compounds, suggest that the metal is strongly retained in the body, possibly by binding to proteins, and the retained dose is slowly eliminated in the urine with a terminal half-life of several years. It is worth mentioning that, among platinum-containing antineoplastic drugs, cisplatin has been classified as probably carcinogenic to humans (Group 2A) by the International Agency for Research on Cancer (N.B. etoposide in combination with cisplatin and bleomycin has been classified as a Group 1 carcinogen).

Name of the diseases and ICD code: **Diseases caused by platinum or its compounds**
(Specific disease code) **T56.8 +Z57**

Allergic rhinitis (J30.3), Sensitizer-induced occupational asthma (J45.0), Allergic urticaria (L50.0)

Short description of the disease

Among platinum compounds, the halogeno-complex salts are the most potent sensitizers especially chloroplatinic acid and ammonium hexachloroplatinate. These compounds, absorbed both via skin absorption and through inhalation, are able to cause type I allergic reactions, including rhinitis, asthma and urticaria. Sensitization is characterized by a latency period – which may last from several weeks or months to, very seldom, years – between first exposure to the sensitizer at work and the development of immunologically mediated symptoms. Once the subject is sensitized, even very low concentrations of the sensitizing agent can trigger the clinical manifestations; symptoms tend to worsen as long as the workers are exposed in the workplace but usually disappear after removing them from exposure. Nonetheless, if long-duration exposure keeps occurring after sensitization, workers may never become completely free of symptoms. Smoking, atopy, and nonspecific pulmonary hyper-reactivity have been associated with platinum salt hypersensitivity and could be predisposing factors. Platinum refinery workers have a particularly high risk of sensitization.

After exposure to halogenated platinum salts, allergic inflammation of the nasal mucosae, congestion, rhinorrhoea and sneezing can occur, due to production and release of mediators through IgE-dependent reactions, which produce eosinophilic infiltration and tissue oedema. Symptoms and signs of asthma can follow many clinical patterns, including progressive worsening of symptoms through the working week with improvement on rest days. Nasal symptoms may either precede the onset of occupational asthma symptoms or commence at the same time. Watery eyes due to ocular irritation may be present.

Urticaria may appear as a red, non-pitting oedema which involves only the superficial portion of the dermis. The most common sites for urticaria are the extremities and face but may involve any area of the body from the scalp to the soles of the feet. Urticarial eruptions are very pruritic and appear in crops with a variable duration of minutes to 24 hours. The term platinosis has been sometimes used to define the clinical picture of workers showing all three allergic manifestations with involvement of the nasal mucosae, bronchi and skin, and symptoms becoming progressively worse with the length of employment. Other terms used to comprehensively identify the clinical manifestations associated with exposure to sensitizing platinum salts are *platinum salt allergy*, *allergy to platinum compounds containing reactive halogen ligands*, and *platinum salt hypersensitivity*.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms:
  - *Rhinitis:* rhinorrhoea, sneezing, lacrimation, red eyes, itchy eyes, nose and throat, nasal cavity obstruction, watery and pale nasal mucosa, congested conjunctivae.
  - *Asthma:* episodic wheezing, difficulty in breathing, chest tightness and cough; excess sputum production is common.
  - *Urticaria:* acute wheals and flare skin reactions and itch within minutes after exposure.

1.1.29 Diseases caused by platinum or its compounds ICD Code T56.8 +Z57

- Examinations:
  - Lung function testing may show evidence of airway obstruction. Bronchodilator response may be seen in certain workers with occupational asthma when given ß2 agonists.
  - Monitoring of the peak nasal inspiratory flow (PNIF) and peak expiratory flow (PEF) can help highlight the correlation between symptoms and workplace exposure (serial PEF recording over three weeks with at least 4 recordings a day has shown very high specificity and moderately good sensitivity for making a diagnosis of occupational asthma).
  - To confirm the clinical history, skin prick tests with a standardized dilute solution of platinum salt (e.g. 1 mg of sodium hexachloroplatinate per mL) may be performed.
  - The diagnosis may require specific bronchial challenge with diluted platinum salts; as the reactions may be of the immediate or dual type, this test should be performed in specialist facilities where a medium-term follow-up can be performed.

Exposure assessment

- History of occupational exposure: evidence of occupational exposure to platinum compounds (especially chloroplatinic acid and ammonium hexachloroplatinate).
- Minimum duration of exposure: for both rhinitis and asthma, usually at least few weeks (up to years) are necessary, as they require a sensitization period. In exceptional cases, this period may be as short as a few days; for contact urticaria, the sensitization period is generally 10-15 days.
- Maximum latent period: the onset of symptom development following exposure has been observed to range from a few months to six years. In sensitized subjects, the latency between exposure and onset of symptoms is usually no longer than 48 hours (24 hours for contact urticaria).

Key actions for prevention	Most uses of platinum in the chemical industry and in manufacture are unlikely to be replaced in the future although the scarcity of this rare metal may encourage substitution. Car producers are putting major efforts into improving the recovery process of platinum especially from spent catalytic converters and to manufacture converters with a far lower release of the metal during their use. Technological improvements have lowered the release of platinum from the converters from about 1 µg/km travelled (old pellet-type catalysts) to some tens of ng/km (in monolith-type catalysts). These developments mean that platinum recycling from catalytic converters is only possible in industrial plants where occupational exposure can be strictly controlled. This effectively phases out most environmentally hazardous processes, but these continue to take place in the recycling of technological waste in the informal sector. Control of platinum hazards in the occupational setting can be achieved by preventing the release of the soluble complex platinum salts to the atmosphere of the workshop. Since platinum dust is more potentially harmful than the spray, the soluble complex salts should not be dried unless retaining moisture is not necessary for the production process. Good exhaust ventilation is necessary in platinum refineries. Chemical procedures which may generate these salts should be carried out in ventilated fume hoods. Open centrifuges should not be used. Among workers at higher risk of platinum dusts exposure are those in the handicraft sector (e.g. jewellery), where localized aspiration can lead to a substantial decrease of airborne concentration and consequent occupational exposure. Good personal hygiene, proper protective clothing, and periodic medical surveillance are important preventive measures. Halogeno-platinum compounds are among the most potent respiratory and skin sensitizers known: it is therefore fundamental to carefully control skin and respiratory exposure. Pre-placement assessment of platinum-exposed workers should aim to identify pre-existing medical conditions (e.g. allergic or respiratory diseases) that may help in job placement, and provide baseline data for subsequent functional, physiological or pathological changes. In case of sensitization, immediate cessation of exposure prevents the development of overt disorders. The group of experts considered that the following limits of exposure of workplace atmospheric concentrations have been observed to provide reasonable level of protection for workers' health and to be used in a number of countries: • Platinum: 1 mg/m^3 as 8hr TWA. • Platinum tetrachloride: 0.002 mg/m^3 as 8hr TWA.

1.1.29 Diseases caused by platinum or its compounds ICD Code T56.8 +Z57

Further reading

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For the chemical entities listed below an entry exists in the collection of International Chemical Safety Cards (ICSC) hosted in the ILO website

Name	Synonyms	ICSC
Platinum tetrachloride	Platinum (IV) chloride	1145
Platinium	Platinum sponge; Platinum black (powder)	1393

▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
1.1.29	Diseases caused by platinum or its compounds	T56.8	NE61&XM6NP0
1.1.29	Allergic rhinitis	J30.3	CA08.0Z
1.1.29	Sensitizer-induced occupational asthma	J45.0	CA23.0
1.1.29	Allergic urticaria	L50.0	EK10
	Occupational exposure to risk factors	Z57	QD84.Y

1.1.30 Diseases caused by tin or its compounds	ICD Code T56.6 +Z57
General characteristics of the causal agent	Tin (Sn), CAS number 7440-31-5, is the element with atomic number 50 in the periodic table of elements, has the largest number of stable isotopes, and a mean atomic mass of 118.71 Da. Tin is classified in Group 14 (IV-A; Main group) and features two oxidation numbers, II (stannous) and IV (stannic). Both oxidation states of tin give rise to amphoteric oxides. Sn(IV) is the more stable in aqueous solution over the entire range of acidity, and Sn(II) is a strong reducing agent in acidic solution. Elemental tin has a low melting point at 232°C and a high boiling point at >2000°C. At ambient temperature, tin is a pliable silvery-white metal that mixes readily with other metals to form alloys and is easily shaped. Important alloys of tin are bronze the copper-tin alloy known to humans since pre-historic times, pewter (a tin, antimony, and lead alloy) and brass (a zinc-tin alloy) which are mostly formed when naturally occurring mixtures of mineral ores are smelted together. Elemental tin in solid metal form is fairly resistant to acid corrosion in ambient conditions, but its powder form is combustible and reacts violently with oxidants, strong acids, powdered sulphur, and some extinguishing agents such as bicarbonate powder and carbon dioxide. Among naturally occurring tin compounds of industrial relevance are tin dioxide (SnO_2), which constitutes its most abundant ore, cassiterite, and the sulphide ores, such as stannite and teallite. Tin dichloride ($SnCl_2$) is an odourless, colourless to brown solid. Tin tetrachloride ($SnCl_4$) is a colourless to yellow fuming liquid with an acid odour. Tin (II) sulfate ($SnSO_4$) and potassium stannate are both odourless and colourless to brown solid. While inorganic tin compounds are of little toxicological concern, organotins are the compounds of the highest toxicological relevance. The most toxic in the group are the trialkyltins followed by dialkyltins and monoalkyltins; the tetraalkyltins are biotransformed to the corresponding trialkyltin compounds. Tetra-alkyl-tin, such as tetra-methyl-, tetra-ethyl- and tetra-butyl-tin are colourless liquids soluble in organic solvents but not in water. Triethyltin and trimethyltin are colourless liquids, which are soluble in organic solvents but not in water. Both these compounds are neurotoxic.
Occupational exposures	Tin has several industrial applications of varying technical complexity, ranging from metal coatings, to manufacturing of chemical compounds for diverse purposes to high-end technological applications. An important industrial use of tin is low-temperature soldering of tin-plated steel and of non-ferrous metals and alloys, performed with soldering fluxes composed of tin and lead. This is a key operation in manufacturing electric and electronic appliances, and hydraulic piping, and is considered the main contemporary use of tin. Next, in a quantitative terms is the protection (by plating) of soft steel band used for the manufacturing of food cans (“tin-plated steel”). Specialized tin alloys of different compositions are used in manufacturing diverse items including ball bearings, organ pipes, bells and other musical instruments, coinage, and hitech superconducting magnets (niobium-tin alloy). Another specialized use of tin is in the manufacture of flat glass panes with the float-glass or Pilkington process, in which molten glass is poured onto a flowing surface of molten tin, taking advantage of its boiling-point and its resistance to oxidation by air. Chemical compounds of tin are used in several technological applications. At present, organic tin compounds are much more abundantly used than inorganic ones. In particular, dibutyltin dilaurate is used in the stabilization of PVC plastics and this use is generally considered the main commercial application of organotin compounds. Organic tin compounds are widely used as biocides: fungicides, pesticides, algicides, antifouling agents, and wood preservatives (tributyltin oxide). Tributyltin is used as an additive to naval paints to protect ships’ hulls from the growth of marine organisms (which not only degrade the metal, but also increase hydrodynamic drag and slow down navigation). Since this compound has been demonstrated to be a persistent pollutant, its use has been banned by the International Marine Organization (IMO) and limited to the hulls of large commercial vessels, where it has been mostly replaced by red copper oxide. Occupational exposure to tin is possible in several productive activities, such as tin mining, smelting, and refining, the production of tin alloys including a large number of non-ferrous alloys, (e.g. phosphor bronze, light brass, gunmetal, high-tensile brass, manganese bronze, die-casting alloys, bearing metals, type metal, and pewter), industrial soldering in building and in the automobile and electrical industries, in food and beverage canning industries (tin plate), and in the production of window glass, household utensils, and roofing tiles (terneplate). A number of tin alloys are potentially harmful, particularly at high temperatures, due to the other alloyed metals, such as lead (see item 1.1.8), zinc (see item 1.1.31), and manganese (see item 1.1.5).

1.1.30 Diseases caused by tin or its compounds	ICD Code T56.6 +Z57
Occupational exposures	Occupational exposure to tin compounds is possible in the plastics industry, in particular in the production of polyvinyl chloride (trichlorobutyltin and dichlorodibutyltin), and for their use as catalysts in the production of polyurethane foams; in the manufacturing and application of biocides (trimethyltin, triethyltin chloride, triphenyltin chloride); and for their use in disinfectants, molluscicides and antifouling agents in marine paints (triphenyltin). Minor uses with possible exposure include that of stannous chloride used as a stabilizer in soaps and perfumes, as a mordant for textiles, and (as stannous fluoride) in the formulation of toothpaste to prevent dental caries. The use of stannous chloride as a reducing agent in the manufacture of silver-backed glass mirrors is now limited to restoring antique items. Tin powder is a moderate irritant to the eyes and airways; it is combustible and reacts violently with oxidants, strong acids, powdered sulphur, and some extinguishing agents such as bicarbonate powder and carbon dioxide.
Toxicological profile, main health effects and diagnostic criteria	
Short toxicological profile	Tin is a naturally occurring element to which workers can be exposed through inhalation, skin absorption, and ingestion. Systemic absorption of tin after inhalation and ingestion is low and, in particular, the absorption of metallic tin or of its inorganic salts from the alimentary tract seems to be poor. The ingestion of small amounts does not elicit any toxic effect since humans can easily tolerate a daily intake of 800 to 1,000 mg. Acute poisoning with nausea, vomiting, and diarrhoea has been reported following consumption of foods contaminated with inorganic tin, which can be released especially by containers of pickled vegetables. Acute ingestion of inorganic tin compounds in large amounts can cause gastrointestinal irritation. In particular, stannous chloride has a very strong metallic taste and is astringent towards the oral mucosae, so that accidental ingestion in the informal sector (the only use being restoration of antique mirrors) is often prevented. Organotin compounds are generally much more toxic than inorganic tin compounds, particularly towards the target species when used as pesticides, and have been shown to interfere with mitochondrial enzyme pathways (e.g. ATP synthase) and uncouple oxidative phosphorylation. Among di-, tri-, and tetra-substituted organotin compounds, some tri-substituted compounds have a specific effect on the central nervous system producing cerebral oedema, while di-substituted compounds are potent irritants that can induce an inflammatory reaction in the bile duct. The tetra-substituted compounds resemble tri-substituted compounds, which are, generally, more toxic than the mono- and di-substituted derivatives.

Name of the diseases and ICD code: **Acute diseases caused by tin or its compounds**
(Specific disease code) **+T56.6 +Z57**

Irritant contact dermatitis (L24), Mucous membrane irritation (J68), Burns and corrosions of external body surface (T20-T25), Burns and corrosions of eyes and adnexa (T26.0-T26.1, T26.5-T26.6), Acute toxic conjunctivitis (H10.2), Acute chemical bronchitis and pneumonitis (J68.0), Upper respiratory inflammation (J68.2), Pulmonary oedema (J68.1), Gastrointestinal toxicity (K52.1), Toxic encephalopathy (G92), Cerebral oedema (G93.6), Acute hepatotoxicity (K71.9), Acute nephropathy (N14.4)

Short description of the disease

Organotin compounds are in general strong irritants, and acute exposure can cause mild irritation of the eyes, skin, and mucous membranes. Irritation of the respiratory tract causes pulmonary effects, including bronchitis and pneumonitis. The irritation of the airways may lead to pulmonary oedema. The gastrointestinal tract may be involved too, mainly through ingestion of the dialkyl compounds (which is a very unlikely event in occupational settings). Acute intoxication caused by organotin compounds also involves the liver, with hepatic necrosis. Absorption of high doses of organotin compounds such as triphenyltin acetate or TPTA, can cause kidney damage, acute nephropathy results mainly from proximal renal tubular damage. Organotins, especially triethyltin (TET) and trimethyltin (TMT), are neurotoxic. Triethyltin is myelinotoxic, while trimethyltin is toxic to neurons of the limbic system of the brain.

1.1.30 Diseases caused by tin or its compounds ICD Code T56.6 +Z57

Diagnostic criteria

Clinical manifestations

- Signs and symptoms:
  - Acute conjunctivitis can be observed as a consequence of eye splashes, and corneal opacities have been reported.
  - Prolonged contact of the skin with clothes moistened with vapour as well as direct spillage on the skin have been responsible for acute local burns and subacute diffuse erythematous dermatitis, with pruritus and some pustular eruption in the hair-covered areas.
  - Irritant contact dermatitis and folliculitis have been reported in workers manufacturing or applying paints containing triphenyl tin fluoride or butyltin compounds (for further details on irritant contact dermatitis, refer to item 2.2.2).
  - Productive cough, breathlessness, chest pain, crackles, wheeze and haemoptysis. In the most severe cases, pulmonary oedema can be observed.
  - Gastrointestinal disturbances include nausea, vomiting, and diarrhoea.
  - Acute nephropathy shows significant hyperazotaemia, proteinuria, haematuria, and polyuria.
  - Main neurologic symptoms of poisoning are headache, vomiting, dizziness, dysuria, and visual disturbances such as photophobia. In the most severe cases, convulsions, flaccid paralysis, and urinary retention can be observed, followed by coma and death.
  - The clinical presentation of TMT poisoning includes aggressiveness, hyperphagia, disorientation, hallucinations, memory impairment, and complex partial seizures. Psychomotor disturbances including tremor, convulsions, nystagmus and ataxia have been reported. An impairment of the brainstem and inner ear may cause tinnitus and hearing difficulty.
- Examinations:
  - Chest X-rays may reveal a picture of pneumonitis or bronchitis, with increased bronchovascular markings.
  - Liver function tests may show elevated aspartate aminotransferase (AST), alanine aminotransferase (ALT), and bilirubin levels, while blood tests may show signs of haemolysis.
  - At liver biopsy, a centrilobular hepatitis with steatosis can be observed.
  - Renal biopsy shows focal fusion of glomerular cell processes and proximal tubular damage with cellular necrosis.
  - On lumbar puncture, the cerebrospinal fluid pressure is often elevated but cell count, and glucose and protein concentrations in the cerebrospinal fluid are normal. The main sign of TET poisoning is diffuse leucoencephalopathy without any localized abnormalities. Fundoscopy and cerebrospinal fluid pressure may be normal. Electroencephalogram (EEG) may show abnormalities in the temporal regions (spikes and slowing of EEG waves).

Exposure assessment

- History of occupational exposure: evidence of occupational exposure to inorganic or (mostly) organic tin compounds via inhalation, skin or direct contact and, when available, measurement of workplace air organic tin and detection of organotins in the urine 4-5 days after exposure. Organotin blood levels might remain elevated for 10 days after exposure.
- Minimum duration of exposure: few minutes.
- Maximum latent period: few days.

Name of the diseases and ICD code: **Chronic diseases caused by tin or its compounds**
(Specific disease code) **+T56.6 +Z57**

Stannosis (J63.5)

Short description of the disease

Stannosis occurs following chronic inhalation of respirable particles of tin oxide (cassiterite). The typical picture is of benign pneumoconiosis with radiological changes but without any pulmonary impairment. Tin dust does not excite an inflammatory reaction when inhaled. However, since it is radioopaque, it produces a typical picture of disseminated small, high density nodules on the chest radiograph.

1.1.30 Diseases caused by tin or its compounds — ICD Code T56.6 +Z57

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: affected subjects are usually asymptomatic.
- Examinations: the chest X-ray is characteristic, showing widespread mottling (non-fibrous); alterations of lung function are usually absent. High resolution computed tomography (CT) can show small (1-4 mm) opacities (usually denser than silicotic nodules), spread initially in the upper zones of the lungs and, subsequently, in the middle and lower zones. Note that radiological manifestations may improve if the exposure ends.

Exposure assessment

- History of occupational exposure: confirmed repeated or prolonged exposure to dusts of tin oxide at workplace and, when available, measurement of workplace air organic tin and detection of organotins in the urine.
- Minimum duration of exposure: five years.
- Maximum latent period: not applicable.

Key actions for prevention	During tin ore extraction, exposure can be minimized through wet processes; during some operations such as bagging, smelting, and refining, dust and fumes may still escape. For this reason, and also considering the increasing use of alloys and organotins, employers need to be educated about the risk of organotin exposure and implement strategies to minimize exposure of the skin, lungs, and gastrointestinal tract. Most prevention activities may follow the common practices and standards of occupational hygiene, i.e., to avoid unnecessary exposure by source segregation and the use of personal protective equipment whenever necessary. Particular attention should be paid to the (now residual) use of organo-stannic biocides, especially in ship construction, maintenance and in ship-breaking, where substantial exposure of workers can occur, especially in low-end activities performed in the informal sector. Periodic sampling of the working environment may be useful in assessing and mitigating risks. The group of experts considered that the following limits of exposure of workplace atmospheric concentrations have been observed to provide a reasonable level of protection for workers' health and have been used in a number of countries: Di-n-butyltin oxide, Dibutyltin dilaurate: 0.1 mg/m^3, as 8hr TWA; 0.2 mg/m^3 as STEL. Tin (II) chloride dihydrate, Tin (II) fluoride, Tin (IV) chloride (anhydrous), Tin (IV) oxide, Tin (II) chloride (anhydrous), Tin (II) oxide, Tin: 2 mg/m^3, as 8hr TWA.

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For the chemical entities listed below an entry exists in the collection of International Chemical Safety Cards (ICSC) hosted in the ILO website

Name	Synonyms	ICSC
Di-n-butyltin oxide	Dibutyltin oxide; Dibutyloxostannane; Dibutyloxotin	0256
Tin (II) chloride dihydrate	Stannous chloride dihydrate	0738
Tin (II) fluoride	Stannous fluoride; Tin bifluoride; Tin difluoride	0860
Tin (IV) chloride (anhydrous)	Tin tetrachloride; Stannic chloride	0953
Tin (IV) oxide	Stannic oxide; stannic anhydride; Tin dioxide	0954
Tin (II) chloride (anhydrous)	Tin dichloride; Tin protochloride; Stannous chloride	0955
Tin (II) oxide	Tin monoxide; Stannous oxide	0956
Dibutyltin dilaurate	Dibutylbis((1-oxododecyl)-oxy) stannane; Dibutylbis(lauroyloxy)tin	1171
Tributyltin oxide	Hexabutyldistannoxane; Tri-n-butyltin oxide; TBTO	1282
Triphenyltin hydroxide	Hydroxytriphenylstannane; Hydroxytriphenylstannate; Fentin hydroxide	1283
Tin		1535

▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
1.1.30	Acute/chronic diseases caused by tin or its compounds	T56.6	NE61&XM1NS5
1.1.30	Irritant contact dermatitis	L24	EK02
1.1.30	Mucous membrane irritation	J68	CA81.0
1.1.30	Burns and corrosions of external body surface	T20-T25	ND9Z
1.1.30	Burns and corrosions of eyes and adnexa	T26.0-T26.1, T26.5-T26.6	NE00
1.1.30	Acute toxic conjunctivitis	H10.2	9A60.Z
1.1.30	Acute chemical bronchitis and pneumonitis	J68.0	CA81.0
1.1.30	Upper respiratory inflammation	J68.2	CA81.2
1.1.30	Pulmonary oedema	J68.1	CA81.1
1.1.30	Gastrointestinal toxicity	K52.1	DE2Z
1.1.30	Toxic encephalopathy	G92	8D43.0Z
1.1.30	Cerebral oedema	G93.6	8D60.1
1.1.30	Hepatotoxicity	K71.9	DB95.Z
1.1.30	Nephropathy	N14.4	GB55.1
1.1.30	Stannosis	J63.5	CA60.9
	Occupational exposure to risk factors	Z57	QD84.Y

1.1.31 Diseases caused by zinc or its compounds	ICD Code T56.5 +Z57
General characteristics of the causal agent	Zinc (Zn), CAS number 7440-66-6, is the element with atomic number 30 in the periodic table of elements and is classified in Group 12 (II-B; Transition metals). This metal has five main natural and non-radioactive isotopes: ^{64}Zn (48.6%), ^{66}Zn (27.9%), ^{67}Zn (4.1%), ^{68}Zn (18.8%), ^{70}Zn (0.6%), and an atomic mass of 65.38 Da. Elemental zinc is of medium density (7.14 g/cm^3), silver-grey in colour, low melting (419.5°C), mechanically hard and brittle, and it easily and completely dissolves in mineral and organic acids. Zinc is ubiquitous in rocks, soil, water, and food but never occurs as a free metal. The main zinc ores in soil and rock are the "primordial" zinc sulphides, sphalerite, and wurtzite. The other minerals of zinc – smithsonite (zinc carbonate), hemimorphite (zinc silicate), and hydrozincite (a basic zinc carbonate) – derive from weathering processes of the primordial zinc sulphides. Zinc is a biologically essential element that operates as a co-factor in several enzymes.
Occupational exposures	*Zinc* is the fourth most widely employed metal in industrial manufacturing, with approximately 70% of the consumption deriving from mining, more than 13 million tons in 2017 and 30% from recycling (secondary zinc). On exposure to air, zinc becomes covered with a tenacious film of oxide, which protects the metal from further oxidation. This resistance to atmospheric corrosion forms the basis for one of the most common uses of the metal: the protection of steelwork by galvanizing. Zinc's ability to protect ferrous metals against corrosion is reinforced by electrolytic action. It acts as an anode with respect to iron and other structural metals, except aluminium and magnesium, and is thus preferentially attacked by corrosive agents. This property is used in many other important applications of zinc (e.g. in the use of zinc plates as anodes for cathodic protection of ships' hulls and underground tanks). Zinc metal is die-cast for components in the automobile industry, electrical equipment industry, and in the light machine tool, hardware, toys, and fancy goods industries. It is rolled into sheets in rolling mills for the manufacture of roofing, weather stripping, cases for dry batteries, and printing plates. Zinc is alloyed with other non-ferrous metals, thus producing brasses and bronzes with copper and tin, respectively, roofing zinc with copper and titanium, "nickel silver", and other alloys for die-casting with copper, aluminium and magnesium and for coinage. Zinc is widely employed in the production of non-rechargeable (zinc-carbon) electric accumulators (batteries), while minor uses are found in chemical applications as a generic acidic catalyst ("Lewis acid" for Friedel-Crafts aromatic acylation and alkylation). *Zinc oxide* (ZnO), or zinc white (flowers of zinc), is produced by the oxidation of vaporized pure zinc or by the roasting of zinc oxide ore. It is used as a pigment in paints, lacquers, and varnishes, as well as a filler for plastics and rubber. Zinc oxide is found in cosmetics, quick-setting cements, and pharmaceuticals. It is useful in the manufacture of glass, automobile tyres, matches, white glue, and printing inks. Zinc oxide is used as a semiconductor in the electronics industry. *Zinc chloride* ($ZnCl_2$), or butter of zinc, is a component of soldering flux for galvanized iron and steel and has numerous uses in the textile industry, including dyeing, printing, sizing, and weighting fabrics. It is a component of cement for metals, dentifrices (pastes or powders for cleaning the teeth), and soldering fluxes. It is used alone or with phenol and other antiseptics for preserving railway ties. Zinc chloride is used for glass etching and for the manufacture of asphalt. It is a vulcanizing agent for rubber, a flame retardant for wood, and a corrosion inhibitor in water treatment. Zinc chloride can be used in topical ointments. *Zinc chromate* ($ZnCrO_4$), or zinc yellow, is produced by the action of chromic acid on slurries of zinc oxide or on zinc hydroxide. It is used in pigments, paints, varnishes, and lacquers and in the manufacture of linoleum. Zinc chromate acts as a corrosion inhibitor for metals and epoxy laminates. The term zinc chromate can also be used to refer to a wide range of commercial zinc and zinc potassium chromates. *Zinc cyanide* ($Zn(CN)_2$) is produced by the precipitation of a solution of zinc sulphate or chloride with potassium cyanide. It is used for metal plating and for gold extraction. Zinc cyanide acts as a chemical reagent and as a pesticide. *Zinc sulphate* ($ZnSO_4 \cdot 7H_2O$), or white vitriol, is produced by roasting zinc blende or by the action of sulphuric acid on zinc or zinc oxide. It is used as an astringent, a preservative for hides and wood, a bleach for paper, a pesticide adjuvant, and a fungicide. Zinc sulphate also serves as a fireproofing agent and as a depressant in froth flotation. It is used in water treatment and in textile dyeing and printing.

1.1.31 Diseases caused by zinc or its compounds	ICD Code T56.5 +Z57
Occupational exposures	*Zinc sulphide* (ZnS) is used as a pigment for paints, oilcloths, linoleum, leather, inks, lacquers, and cosmetics. *Zinc phosphide* (Zn_3P_2) is produced by passing phosphine through a solution of zinc sulphate. It is used mainly as a rodenticide. Zinc salts are added to animal feed as growth-promoting minerals and can be found in mineral supplements for humans. Occupational exposure to zinc or its compounds can thus occur in several productive activities that include extraction of zinc ores, smelting, refining and other primary metallurgy activities, melting and alloying, welding, metal recycling, manufacturing in chemical, pesticide, pharmaceutical and cosmetics industries, battery manufacturing and recycling, and the preparation of supplemented animal feed and feeding operations. Primary routes of occupational exposure comprise inhalation of fumes especially zinc oxide, such as during operations in which galvanized steel, brass, or other zinc alloys are melted or produced by welding and soldering, or during metal smelting and cutting operations. Contact of zinc compounds especially zinc chloride and sulphate with the skin and mucous membranes can be harmful. Other workers potentially exposed to zinc and its compounds include moulding and casting machine operators, cleaners, janitors, and machinists within the fabricated metals industry.
Toxicological profile, main health effects and diagnostic criteria	
Short toxicological profile	*Zinc* is an essential micro-nutrient element in the human diet. It is a constituent of metalloenzymes, which play an important role in nucleic acid metabolism and protein synthesis. A minimum daily intake of dietary zinc is recommended; absorption of the metal from the gastrointestinal tract is tightly controlled by carrier-mediated pathways, and any excess that is not absorbed is eliminated through faeces. The bulk of the body pool of zinc is stored in the liver and regulated by a low molecular weight, cysteine-rich storage protein (metallothionein), from which the metal ion is transferred by specific mechanisms to the distribution proteins (albumin, transferrin, and alpha-2-macroglobulin). The main toxic effects of occupational overexposure to zinc are related to the inhalation of poorly soluble solid granules of *zinc oxide* that occur in soldering, in electric welding and, more generally, in zinc metallurgy and manufacturing, cutting of galvanized or zinc-coated metal, or melting and casting of brass or bronze. The inert particles of zinc oxide generated by sintering at welding temperature are taken up by clearing cells of the immune system (macrophages). Since they usually cannot efficiently dissolve in the acid environment of the phagosome, the cells trigger a cytokine-mediated inflammatory response that results in flu-like symptoms (*welder's* fever or *metal fume fever*) until the particles are naturally cleared through the lymphatic circulation. This response mechanism of the body is common to other inert and insoluble particles that can be inhaled. It has been reported that zinc oxide dust may block the ducts of the sebaceous glands and give rise to papular, pustular eczema in people employed in the packaging of this compound. *Zinc chloride* fumes are irritating to the eyes, the skin, and mucous membranes and have been reported to cause chemical pneumonia. The electrolytic manufacturing of zinc can produce mists containing sulphuric acid and zinc sulphate that can irritate the respiratory system. Dental erosion has been reported among exposed workers. Metallurgic processes involving zinc can lead to arsenic, cadmium, manganese, lead and possibly chromium and silver exposures, with their associated hazards. Since arsenic is frequently present with zinc, it can be a source of exposure to highly toxic arsine gas whenever zinc is dissolved in acids or alkalis (for further details, refer to item 1.1.6). *Zinc chromate* exposure has been associated with irritation and lesions of the nasal mucosae and dermatitis. Zinc chromates, as a subset of the larger group of chromium (VI) compounds, are classified as Group 1 carcinogens by IARC (for further details, refer to item 3.1.4). The consequences of long-term occupational exposure to zinc, in the absence of acute and subchronic effects, are not well characterized. Pneumoconiosis in zinc miners has been reported in the absence of metal fume fever manifestations or exposure to coal dust; nonetheless, uncertainties remain regarding the causal agent in these cases.

1.1.31 Diseases caused by zinc or its compounds — ICD Code T56.5 +Z57

Name of the diseases and ICD code: **Diseases caused by zinc or its compounds**
(Specific disease code) **+T56.5 +Z57**

Upper respiratory tract inflammation (J68.2), Mucous membrane irritation (J68), Burn and corrosion of the eye and adnexa (T26), Irritant contact dermatitis (L24), Ulceration of nose (J34.8), Allergic contact dermatitis (L23)

Short description of the disease

Inhalation of most zinc salts has been associated with symptoms of irritation of the respiratory mucosae. Skin and ocular lesions have been reported after contact with zinc compounds.

Diagnostic criteria

Clinical manifestations

- Transient cough, sore throat, hoarseness, a metallic taste in the mouth and chest pain can be observed after inhalation of most zinc compounds.
- Zinc chloride has a caustic action, which may result in ulceration of the skin of fingers, hands, and forearms of those who handle timber impregnated with it or use it as a flux in soldering.
- Both zinc chloride and zinc sulphate cause corneal ulceration and conjunctivitis. In case of contact with concentrated zinc chloride solutions (e.g. 50%), cataracts, glaucoma, and iritis have been observed.
- Zinc oxide dust may obstruct the ducts of sebaceous glands giving rise to pustular eczema.
- Zinc chromate in primer paints used by car-body builders, tinsmiths and steel cupboard makers has been reported to cause nasal ulceration and skin allergy, with itching and skin rash, in exposed workers.

Exposure assessment

- History of occupational exposure: evidence of exposure to zinc or (more likely) its compounds through inhalation or contact, either at the workplace or during a working activity.
- Minimum duration of exposure: few minutes; more time might be necessary to cause ulceration of the nasal septum in low exposure scenarios; for skin sensitization, usually several instances of exposure are required over long periods but in exceptional cases, even a single contact might be sufficient.
- Maximum latent period: few hours; for skin dermatitis, in sensitized subjects, any further exposure to zinc chromate may cause the onset of clinical signs, usually within 12-72 hours, or even later (up to 1-2 weeks).

Metal fume fever (T56.5)

Short description of the disease

Metal fume fever is a flu-like syndrome that can be caused by inhalation of sintered solid particles of zinc oxide, although the role of concurrent exposure to other metallic fumes in the pathogenesis of the disease cannot be completely ruled out. The disease is similar to the one caused by the inhalation of other inert solids such as refractory oxides and polymer fumes. In the case of zinc, the disease affects most often smelters and welders. The symptoms of metal fume fever are nonspecific; they generally appear a few hours after exposure and are reversible 1-4 days after cessation of exposure.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms:
  - Fever, chills, nausea, headache, fatigue, malaise, muscle aches, and joint pains appearing some hours after exposure.
  - A sweet or metallic taste in the mouth, which distorts the taste of food and cigarettes, is also normally reported, along with a dry or irritated throat which may lead to hoarseness.
  - Symptoms may include a burning sensation in the body, shortness of breath, chest pain, cough, dyspnoea, rash, vomiting, watery or bloody diarrhoea and low blood pressure.
- Examinations:
  - Pulmonary function is commonly unaffected, but tests may show reduced lung volumes (e.g. minimal changes in forced expiratory flow were observed after exposure to about 75 mg/m^3 of zinc oxide for 15-30 minutes, while decreased vital capacity has been reported for levels above 300 mg/m^3).
  - Chest X-ray findings are generally unremarkable.
  - There is an increase in white blood cell count (leucocytosis), although not in all cases.

1.1.31 Diseases caused by zinc or its compounds ICD Code T56.5 +Z57

Exposure assessment

- History of occupational exposure: evidence of exposure to zinc oxide, especially in metal smelting, galvanizing, and welding operations, and in foundries and, when available, workplace air monitoring.
- Minimum duration of exposure: few minutes.
- Maximum latent period: few hours.

Chemical bronchitis and pneumonitis (J68.0), Adult respiratory distress syndrome (ARDS) (J80)

Short description of the disease

Exposure to high zinc chloride concentrations has been associated to chemical pneumonitis and adult respiratory distress syndrome (ARDS). Diagnosis of ARDS is based on the presence of respiratory distress, severe hypoxaemia, and bilateral pulmonary infiltrates in the absence of cardiogenic pulmonary oedema.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms:
  - Symptoms of pneumonitis include marked dyspnoea, a productive cough, fever, chest pain and cyanosis.
  - ARDS is characterized by the rapid onset of dyspnoea (usually occurring 12-48 hours after the exposure), with tachypnoea, intercostal retractions, and crackles which may be noted at physical examination.
- Examinations:
  - Chest radiograph shows bilateral infiltrates, that may rapidly become confluent, and air bronchograms; heart size is usually normal, with small or absent pleural effusions.
  - Impaired oxygenation may be documented by the ratio of partial pressure of oxygen in arterial blood (PaO_2), to fractional concentration of inspired oxygen (FiO_2). Values lower than 300 mmHg are considered significant.

Exposure assessment

- History of occupational exposure: evidence of exposure to high levels of zinc chloride and, when available, workplace air monitoring.
- Minimum duration of exposure: few minutes.
- Maximum latent period: few hours.

Key actions for prevention	Zinc is a fundamental component of several manufacturing processes and is not likely to be eliminated from the occupational environment. Moreover, due to the extent of mining, and to the forecasted exhaustion of primary ores, it is anticipated that extraction from lower-grade ores and recycling from spent manufactured products will likely increase in the future. Prevention of exposure at mining, smelting and purification facilities is the first line of intervention, especially as soon as exploitation of lower-grade ores becomes economically convenient and processes become increasingly complex. In particular, purification by electrochemical (rather than by thermal) processes may become more feasible, and this should significantly reduce the levels of inhalation exposure. Efficient use of energy in thermal zinc processing may carry the benefit of higher insulation of plants and of a consequent reduction of workers' exposure to fumes. In all cases where zinc is heated to the point where fumes are produced, it is most important to ensure that adequate ventilation is provided. Individual protection is best ensured by education of the worker concerning metal-fume fever and the provision of local exhaust ventilation, or, in some situations, by wearing a supplied-air hood or mask. Workers who are nonetheless exposed to zinc chloride fumes should wear personal protective equipment, including protective clothing, eye and face protection and appropriate respiratory protective equipment. Several national and international agencies have proposed occupational exposure limits for zinc. The group of experts considered that the following limits of exposure of workplace atmospheric concentrations have been observed to provide a reasonable level of protection for workers' health and have been used in a number of countries: • Zinc chloride (fume): 1 mg/m^3 as 8hr TWA, 2 mg/m^3 as short-term exposure limit. • Zinc oxide: 2 mg/m^3 as 8hr TWA, 10 mg/m^3 as short-term exposure limit.

1.1.31 Diseases caused by zinc or its compounds ICD Code T56.5 +Z57

Further reading

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For the chemical entities listed below an entry exists in the collection of International Chemical Safety Cards (ICSC) hosted in the ILO website

Name	Synonyms	ICSC
Zinc oxide	Zinc white; Zinc monoxide; C.I. Pigment White 4	0208
Ziram	Zinc dimethyldithiocarbamate; (T-4)-bis (Dimethylcarbamodithioato-S,S')zinc	0348
Zinc sulfate heptahydrate	White Vitriol	0349
Zineb	Zinc ethylenebis(dithiocarbamate); ((1,2-Ethanediylbis(carbamodithioato))(2-))zinc	0350
Zinc phosphide	Trizinc diphosphide	0602
Mancozeb	Manganese ethylenebis (dithiocarbamate)(polymeric) complex with zinc salt; Manzeb; Manganese-zinc ethylenebis (dithiocarbamate)	0754
Zinc chromate	Chromium zinc oxide; Zinc tetraoxychromate; Chromic acid, zinc salt (1:1)	0811
Zinc stearate	Octadecanoic acid, zinc salt; Zinc distearate; Stearic acid, zinc salt	0987
Zinc chloride	Zinc dichloride	1064
Zinc powder	Blue powder; Merrillite	1205
Zinc nitrate	Zinc dinitrate; Nitric acid, zinc salt	1206
Zinc sulfide	Zinc monosulfide; Zinc sulphide	1627
Zinc sulfate	Zinc sulfate (anhydrous); Sulfuric acid, zinc salt (1:1); Zinc sulphate	1698

▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
1.1.31	Diseases caused by zinc or its compounds	T56.5	NE61&XM1U95
1.1.31	Upper respiratory tract inflammation	J68.2	CA81.2
1.1.31	Mucous membrane irritation	J68	CA81.Z
1.1.31	Burn and corrosion of the eye and adnexa	T26	NE00
1.1.31	Irritant contact dermatitis	L24	EK02
1.1.31	Ulceration of nose	J34.0	CA0K.Y
1.1.31	Allergic contact dermatitis	L23	EK00
1.1.31	Metal fume fever	T56.5	NE61&XM1U95
1.1.31	Chemical bronchitis and pneumonitis	J68.0	CA81.0
1.1.31	Adult respiratory distress syndrome (ARDS)	J80	CB00
	Occupational exposure to risk factors	Z57	QD84.Y

1.1.32 Diseases caused by phosgene	ICD Code T59.8 +Z57
General characteristics of the causal agent	Phosgene, $COCl_2$, CAS number 75-44-5, is a heavier than air, chemically reactive gas (boiling point 8.33° C) that can be easily compressed and liquefied. As phosgene is denser than air, emissions of phosgene may settle and collect at lower levels. At diluted concentrations in air (about 1 ppm), it shows a characteristic odour described as "of mouldy hay" and at about 0.5 ppm as "sweet". Workers exposed to phosgene can lose their ability to detect it at low concentrations through olfactory fatigue. Phosgene is produced industrially by reacting a dry mixture of carbon monoxide (see item 1.1.16) with chlorine gas (see item 1.1.40) at a mild temperature in a catalyst composed of porous charcoal. The reaction is exothermic, and the reactor needs to be cooled. In its bulk industrial uses, phosgene is mostly generated at the plant site and used immediately after production. For uses at a small industrial or laboratory scale, such as in the batch synthesis of speciality chemicals, phosgene is deployed as a liquid in cylinders. Phosgene is generated when volatile and chlorinated hydrocarbons are heated to their decomposition by contact with flames or hot metal, such as in fires involving chlorinated solvents, refrigerating gases, plastics such as PVC and transformer oils containing polychlorinated biphenyls. Chlorinated solvents, in particular, methylene chloride and chloroform (see item 1.1.11), produce phosgene upon exposure to light and become acidic and corrosive, especially towards some metals such as aluminium. To avoid this phenomenon, the solvents are stored in the dark (dark glass bottles), and a small amount of an alcohol (usually methyl alcohol) is added to scavenge phosgene, although the corrosive effect of the released hydrochloric acid on the metal (when solvents are stored in metal cans or drums) cannot be entirely avoided. Phosgene thermally decomposes above 200°C producing toxic and corrosive gases of carbon monoxide and hydrogen chloride. On contact with water and moisture, phosgene decomposes into hydrogen chloride (hydrochloric acid, see item 1.1.22) and carbon dioxide (see item 1.1.16). Moist phosgene corrodes most industrial metals, and even when dry, it is able to react with aluminium, industrial alcohols, and amines, releasing hydrochloric acid as a reaction by-product.
Occupational exposures	Phosgene is a bulk chemical compound with millions of tons produced each year worldwide. Among the main chemical products that are manufactured from phosgene are several types of industrial monomers, such as methylene-diphenyl-diisocyanate (MDI) and toluene diisocyanate (TDI) (see item 1.1.35), and polymers of the class of polycarbonates. Other chemical processes that use phosgene are quantitatively less important, such as the industrial preparation of acyl chlorides and chloroformates used in the synthesis of speciality chemicals. Exposure in the chemical industry can occur in production plants where manufacturing of monomers for polyurethane plastics occur, in the manufacturing of polycarbonate polymers, in the synthesis of organic intermediates for pharmaceuticals, pesticides, and dyes, and in other small-volume production. Other scenarios for the unwanted and uncontrolled generation and release of phosgene are combustion or high-temperature thermal degradation of chlorinated thermoplastic polymers (such as PVC) in industrial fires, and the use of chlorinated fluids as fire extinguishers, as cooling fluids in refrigeration systems, and as solvents for metal cleaning and degreasing (see item 1.1.11). Phosgene was employed as a chemical weapon in the First World War and in some episodes even after the ban of their use (1925 Geneva Protocol). Stockpiles were often dumped along with other military ordnance in lakes and at sea, in scuttled ships, with little record of the sites. People engaged in the recovery of shipwrecks, remediation of water-basins, and professional or recreational scuba diving must be aware of these hazards. Rusting cylinders containing hazardous chemicals like phosgene are prone to leak, especially when disturbed during removal operations.
Toxicological profile, main health effects and diagnostic criteria	
Short toxicological profile	Phosgene is quickly absorbed in the lungs, and the severity and rapidity of the effects on the respiratory system depend on its concentration. Most information on the effects at high concentration derives from its extensive use as a "knock-down" chemical weapon. The olfactory detection threshold for phosgene is 0.4-1.5 ppm (perceived as "sweet" by subjects that survived the experience), but the typical "musky" or "newly mown hay" smell perceived at about 1 ppm is difficult to identify as a threat and is quickly overcome by olfactory fatigue.

1.1.32 Diseases caused by phosgene — ICD Code T59.8 +Z57

Short toxicological profile	Breathing phosgene at high concentration leads to coughing and irritation of the eyes and respiratory tract, that can be rapidly worsen or temporarily improve. The onset of serious and often irreversible toxic effects can be delayed by as much as 24 to 36 hours after the cessation of exposure. They start with pulmonary oedema and quickly progress to respiratory failure and death. Absorbed phosgene quickly degrades by hydrolysis to carbon dioxide and hydrogen chloride, but its toxicity is much higher than the equivalent inhaled dose of the latter. Phosgene reacts with the proteins of the lung epithelium with the formation of urea-like linkages: the result is a reduction of gas exchange capacity of the lung alveoli. Chronic inhalation exposure to phosgene may, theoretically and based on limited and very old investigations, cause pulmonary emphysema, and pulmonary fibrosis has been reported as a delayed consequence of acute exposure. However, evidence on workers chronically exposed to phosgene are scarce and the conclusions that can be drawn regarding the chronic effects of phosgene are limited.

Name of the diseases and ICD code: **Acute disesases caused by phosgene** *(Specific disease code)* **(T59.8) +Z57**

Respiratory tract irritation (J68), Acute chemical pneumonitis and bronchitis (J68.0), Pulmonary oedema (J68.1), Upper respiratory inflammation (J68.2), Reactive airways dysfunction syndrome (RADS) (J68.3), Irritant-induced occupational asthma (J68.3)

Short description of the disease

Direct contact with phosgene can damage the respiratory system with insidious onset. Due to its low solubility, phosgene causes only very mild upper airway irritation but may penetrate to the bronchioles and alveoli in sufficient quantities to produce intense delayed damage in the lower airways, which can be life-threatening. Such effects can be delayed (6 to 24 or even up to 72 hours). Initial symptoms after inhalation are usually very mild but may include coughing, sore throat and dyspnoea. The main feature of phosgene poisoning is massive delayed pulmonary oedema, observed with a latency of approximately 12 hours after the causal exposure.

It is important to remember that exposed workers can lose their ability to detect the typical smell of phosgene due to olfactory fatigue and irritant properties. This often limits awareness of exposure.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: exposure to phosgene at high concentrations causes a triphasic pattern of symptomatology:
  1) In the initial phase (sometimes known as the reflex phase), a vagal reflex response produces frequent, shallow respirations, which may be accompanied by shortness of breath, wheezing, coughing, and chest tightness.
  2) The second phase (often referred to as the latent phase) is generally characterized by a lack of symptoms or signs, and can last for several hours after exposure.
  3) In the third phase (i.e., the terminal phase), pulmonary oedema develops (usually not before 6-48 hours after exposure), and the consequent respiratory insufficiency manifests as tachypnoea, dyspnoea and cyanosis with hypoxia.

  In cases of exposure to extremely high concentrations, immediate death may result from occlusion of the pulmonary circulation as a consequence of clotting and intravascular haemolysis.
- Examinations:
  - Pulmonary function tests can be performed in less severe cases and may show obstruction consequent to acute bronchitis.
  - Chest X-rays may show the typical signs of bronchitis, pneumonitis, and lung oedema (e.g. increased bronchovascular markings, blurred enlargement of the hila, patches or strip shadows at the center of the lung).
  - Arterial blood gas testing may demonstrate hypoxia.

Exposure assessment

- History of occupational exposure: evidence of acute exposure to phosgene (mostly by inhalation) and, when available, workplace air monitoring measurements.
- Minimum duration of exposure: few seconds.
- Maximum latent period: 72 hours.

1.1.32 Diseases caused by phosgene	ICD Code T59.8 +Z57
Key actions for prevention	Phosgene is a staple precursor in the synthesis of bulk chemical products mainly the urethane monomers for polyurethane polymers. Due to the large volumes needed, and its inherent toxicity, it is mostly produced at the point of use rather than off-site, and its use in chemical manufacture is subject to stringent regulations. To avoid massive release following chemical accidents, plants should have the facility to divert gaseous streams containing phosgene to alkaline chemical scrubbers, where it is degraded to innocuous products. However, chemical scrubbing plants contain large quantities of strongly alkaline material usually concentrated sodium hydroxide, and may themselves be hazardous for workers. In some processes, phosgene gas can be substituted with a less hazardous liquid formulation. For example phosgene in a toluene solution, diphosgene (trichloromethyl chloroformate), and triphosgene (*bis*(trichloromethyl)-carbonate) can be used as substitutes for gaseous phosgene for small-volume work, such as "chloroformylation" reactions performed in batches in the industrial or laboratory synthesis of speciality chemicals. Substitution is driven by environmental concerns and regulations about ozone depletion caused by hydrogen chloride, released as a by-product of phosgene use. For example, since the 1980s, dimethyl carbonate has been produced by catalytic oxidative carbonylation of methanol with oxygen rather than from phosgene itself. A further option for risk control is the production of phosgene just upstream of its utilization, with limited, if any, intermediate storage. Maintenance procedures typically require work close to plant equipment. Worker safety can be maintained by isolation of tanks and reactors with valves. Purging pipe systems with inert gas can lower the concentration of phosgene to manageable levels. Particular attention should be paid to workers who need to operate close to leaks of phosgene in industrial plants, especially in the case of accidents that require an immediate response. In this case, workers must be equipped with appropriate clothing (hazmat suits, gloves, boots, head and face protection). Self contained breathing apparatus is also necessary. Following prolonged work, vapour filter respiratory protective equipment may become saturated with toxic material, allow breakthrough to the wearer, and will not provide adequate protection. Phosgene detection badges should be worn. These devices turn progressively from a yellowish to a red colour on exposure to phosgene. Appropriate supervision of workers in the critical areas, and first aid equipment including respiratory resuscitators and fresh respiratory protective equipment for emergency use should be provided. Air-purifying, fullface piece respirators with a chinstyle, front or back-mounted canister are neccessary protection equipment for escape. The unwanted generation of phosgene can occur during fires that involve chlorinated organic compounds, such as refrigeration fluids (R-22, or chlorodifluoromethane), especially in car and truck road accidents. Fire extinguishers containing Halon 1211, or Bromochlorodifluoromethane ($CBrClF_2$) can also lead to phosgene production. Fire alarms may trigger automated release, and hazardous levels may be generated in confined environments, such as technical cabinets. In both cases, operator protection can only be achieved with self-contained breathing apparatus that is standard for firefighting in chemical and other hazardous situations. The group of experts considered that a limit of exposure of workplace atmospheric concentrations of 0.1 ppm (as 8hr TWA) has been observed to provide a reasonable level of protection for workers' health and to be used in a number of countries.

1.1.32 Diseases caused by phosgene ICD Code T59.8 +Z57

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For the chemical entities listed below an entry exists in the collection of International Chemical Safety Cards (ICSC) hosted in the ILO website

Name	Synonyms	ICSC
Phosgene	Carbonyl chloride; Chloroformyl chloride	0007
Diphosgene	Formic acid, trichloro-methyl ester; Trichloromethyl chloroformate	1630

▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
1.1.32	Acute diseases caused by phosgene	T59.8	NE61&XM91W5
1.1.32	Respiratory tract irritation	J68	CA81.Y
1.1.32	Acute chemical pneumonitis and bronchitis	J68.0	CA81.0
1.1.32	Pulmonary oedema	J68.1	CA81.1
1.1.32	Upper respiratory inflammation	J68.2	CA81.2
1.1.32	Reactive airways dysfunction syndrome (RADS)	J68.3	CA81.Y
1.1.32	Irritant-induced occupational asthma	J68.3	CA81.Y
1.1.32	Chemical burns and corrosions of external body surface	T20-T25	ND9Z
1.1.32	Burns and corrosions of eyes and adnexa	T26.0-T26.1, T26.5-T26.6	NE00
1.1.32	Irritant contact dermatitis	L24	EK02
1.1.32	Frostbite	T35	NE4Z
1.1.32	Conjunctivitis	H10.2	9A60.Z
1.1.32	Corneal ulcer	H16.0	9A78.8
1.1.32	Blurred vision	H53.8	9D7Z
	Occupational exposure to risk factors	Z57	QD84.Y

1.1.33 Diseases caused by corneal irritants like benzoquinone	ICD Code T52.2 +Z57
General characteristics of the causal agent	Benzoquinone is a quinone with a single benzene ring containing two carbonyl groups, usually in the para (1,4) position (p-benzoquinone). p-Benzoquinone (2,5-Cyclohexadiene-1,4-dione, Quinone, 1,4-Benzoquinone, p-Quinone, CAS number 106-51-4, chemical formula $C_6H_4O_2$, molecular mass 108.1 g/mol) is a sublimating yellow crystalline solid with appreciable volatility even at room temperature and a penetrating, pungent and irritating odour resembling that of chlorine. Benzoquinone is an oxidizing agent, which usually reacts smoothly with reducing agents and strong bases but, in some cases, gives rise to strongly exothermic reaction with combustible substances even under ambient conditions; it decomposes on warming above 60°C, even when moist. Dust explosion in air is possible for powders or granular forms, especially when the dry product in bulk amounts gets electrostatically charged by swirling, pneumatic transport, pouring, etc. On decomposition, benzoquinone produces toxic gases, such as carbon monoxide. For more information, see the summary table at the end of the item.
Occupational exposures	*p*-Benzoquinone is industrially prepared by air or catalytic oxidation of hydroquinone. Occupational exposure is possible in the chemical industry, where it is produced or used as a starting material, in the manufacture of hydroquinone, for fine chemicals (pharmaceuticals, pesticides, fungicides, dyes), in the rubber industry as a vulcanization accelerator, and in the textile, leather and cosmetic industries. *p*-Benzoquinone is also formed from hydroquinone in photographic development by oxidation from light-activated silver halogenides, which are reduced to black elemental silver nanoparticles embedded into the paper substrate.
Toxicological profile, main health effects and diagnostic criteria	
Short toxicological profile	*p*-Benzoquinone and most chemically similar compounds are highly distasteful with a strongly astringent taste, they exacerbate mucosal irritation and are emetogenic, such that occupational exposure by accidental swallowing is highly unlikely. Inhalation can cause irritation to the eyes, resulting in discolouration of the conjunctivae and cornea, while dermal exposure causes dermatitis with skin discolouration and erythema. Effects on the kidneys have been reported in animal studies. Contact with the skin is possible through splashes of solutions especially in low-technology applications and can cause painful chemical burns with susceptibility to infection, similar to alkali burns. Skin depigmentation can occur due to melanocyte toxicity. Chronic dermal contact may result in skin ulceration, while chronic inhalation exposure may result in visual disturbances. Contact with the eyes and mucous membranes can give rise to severe effects, especially since benzoquinone can evaporate from solutions kept in the open.

Name of the diseases and ICD code: **Health effects due to corneal irritants like benzoquinone**
(Specific disease code) **+T52.2 +Z57**

Burns and corrosions of eye and adnexa (T26.0-T26.1, T26.5-T26.6), Conjunctivitis (H10.2), Pterygium (H11.0), Corneal ulcer (H16.0), Keratoconjunctivitis (H16.2), Corneal scar and opacity (H17.9), Corneal pigmentation (H18.0), Corneal oedema (H18.2)

Short description of the disease

Quinone is solid with appreciable vapour pressure, and the vapour or dust is very hazardous to the eyes. Contact with the eyes may cause irritation, discolouration, and damage, which may produce vision difficulties and may be permanent.

Acute exposure causes conjunctival irritation, and in some cases corneal oedema, ulceration and scarring; transient eye irritation may be noted above 0.1 ppm and becomes marked at 1 to 2 ppm.

Chronic exposure causes the gradual development of changes characterized as: (1) brownish discolouration of the conjunctivae and cornea, confined to the intrapalpebral fissure; (2) small opacities of the cornea; and (3) structural corneal changes which result in loss of visual acuity. The pigmentary changes are reversible, but the more slowly developing structural changes in the cornea may progress. Pigmentation may occur with less than five years of exposure.

Quinone is mainly known as a corneal irritant; however, in contact with the skin or the lining of the nose and throat, it may cause severe irritation, discolouration, redness, swelling, blistering, erythema, and formation of papules and vesicles. Hypoaesthesia of the cornea is also a feature. Prolonged contact with the skin may cause ulceration. Skin irritation is uncommon and is usually not associated with serious injury (for further details on irritant contact dermatitis, refer to item 2.2.2).

1.1.33 Diseases caused by corneal irritants like benzoquinone ICD Code T52.2 +Z57

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: reversible and gradual brownish discolouration of the conjunctivae and cornea. The injury usually extends through the entire layer of the conjunctivae and is characterized by the deposit of a pigment.
- Examinations: an ophthalmic examination should be performed, including visual acuity and slit lamp inspection of the cornea. Corneal ulceration and cystic changes may be seen on corneal examination. Pterygium may be present following chronic irritation.

Exposure assessment

- History of occupational exposure: confirmed acute or prolonged exposure to benzoquinone and, if available, workplace air monitoring of 1,4-benzoquinone (or other quinones) concentration. The potential for splash exposure or direct transference to the eye should be considered.
- Minimum duration of exposure: minutes for acute irritant effects; inflammation and discolouration of the cornea and conjunctivae have been observed after at least two years of exposure; severe cases have not been observed for exposure shorter than five years.
- Maximum latent period: one year.

Irritant contact dermatitis (L24)
Refer to item 2.2.2.

Vitiligo (leukoderma) (L81.5)
Refer to item 2.2.3.

Key actions for prevention	Since benzoquinone is a very strong irritant and the most serious effects are on the eye and sight, protection with well-fitting goggles ensuring good vision and correction of possible visual impairment is strongly recommended, especially for craft workers in photography, art printing and dyeing. A likely scenario for accidental eye injury from benzoquinone is rubbing eyes with contaminated hands or even worse with gloves. Unless a less toxic chemical can be substituted for a hazardous substance, engineering controls are the most effective way of reducing exposure. The best protection is to enclose operations and provide local exhaust ventilation at the site of chemical release. Isolating operations can reduce exposure. Where possible, automated transfer of p-benzoquinone from drums or other storage containers to process containers is recommended. Using respirators or protective equipment is less effective than the controls mentioned above, but is sometimes necessary. Improper use of respirators can be dangerous. Such equipment should only be used according to an established written program adapted to the workplace conditions. Workers should be properly trained on the correct use of the respirators, use respirators which have been fit tested, and be medically fit for wearing respirators. Protective gloves and clothing must be appropriate for the operation. Appropriate eye protection with side shields or goggles and a face shield along with goggles when working with corrosive, highly irritating or toxic substances should be worn and take account of the physical form of the exposure. Good work practices can help to reduce hazardous exposures. They include prompt change of clothing contaminated by p-benzoquinone into clean clothing, at the end of the work shift washing of any area of the body that may have contacted *p*-penzoquinone, placing of eye wash fountains and emergency shower facilities in the immediate work area for emergency use. Proper welfare facilities should be provided and careful hand washing before eating, drinking, smoking, or using the toilet should be performed. Eating, drinking and smoking should be forbidden at the workplaces where p-benzoquinone is handled, processed, or stored. Using a vacuum or a wet method to reduce dust during clean up and not dry sweeping are recommended practices. An 8hr TLV-TWA of 0.1 ppm (0.44 mg/m^3) is indicated as an occupational exposure limit for benzoquinone in the corresponding International Chemical Safety Card (ICSC). This value is intended to minimize the potential for eye irritation, disturbances in vision, and following skin contact, depigmentation, erythema, swelling, and cutaneous lesions. Prolonged dermal contact is reported to produce necrosis. Sufficient data seem not to be available to recommend skin, SEN (sensitizer), or carcinogenicity notations or a TLV–STEL.

1.1.33 Diseases caused by corneal irritants like benzoquinone — ICD Code T52.2 +Z57

Further reading

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For the chemical entities listed below an entry exists in the collection of International Chemical Safety Cards (ICSC) hosted in the ILO website

Name	Synonyms	ICSC
Hydroquinone	1,4-Dihydroxybenzene; Hydroquinol Quinol	0166
p-Benzoquinone	2,5-Cyclohexadiene-1,4-dione; Quinone; 1,4-Benzoquinone; p-Quinone	0779
Chloranil	2,3,5,6-Tetrachloro-p-benzoquinone; 2,3,5,6-Tetrachloro-2,5-cyclohexadiene-1,4-dione; Tetrachloro-p-benzoquinone; Tetrachloro-p-quinone	0780
4-Methoxyphenol	Hydroquinone monomethyl ether; Mequinol; p-Hydroxyanisole	1097
1,4-Dimethoxybenzene	Benzene, 1,4-dimetoxy-; Hydroquinone dimethyl ether; p-Methoxyanisole	1297
1,4-Naphthoquinone	1,4-Dihydro-1,4-naphthalenedione; 1,4-Naphthalenedione; 1,4-Dihydro-1,4-diketonaphthalene	1547
2-Aminoanthraquinone	2-Amino-9,10-anthracenedione; 2-Amino-9,10-anthraquinone; beta-Aminoanthraquinone	1579
Anthraquinone	9,10-Anthraquinone; 9,10-Anthracendione; Diphenyl ketone	1605

▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
1.1.33	Diseases caused by corneal irritants like benzoquinone	T52.2	PB31&XM2738
1.1.33	Irritant contact dermatitis	L24	EK02
1.1.33	Vitiligo (leukoderma)	L81.5	EK5Y
1.1.33	Burns and corrosions of eye and adnexa	T26.0-T26.1, T26.5-T26.6	NE00
1.1.33	Conjunctivitis	H10.2	9A60
1.1.33	Pterygium	H11.0	9A61.1
1.1.33	Corneal ulcer	H16.0	9A76
1.1.33	Keratoconjunctivitis	H16.2	9A79
1.1.33	Corneal scar and opacity	H17.9	9A77
1.1.33	Corneal pigmentation	H18.0	9A78.1
1.1.33	Corneal oedema	H18.2	9A78.2
	Occupational exposure to risk factors	Z57	QD84.Y

1.1.34 Diseases caused by ammonia	ICD Code T54.3 +Z57
General characteristics of the causal agent	Ammonia (anhydrous) NH_3, CAS number 7664-41-7, molecular mass 17.03 g/mol is a colourless gas at ambient temperatures and pressures. It can easily be liquefied by moderate pressure and cooling to produce a compressed liquid gas. It has a characteristic pungent smell of stale urine. Ammonia is commonly produced in bulk in the chemical industry. It also occurs naturally in soil, water, and air, and is a decomposition product of human and animal urine and faeces. It is corrosive for several materials. These include copper, aluminium, zinc and its alloys, natural and vulcanized rubber, and other elastomeric materials. Ammonia reacts violently with acids (neutralization with formation of ammonium salts), with some strong oxidants, and with halogens. Its reaction with hypochlorous acid generates chloramine, which is explosive and toxic. It easily dissolves in water with an exothermic reaction to generate a strongly alkaline solution of ammonium hydroxide (NH_4OH).
Occupational exposures	Ammonia is a common feed stock for largescale production in the chemical industry. In 2016, China was the largest producer worldwide, followed by Russia, India, and the USA. In 2017, the global production was about 150 million tons. Most is produced using the Haber process, comprising direct reaction of hydrogen usually from methane in natural gas with nitrogen from air, at pressure levels above 60-180 bar, and temperatures higher than 400°C. This is undertaken in large reactors containing beds of catalysts based on transition metals such as iron and ruthenium. The commonest use of ammonia worldwide, approximately 80%, is in the manufacture of agricultural fertilizers (ammonium nitrate and ammonium sulphate). Other bulk uses include the production of nitric acid, synthetic urea, and sodium carbonate (via the Solvay process). It is used in the manufacture of organic chemicals including acrylonitrile, caprolactam and diamines; for the production of fibre monomers, nylon, rubbers and polymer resins. It is also used in the manufacture of dyes, pesticides, plastics, explosives, pharmaceuticals and other fine chemicals. It is commonly employed in the pulp and paper, food and beverage, textile, leather, and metallurgical industries. For example, as an industrial refrigerant in cooling and chilling of foodstuffs, especially in seafood facilities and trawlers. As a fumigant for foodstuffs, an industrial cleaner typically as dilute ammonium hydroxide, and a purifier for water supplies. It finds use as a corrosion inhibitor, in steel hardening by nitriding, and as a neutralizing agent for acidic gases and nitrogen oxides in industrial emissions. It is commonly used in the illegal production of methamphetamine in small covert facilities. Occupational exposure to ammonia gas occurs primarily from spills or leaks from ammonia tanks or pipelines, in the different production and application settings described above. This is problematic in illegal methamphetamine laboratories employing poor control measures, and for local people, when the laboratory is situated in densely populated urban areas. Ammonia is generated in coal distillation for the production of metallurgical coke and of coal gas in gasworks. Large quantities of gaseous ammonia can be released by the decomposition of biological materials such as sludge from wastewater processing plants, manure and concentrated animal feed (e.g. in intensive animal rearing facilities). This can be hazardous in enclosed environments like tanks and pits.
Toxicological profile, main health effects and diagnostic criteria	
Short toxicological profile	The odour threshold of ammonia can vary from very low values around 0.05 ppm, up to a maximum of around 60 ppm. Ammonia is a physiological component of living matter that undergoes extensive biotransformation to nitrogen-containing molecules and tissues. It is the main product of nitrogen metabolism, excreted as urea in the urine. It contributes to systemic toxicity in the terminal stages of liver and kidney diseases, with neurological impairment, and can lead to coma and death. Ammonia dissolves in water present in skin, and mucous membranes to form ammonium hydroxide. This is a highly ionized base that causes saponification of cell membrane lipids, cell disruption and tissue necrosis. It initiates an inflammatory response, which further damages the surrounding tissues. In addition to these caustic alkali burns, contact with liquid ammonia can result in cold injury. The toxic effects are typically limited to tissues in direct contact with ammonia. Exposure to high concentrations of liquid or vapour causes severe burns to the skin, eyes, upper airways and gastrointestinal tract. In the respiratory tract it can cause laryngeal oedema, pneumonitis and pulmonary oedema. Airway obstruction and respiratory insufficiency may be fatal. Survival may be compromised by complications such as infection and scarring, that may develop days or weeks after inhalation or ingestion. There may be permanent effects including visual impairment, and chronic pulmonary disease such as obstruction of small and large airways, bronchiectasis and interstitial lung disease.

1.1.34 Diseases caused by ammonia ICD Code T54.3 +Z57

Name of the diseases and ICD code: **Acute diseases caused by ammonia** *(Specific disease code)* **T54.3 +Z57**

Chemical burns and corrosions of the eyes (T26), Chemical burns and corrosions of respiratory tract (T27), Conjunctivitis (H10.2), Corneal ulcer (H16.0), Respiratory tract irritation (J68), Acute chemical pneumonitis and bronchitis (J68.0), Pulmonary oedema (J68.1), Upper respiratory inflammation (J68.2), Reactive airways dysfunction syndrome (RADS) (J68.3), Rhinitis (J31.0; J31.1), Sinusitis (J01.8), Pharyngitis (J31.2), Laryngitis (J37.0), Irritant-induced occupational asthma (J68.3), Chronic obliterative bronchiolitis (J68.4), Pulmonary fibrosis (J68.4)

Short description of the disease

Exposure to ammonia vapours causes irritation and caustic burns of the respiratory tract, the mucous membranes and the eyes. Nasopharyngeal and tracheal burns, airway obstruction, and bronchiolar and alveolar oedema can happen. Ingestion of ammonium hydroxide, while uncommon, results in corrosive damage to the mouth, throat, and stomach. For this reason, ingestion of ammonia rarely results in systemic poisoning. The full extent of damage to the eyes may not be clear until up to one week after the injury. Contact with liquefied ammonia can cause cold injury (frostbite).

Diagnostic criteria

Clinical manifestations

- Signs and symptoms:
  - Nonspecific symptoms of acute poisoning include headache, loss of sense of smell, nausea and vomiting.
  - Typical symptoms include eye irritation, lacrimation, rhinitis, sore throat, cough, wheeze, chest pain, chest tightness and shortness of breath. In severe cases, there may be oedema of the mucous membranes, airways ulceration and obstruction, pulmonary oedema, hypoxia and agitation.
  - Exposure to increasing concentrations of airborne ammonia cause a progressively worsening clinical picture:
    > Irritation of mucous membranes and eyes (with eye swelling, dry lips, and burning throat) can occur above 50-100 ppm.
    > Exposure to an air concentration of 250 ppm is bearable for most persons for 30 to 60 minutes.
    > Exposure to concentration levels above 500 ppm for few minutes usually provokes acute symptoms.
    > Exposure levels above 1,500 ppm usually causes coughing, breathing difficulties, and severe lacrimation.
    > Levels of about 2,000-3,000 ppm can generate skin blisters and burns within seconds.
    > Levels around 5,000-10,000 ppm can cause severe damage of the lower respiratory tract, possibly with suffocation and death within minutes.
- Examinations:
  - Physical examination shows mucosal irritation. Upper airways obstruction causes stridor. In pulmonary oedema, there may be respiratory distress, and auscultation can reveal reduced air entry, fine crackles and wheeze.
  - Chest X-ray may show increased bronchovascular markings, diffuse bilateral alveolar infiltrates or severe bilateral pulmonary oedema.

Exposure assessment

- History of occupational exposure: confirmed occupational exposure to high concentrations of ammonia and, if available, workplace air monitoring data.
- Minimum duration of exposure: few seconds.
- Maximum latent period: few hours.

1.1.34 Diseases caused by ammonia — ICD Code T54.3 +Z57

Name of the diseases and ICD code: **Acute diseases caused by ammonia** *(Specific disease code)* **T54.3 +Z57**

Chronic obstructive pulmonary disease (COPD) (J68.4), Pulmonary fibrosis (J68.4), Corneal ulcer (H16.0)

Short description of the disease

Long-term exposures to ammonia vapour can cause chronic irritation of the respiratory tract, mucous membranes, eyes and skin.

Long-term sequelae of acute high exposures include chronic cough, bronchial hyper responsiveness, asthma, chronic bronchitis, bronchiolitis obliterans, bronchiectasis, and lung fibrosis. Severe cases are accompanied by progressive airway obstruction and falls in diffusion capacity.

Diagnostic criteria

Clinical manifestations

- Chronic respiratory toxicity caused by ammonia gives a picture resembling different phases of chronic obstructive pulmonary disease (COPD). Symptoms include chronic progressive breathlessness, cough and sputum production. On physical examination, diminished breath sounds, wheeze and prolonged exhalation can be found. For further details, refer to item 2.1.9.
- Following eye contact, ulceration and perforation of the cornea can occur after weeks or months, resulting in visual impairment. Cataracts and glaucoma have been reported.
- Ingestion of ammonia may cause permanent damage to the mucous membranes of the gastrointestinal tract, with bleeding, perforation, scarring, or stricture formation.

Exposure assessment

- History of occupational exposure: confirmed prolonged occupational exposure to high levels of ammonia and, when available, workplace air monitoring.
- Minimum duration of exposure: some months.
- Maximum latent period: some months.

Key actions for prevention	Protection of workers can usually be achieved using the hierarchy of controls: elimination, substitution, engineering controls and personal protective equipment. These should include controls for both routine production and maintenance work especially in confined spaces. Leaks and spills from piping and tanks are usually readily detected because of ammonia's pungent smell, but portable samplers are available to quantify airborne concentrations. All facilities with an ammonia refrigeration system should have ammonia detection sensors installed that will identify an ammonia leak, trigger an alarm and activate an independent ventilation system. Sewage plants and intensive animal rearing facilities should employ good housekeeping measures. Following exposure to high levels of ammonia, workers should be instructed to leave the contaminated area and move to fresh air; remove contaminated clothing, avoid touching any areas that may be contaminated with liquid ammonia; and wash affected areas of the skin with copious soap and water. If the eyes are burning or vision is blurred, wash the eyes with plain water for 10 to 15 minutes. Eyewash stations and showers should be available. During routine production, ammonia emissions to the environment should comply with local environmental legislation. In large plants where there are large amounts of flammable gases, high pressure processes and high temperatures, detailed emergency response plans should be made in case of catastrophic accidents. These should include provision for training, exposure assessment, personal decontamination, emergency repairs, evacuation procedures, liaison with emergency and public health services in adjacent populated areas, and environmental decontamination. The group of experts considered that the following workplace exposure limits for airborne concentrations of ammonia, have been observed to provide a reasonable level of protection for workers' health, and are used in a number of countries: • 25 ppm (17 mg/m^3) 8hr TWA. • 35 ppm (24 mg/m^3) for short term exposures.

1.1.34 Diseases caused by ammonia ICD Code T54.3 +Z57

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For the chemical entities listed below an entry exists in the collection of International Chemical Safety Cards (ICSC) hosted in the ILO website

Name	Synonyms	ICSC
Ammonia (anhydrous)	R717, Refrigerant gas 717	0414

▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
1.1.34	Acute/chronic diseases caused by ammonia	T54.3	NE61&XM4TP4
1.1.34	Respiratory tract irritation	J68	CA81.Z
1.1.34	Acute chemical pneumonitis and bronchitis	J68.0	CA81.0
1.1.34	Pulmonary oedema	J68.1	CA81.1
1.1.34	Upper respiratory inflammation	J68.2	CA81.2
1.1.34	Reactive airways dysfunction syndrome (RADS)	J68.3	CA81.Y
1.1.34	Irritant-induced occupational asthma	J68.3	CA81.Y
1.1.34	Burns and corrosions of eyes	T26	NE00
1.1.34	Burns and corrosions of respiratory tract	T27	NE01
1.1.34	Conjunctivitis	H10.2	9A60.Z
1.1.34	Corneal ulcer	H16.0	9A73
1.1.34	Chronic obstructive pulmonary disease (COPD)	J68.4	CA81.Y
1.1.34	Chronic obliterative bronchiolitis	J68.4	CA81.Y
1.1.34	Pulmonary fibrosis	J68.4	CA81.Y
1.1.34	Rhinitis	J31.0, J31.1	CA09.0
1.1.34	Sinusitis	J01.8	CA01
1.1.34	Pharyngitis	J31.2	CA02.Z
1.1.34	Laryngitis	J37.0	CA05.0
	Occupational exposure to risk factors	Z57	QD84.Y

1.1.35 Diseases caused by isocyanates	ICD Code T65.0 + Z57
General characteristics of the causal agent	Isocyanates are a group of organic chemical compounds with the general formula R-N=C=O. They are neutral derivatives of primary amines where the R group is an alkyl or aryl hydrocarbon group. Isocyanates react with compounds containing "active hydrogen atoms", such as the hydroxyl group of alcohols (R'-OH), with which they form esters of carbonic acid, called urethanes. The preparation of isocyanates is usually performed by reacting the amine with phosgene; some milder reagents such as dimethyl carbonate are increasingly used to avoid the industrial hazard due to preparing and using phosgene (see item 1.1.32). Most isocyanates of industrial interest are di-isocyanates. Their molecular structures contain two –N=C=O groups, each one at one end of a more or less flexible (polymethylene) or rigid (aromatic) carbon scaffold. The presence of two reactive groups allows the generation of linear polymers (fibres) or three dimensional lattices (resins) with di- or polyfunctional alcohols and phenols. The isocyanates used as polymer precursors are non-volatile liquids or low- melting solids, which are poorly miscible but chemically reactive with water and react with alcohols and amines. Due to the presence of nitrogen, they are usually not very flammable but decompose upon heating and release very toxic combustion products such as carbon monoxide and hydrogen cyanide (see item 1.1.16). Isocyanates are used in large amounts in the production of polyurethanes as foams and bulk polymers for the manufacture of several goods. The most commercially used isocyanates are 2,4- and 2-6- toluene di-isocyanates (TDI), 4,4-methylene diphenyl di-isocyanate (MDI), 1-6- hexamethylene di-isocyanate (HDI), polymeric MDI and isophorone di-isocyanate (IPDI). For further information, see the tables at the end of the present item.
Occupational exposures	Aromatic isocyanates such as MDI and TDI are used in the production of industrial and consumer products such as flexible and rigid foams, varnishes, sealants, and elastomers. Several other products, such as truck bed liners, synthetic leather, and laminated wood, are manufactured from diisocyanates. Aliphatic isocyanates such as HDI are used primarily in car paints and external coatings due to their superior resistance to abrasion and against weathering (longer retention of gloss and colour). HDI is a cross-linking agent in the preparation of dental materials, contact lenses and medical adsorbents. Therefore, occupational exposure to isocyanates has multiple avenues as in their industrial synthesis and in their use as polymer precursors in producing and using consumer goods. Workers who use adhesives for waterproof laminated wood, insulations, di-isocyanate resins and enamels for coating, lacquers, paint sprays, as well as polyurethane makers, rubber workers, shipbuilders, textile processors, and wire coating workers are at risk of exposure to TDI. Undoubtedly, TDI is the most commonly used isocyanate, and because of its volatility, it is the most hazardous. Production of carbamate pesticides such as carbaryl, carbofuran, methomyl, and aldicarb, requires methyl isocyanate as an intermediate compound. Methyl isocyanate is highly toxic to human health. It might be worth remembering that a runaway accident in a storage tank of methyl isocyanate due to lack of proper cooling and other safety precautions caused what most likely is the largest disaster in the history of the chemical industry at a chemical plant in Bhopal, India. A non-exclusive list of industrial sectors and activities where exposure to isocyanates can occur is the following: • Automotive: paints, glues, insulation, sealants and fibre bonding, truck bed lining. • Casting: foundry cores. • Building and construction: sealants, glues, insulation material, fillers. • Electricity and electronics: cable insulation, polyurethane-coated circuit boards. • Mechanical engineering: insulation material. • Paints: lacquers. • Plastics: soft and hard plastics, plastic foam and cellular plastic. • Printing: inks and lacquers. • Timber and furniture: adhesive, lacquers, upholstery stuffing and fabric. • Textile: synthetic textile fibres. • Medical care: polyurethane casts. • Mining: sealants and insulating materials. • Food industry: packaging materials and lacquers.

1.1.35 Diseases caused by isocyanates — ICD Code T65.0 + Z57

Toxicological profile, main health effects and diagnostic criteria

Short toxicological profile

The chemical reactivity of isocyanates towards the nucleophilic functional groups of amino acids is the critical factor in their toxicological properties. The absorption of the compound and binding to circulating proteins, mainly to albumin, leads to the formation of non-self haptens and the development of allergic sensitization. Individual susceptibility relates to dose, duration, frequency, and route of (respiratory and skin) exposure, as well as to the immunological responsiveness of the exposed person. Once sensitization has occurred, an allergic response can be triggered even by minimal doses.

Isocyanates induce somatic toxicity by inducing oxidative stress in cells. The inactivation of enzymes such as glutathione peroxidase, reductase and transferase can increase levels of reactive free radicals and ultimately leads to cell death. Eye, nose, and throat irritation are usually the first clinical manifestations of isocyanate associated illness. A dry cough with chest pain or tightness often follows. Because a cough or wheeze is characteristically worse in the evening or at night, the patient or doctor often find it difficult to recognize its occupational aetiology. Wheezes or coarse crackles are often present. Isocyanate exposure is a common cause of occupational asthma. Chest radiographs taken during the acute stage are usually interpreted as normal, although increased markings and patchy infiltration are occasionally seen. The clinical picture can approximate to acute or chronic bronchitis, bronchial asthma, or, rarely, pneumonitis. Chronic loss of pulmonary function may occur over periods of up to three years. The subjects who show high acute responses are likely to show the most significant chronic changes.

Name of the diseases and ICD code: **Acute diseases caused by isocyanates** *(Specific disease code)* **+T65.0 +Z57**

Respiratory tract irritation (J68), Acute chemical pneumonitis and bronchitis (J68.0), Pulmonary oedema (J68.1), Upper respiratory inflammation (J68.2), Irritant-induced occupational asthma/Reactive airways dysfunction syndrome (RADS) (J68.3), Irritant contact dermatitis (L24), Burn of eye and adnexa (T26), Conjunctivitis (H10.2), Corneal ulcer (H16.0)

Short description of the disease

TDI and other volatile isocyanates are potent irritants and sensitizers of the mucous membranes, respiratory tract, eyes, and skin. Even at low airborne concentration, they may irritate nose and throat. Irritation of the airways may lead to irritant-induced occupational asthma, pneumonitis, upper respiratory tract inflammation and acute pulmonary oedema (e.g. for concentrations of methyl isocyanate >50 ppm or 117.5 mg/m^3) with bronchoconstriction and possible development of severe bronchiolitis or death from acute respiratory distress syndrome.

Diagnostic criteria

Clinical manifestations of respiratory disorders

- Signs and symptoms: cough, chest discomfort, wheezing, dyspnoea, and distress; the symptoms worsen during the night and disappear in the morning with a slight expectoration of mucus. After a few days of rest, they diminish, but they may generally reappear on return to work. Irritant symptoms can appear among non-sensitized workers when exposure exceeds ~3 ppb. At exposures in the range of 8 to 30 ppb, the ventilatory function may be severely affected. RADS can be observed within hours following inhalation of a single exposure at high concentrations. For further details on irritant-induced occupational asthma, refer to item 2.1.7.
- Examinations: pulmonary function tests are either normal or show a mild obstructive pattern.

Clinical manifestations of skin disorders

Isocyanate exposure can cause irritant contact dermatitis, which is addressed in item 2.2.2.

Clinical manifestations of disorders of the eyes and adnexa

- Signs and symptoms are indicative of interpalpebral and corneal impairment, increased risk of eye infections, hyperresponsive phenomena (irritation, watering, and phlyctens) and loss of reduced visual acuity. Disorders of the eyes can be observed from exposures at concentrations > 50 ppm (117.5 mg/m^3). Exposure to methyl isocyanate caused an acute superficial interpalpebral erosion of the cornea and conjunctivae among the Bhopal survivors within three months of the accident. The interpalpebral erosion was probably similar in chemical nature to the "burns" that healed without notable scarring. A follow-up study for three years on a large number of survivors showed an excess of the delayed damage of eyes and surrounding tissues, often referred to as "Bhopal eye syndrome." There was a threefold excess of eyelid inflammation and a twofold increase of new cataracts among the more severely exposed clusters.
- Examinations: slit lamp and fundoscopy should be used to examine conjunctival epithelium in cases complaining of excessive watering; duct patency tests should be performed to assess patency of the lacrimal drainage system; vision (with and without the use of a pinhole), colour vision, and afferent pupillary reflexes should be tested for any damage to the optic nerve.

1.1.35 Diseases caused by isocyanates — ICD Code T65.0 + Z57

Exposure assessment

- History of occupational exposure: confirmed exposure to isocyanates and, as feasible,
  - biological monitoring: urinary analysis of diamines generated in the metabolism of aromatic isocyanates (TDI, MDI); and
  - workplace monitoring: airborne concentration of isocyanates.
- Minimum duration of exposure: few minutes.
- Maximum latent period: usually no more than 48 hours.

Extrinsic allergic alveolitis (EAA), Hypersensitivity pneumonitis (HP) (J67)

Sporadic cases of EAA have been reported in workers exposed to isocyanates. The onset is usually four to six hours after exposure. The presentation of the disease can be acute, sub-acute, or chronic. Individuals with chronic HP often experience progressively more difficult breathing, fatigue, and weight loss. For more details regarding extrinsic allergic alveolitis, refer to item 2.1.8.

Name of the diseases and ICD code: **Chronic diseases caused by isocyanates** *(Specific disease code)* **+T65.0 +Z57**

Allergic rhinitis (J30.3), Allergic conjunctivitis (H10.2), Sensitizer-induced occupational asthma (J45.0), Allergic contact dermatitis (L23)

Short description of the disease

Exposure to isocyanates can cause sensitization with allergic rhinitis, conjunctivitis, dermatitis, and asthma. The prevalence of occupational asthma among the isocyanate exposed workforce is in the range of 5-10%. Atopy does not appear to influence susceptibility. Sensitizer-induced occupational asthma is most likely to develop in the first years of exposure, and individuals may become sensitized to TDI at exposure levels above about 0.1 mg/m^3. The dermal exposure route contributes significantly to sensitization. Different isocyanates show different asthmagenic potency. However, any compound of the group can cause the condition that may persist after cessation of exposure.

Diagnostic criteria

Clinical manifestations of allergic rhinitis

- Signs and symptoms: clear rhinorrhoea, sneezing, tearing, eye irritation, and pruritus. Associated symptoms may include cough, bronchospasm, and eczematous dermatitis.
- Examinations: on physical examination, the mucosa of the turbinates is usually pale or violaceous because of venous engorgement.

Clinical manifestations of allergic conjunctivitis

- Signs and symptoms: itching, tearing, redness, stringy discharge from the eyes, and, occasionally, photophobia and visual loss.
- Examinations: on physical examination, conjunctival hyperaemia and oedema can be noticed, the latter sometimes arising suddenly.

Clinical manifestations of sensitizer-induced occupational asthma

Isocyanate exposure is a common cause of sensitized-induced occupational asthma, which is thoroughly addressed in item 2.1.7.

Clinical manifestations of skin disorders

Isocyanate exposure can cause allergic contact dermatitis, which is addressed in item 2.2.1.

Exposure assessment

- History of occupational exposure: confirmed exposure to isocyanates and, as feasible,
  - biological monitoring: urinary analysis of diamines generated in the metabolism of aromatic isocyanates (TDI, MDI); and
  - workplace monitoring: airborne concentration of isocyanates.
- Minimum duration of exposure: weeks.
- Maximum latent period: few months (usually weeks for allergic contact dermatitis).

1.1.35 Diseases caused by isocyanates — ICD Code T65.0 + Z57

Chronic obstructive pulmonary disease (COPD) (J68.4)

Short description of the disease

COPD is typically associated with the symptoms of a chronic cough, chronic sputum production or shortness of breath. An increasing body of evidence indicates a possible association of a reduction in FEV_1/FVC amongst non-smoking workers exposed to isocyanates.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: chronic cough, chronic sputum production, and shortness of breath.
- Examinations: post-bronchodilator FEV_1/FVC <0.7 at pulmonary function test; bullae on the chest X-ray or CT scan.

Exposure assessment

- History of occupational exposure: confirmed exposure to isocyanates and, as feasible,
  - biological monitoring: urinary analysis of diamines generated in the metabolism of aromatic isocyanates (TDI, MDI); and
  - workplace monitoring: airborne concentration of isocyanates.
- Minimum duration of exposure: a few years.
- Maximum latent period: not applicable.

(For further details on COPD, refer to item 2.1.9).

Key actions for prevention	Isocyanate compounds can irritate the eyes and skin and are not water soluble. Since they can thus be difficult to remove, exposure prevention is essential. Primary prevention is to be preferred with elimination, substitution and the use of engineering controls. Where residual risk remains the use of facial and eye protection as a component of personal protective equipment will be appropriate. The exposure routes for isocyanates are mainly through skin contact and inhalation; hence, the use of appropriate respirators is warranted. In the event of spills or large releases a supplied-air respirator (SAR) or self-contained breathing apparatus (SCBA) will be likely to be required since the concentration of isocyanate is unlikely to be known and may exceed the capacity of respirator filters. Glove/clothing material, should be selected according to the manufacturer's chemical resistance testing guidance. Ergonomic factors should be considered such as the effect on dexterity, comfort, temperature, to ensure the integrity and performance of the personal protective equipment (PPE) ensemble. Secondary prevention should include occupational health surveillance to detect early signs of occupational disease with access to occupational health services for advice. Exposure limits have been recommended for the isocyanates of greatest industrial relevance by different agencies and organizations. These values are intended to minimize effects on the respiratory tract and the high potential for sensitization. The group of experts considered that the following limits of exposure of workplace atmospheric concentrations have been observed to provide a reasonable level of protection for workers' health and have been used in a number of countries: • Threshold limit value (TLV) for TDI is 0.001 ppm (0.007 mg/m^3) as an 8hr TWA, 0.005 ppm (0.05 mg/m^3) as STEL. • TLV for MDI and HDI is 0.005 ppm (0.05 mg/m^3) as 8hr TWA. • TLV for methyl isocyanate is 0.02 ppm (0.047 mg/m^3 as 8hr TWA. Finally, it should also be remembered that thermal degradation of polyurethanes during industrial operation and in the event of fires gives rise to toxic fumes of carbon monoxide and hydrogen cyanide (for further details, refer to item 1.1.16).

1.1.35 Diseases caused by isocyanates ICD Code T65.0 + Z57

Further reading

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Isocyanates: Summary tables
(adapted from the ILO Encyclopaedia of occupational health and safety, 4th edition)

Chemical information

Name	Synonyms	CAS	UN	ICSC
1,5-Naphthalene diisocyanate	1,5-Diisocyanatonaphthalene; 1,5-Naphthalene diisocyanate; Isocyanic acid, 1,5-naphthylene ester; Naphthalene, 1,5-diisocyanato-; NDI.	3173-72-6		0653
Cyanuric acid	1,3,5-Triazine-2,4,6(1H,3H,5H) – trione; Isocyanuric acid; sym-Triazine-2,4,6-triol.	108-80-5		1313
Cyclohexyl isocyanate	Cyclohexane, isocyanato-; Isocyanatocyclohexane; Isocyanic acid, cyclohexyl ester; CHI.	3173-53-3		
Dianisidine diisocyanate	1,1'-Biphenyl, 4,4'-diisocyanato-3,3'-dimethoxy-; 3,3'-Dimethoxybenzidine-4,4'-diisocyanate; 4,4'-Diisocyanato-3,3'-dimethoxy-,1'-biphenyl; Isocyanic acid, 3,3'-dimethoxy-4,4'-biphenylene ester.	91-93-0		
Ethyl isocyanate	Isocyanatoethane; Isocyanic acid, ethyl ester.	109-90-0	UN2488	
Hexamethylene diisocyanate	1,6-Diisocyanatohexane; 1,6-Hexamethylene diisocyanate; 1,6-Hexanediol diisocyanate; 4,4' dicyclohexylmethane diisocyanate; Desmodur H; Desmodur N; HDI; Hexamethylene diisocyanate; Hexamethylene-1,6-diisocyanate; HMDI; Isocyanic acid, hexamethylene ester; Tl 78.	822-06-0		0278
Isocyanic acid, nitroiminodietylenedi	3-Nitro-3-azapentane-1,5-diisocyanate; Nitroiminodiethylenediisocyanic acid.	7046-61-9	UN2481	
Isophorone diisocyanate	3-Isocyanatomethyl-3,5,5-Trimethylcyclohexylisocyanate; Cyclohexane, 5-isocyanato-1-(isocyanatomethyl)-1,3,3-trimethyl-; IPDI; Isocyanic acid, methylene(3,5,5-trimethyl-3,1-cyclohexylene) ester; Isophorone diamine diisocyanate.	4098-71-9	UN2281	0499
Methyl isocyanate	Isocyanatomethane; Iso-cyanatomethane; Isocyanic acid, methyl ester; MIC.	624-83-9		0004
Methylene bisphenyl isocyanate	1,1-Methylenebis(4-isocyanatobenzene); 4,4'-Methylenebis(phenylisocyanate); 4,4'-Diisocyanatodiphenylmethane; 4,4'-Diphenylmethane diisocyanate; 4,4'-Methylenediphenyl diisocyanate; Bis(1,4-isocyanatophenyl)methane; Bis(4-isocyanatophenyl)methane; Bis(p-isocyanatophenyl)methane; Caradate 30; Desmodur 44; Diphenylmethane 4,4'-diisocyanate; Diphenylmethane diisocyanate; Hylene M 50; Isocyanic acid, methylenedi-p-phenylene ester; Isonate; Isonate 125M; Methylene bisphenyl isocyanate; Methylene di(phenylene isocyanate); Methylenebis(4-isocyanatobenzene); Methylenebis(4-phenylene isocyanate); Methylene-di-p-phenylene isocyanate; MDI	101-68-8	UN2906	0298
n-Butyl isocyanate	1-Isocyanatobutane	111-36-4	UN2290	1642
Phenyl isocyanate	Benzene, isocyanato-; Isocyanatobenzene; Mondur P; Phenylcarbimide; Phenyl carbonimide	103-71-9	UN2480	1131
Toluene diisocyanate	Benzene-, 1,3-diisocyanatomethyl-; Desmodur t100; Diisocyanatomethylbenzene; Diisocyanatotoluene; Hylene-T; Isocyanic acid, methylphenylene ester; Mondur-TD; Nacconate-100; Niax isocyanate TDI	26471-62-5	UN2489	
Toluene-2,4-diisocyanate	2,4-Diisocyanato-1-methylbenzene; 2,4-Diisocyanatotoluene; 2,4-TDI; 2,4-Tolylene diisocyanate; 20 TDI; 4-Methyl-meta-phenylene diisocyanate 4-Methyl-phenylene diisocyanate; Cresorcinol diisocyanate; Desmodur T80; Di-iso-cyanatoluene; Hylene T; Isocyanic acid, 4-methyl-m-phenylene ester; Isocyanic acid, methylphenylene ester; Mondur TD; m-tolylene diisocyanate; Rubinate TDI 80; TDI; TDI-80; Toluene diisocyanate; Toluene-2,4-diisocyanate.	584-84-9	UN2485	0339
Toluene-2,6-diisocyanate	2,6-Diisocyanato-1-methylbenzene; 2,6-Diisocyanatotoluene; 2,6-TDI; 2-Methyl-m-phenylene diisocyanate; 2-Methyl-m-phenyleneisocyanate; Hylene TCPA; Isocyanic acid, 2-Methyl-m-phenylene ester; Niax TDI; Niax TDI-p; Tolylene 2,6-diisocyanate.	91-08-7	UN2487	1301

Health hazards

Name	ICSC short-term exposure	ICSC long-term exposure	ICSC routes of exposure and symptoms
1,5-Naphthalene diisocyanate	eyes; skin; resp tract	skin; lungs	Inhalation: cough, laboured breathing, sore throat Skin: redness, pain Eyes: redness, pain
Cyanuric acid			
Cyclohexyl isocyanate	eyes; skin; resp tract	skin	Inhalation: burning sensation, cough, laboured breathing, shortness of breath Skin: redness Eyes: watering of eyes, redness, pain, blurred vision, severe deep burns Ingestion: abdominal cramps, diarrhoea, vomiting
Dianisidine diisocyanate			
Ethyl isocyanate			
Hexamethylene diisocyanate	eyes; skin; resp tract	skin	Inhalation: burning sensation, cough, laboured breathing, shortness of breath, sore throat Skin: may be absorbed, redness, skin burns, blisters Eyes: redness, pain, swelling of eyelids
Isocyanic acid, nitroimino-diethylenedi-			
Isophorone diisocyanate	eyes; skin; resp tract	skin; lungs	Inhalation: cough, sore throat, symptoms may be delayed Skin: redness Eyes: redness
Methyl isocyanate	eyes; skin; resp tract; lungs	skin; lungs	Inhalation: cough, dizziness, laboured breathing, shortness of breath, sore throat, unconsciousness, vomiting Skin: may be absorbed, skin burns, pain Eyes: pain, loss of vision, severe deep burns Ingestion: abdominal cramps, sore throat, vomiting
Methylene bisphenyl isocyanate	eyes; skin; resp tract; lungs	skin	Inhalation: headache, nausea, shortness of breath, sore throat Skin: redness Eyes: pain, may cause corneal damage
N-butyl isocyanate			
Phenyl isocyanate			
Toluene diisocyanate			
Toluene-2,4-diisocyanate	eyes; skin; resp tract; nose	skin; lungs	

Physical and chemical hazards

Name	Physical	Chemical	Un class or division / subsidiary risks
1,5-Naphthalene diisocyanate	eyes; skin; resp tract	The substance decomposes on heating producing toxic fumes (nitrogen oxides)	Toxic (6.1)
Cyanuric acid			
Cyclohexyl isocyanate	The vapour is heavier than air and may travel along the ground; distant ignition possible	The substance may polymerize due to heating and under the influence of incompatible materials. The substance decomposes on burning producing toxic fumes (nitrogen oxides). Reacts with oxidants and strong bases, water, alcohol, acids, and amines	Flammable liquid (3) / toxic (6.1)
Dianisidine diisocyanate			Toxic (6.1)
Ethyl isocyanate			
Hexamethylene diisocyanate		The substance will polymerize under the influence of temperatures above 93°C. On combustion, forms toxic and corrosive fumes including nitrogen oxides and hydrogen cyanide. The substance decomposes on contact with water to form amine and polyureas. Reacts violently with acids, alcohols, amines, bases, and oxidants causing fire and explosion hazard. Attacks copper	
Isocyanic acid, nitroiminodiethylenedi-			Toxic (6.1) / flammable liquid (3)
Isophorone diisocyanate		The substance decomposes on heating producing toxic fumes (nitrogen oxides). Reacts with oxidants, acids, alcohols, amines, amides, mercaptanes. Attacks many metals, plastics, and rubber	Toxic (6.1)
Methyl isocyanate	The vapour is heavier than air and may travel along the ground; distant ignition possible. The vapour mixes well with air, explosive mixtures are easily formed	The substance may polymerize due to heating or under the influence of water and catalysts. The substance decomposes on heating producing toxic gases (hydrogen cyanide, nitrogen oxides, carbon monoxide). Reacts with strong oxidants. Reacts violently with water, acids, alcohols, amines, iron, steel, zinc, tin, copper (or alloys of these metals) causing fire and explosion hazard. Attacks some forms of plastic, rubber and coatings	Toxic
Methylene bisphenyl isocyanate		The substance may polymerize due to heating above 204°C or under the influence of temperatures above 204°C. On combustion, forms toxic and corrosive fumes including nitrogen oxides and hydrogen cyanide. Reacts readily with water to form insoluble polyureas. Reacts violently with acids, alcohols, amines, bases and oxidants causing fire and explosion hazard	Toxic (6.1)
N-butyl isocyanate			Toxic (6.1)
Phenyl isocyanate			Toxic (6.1)
Toluene diisocyanate			
Toluene-2,4-diisocyanate			

Physical and chemical properties

Name	Colour/form	Boiling point (°C)	Melting point (°C)	Molecular weight	Solubility in water	Relative density (water =1)	Relative va-pour density (air=1)	Vapour pressure	Inflam. Limits	Flash point (°C)	Auto ignition point (°C)
1,5-Naphthalene diisocyanate	crystals		130	210.19							
Cyanuric acid											
Cyclohexyl isocyanate	liquid	168		125.16	reacts	0.98	4.3			48	
Dianisidine diisocyanate	grey to brown powder		112	296.3							
Ethyl isocyanate		60		71.1	insol	0.9031					
Hexamethylene diisocyanate	liquid	255	-67	168.2	reacts	1.0528	5.81	7 Pa at 25°C	0.9 ll 9.5 ul	140	454
Isocyanic acid, nitroimino-diethylenedi											
Isophorone diisocyanate	colourless to slightly yellow liquid	158 at 10 torr	-60	222.32	reacts	1.062 g/ml		0.04 Pa		155-161	430
Methyl isocyanate	colourless liquid	39.5	-45	57.1	v sol	0.9599	1.42	46.4	5.3 ll 26 ul	-7	534
Methylene bisphenyl isocyanate	light-yellow, fused solid; crystals	196 at 5 mmHg	37	250.27	0.2 g/100 ml	1.197 at 70°C	8.6			196	240
N-butyl isocyanate											
Phenyl isocyanate	liquid	158-168	-30	119.12		1.0956 at 19.6°C/4 °C					
Toluene diisocyanate	clear colourless to pale yellow liquid	251	11-14			1.22 g/ml at 25°C		0.01 torr			
Toluene-2,4-diisocyanate	a water-white liquid which turns straw-coloured on standing; clear to light yellow liquid or crystals; colourless to pale yellow, solid or liquid	251	20.5	174.15	reacts	1.2244	6	1.3 Pa		132	620

▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
1.1.35	Acute/chronic diseases caused by isocyanates (acute/ chronic)	T65.0	NE61 & XM0YF6
1.1.35	Respiratory tract irritation	J68	CA81.Z
1.1.35	Acute chemical pneumonitis and bronchitis	J68.0	CA81.0
1.1.35	Pulmonary oedema	J68.1	CA81.1
1.1.35	Upper respiratory inflammation	J68.2	CA81.2
1.1.35	Reactive airways dysfunction syndrome (RADS)/irritant-induced occupational asthma	J68.3	CA81.Y
1.1.35	Irritant contact dermatitis	L24	EK02
1.1.35	Allergic contact dermatitis	L23	EK00
1.1.35	Burn of eye and adnexa	T26	NE00
1.1.35	Conjunctivitis	H10.2	9A60.Z
1.1.35	Corneal ulcer	H16.0	9A76
1.1.35	Allergic rhinitis	J30.3	CA08.0Z
1.1.35	Chronic obstructive pulmonary disease (COPD)	J68.4	CA22.Z
1.1.35	Extrinsic allergic alveolitis (EAA)	J68.4	CA70.Z
1.1.35	Sensitizer-induced occupational asthma	J45.0	CA23.0
	Occupational exposure to risk factors	Z57	QD84.Z

1.1.36 Diseases caused by pesticides	ICD Code T60 +Z57
General characteristics of the causal agent	The term 'pesticides' identifies a very broad functional class of chemical compounds or mixtures, which are specifically manufactured and used to eradicate or control undesired organisms. To achieve their intended aim, pesticides are introduced deliberately into the environment to reach their biological targets; therefore, millions of workers of all ages, all over the world, are exposed to pesticides, especially following their use in agriculture and for management of public health issues. Due to the limited selectivity of their toxic action to the target organism(s), the possibility of toxic effects in the exposed workers and in the general population cannot be excluded. Insecticides, herbicides, fungicides, nematocides, rodenticides and other preparations (e.g. crow and mole poisons) are the pesticides for which there is a higher concern for occupational health. The often used terms of 'plant protection product' or 'agrochemical' not only refer to one of the possible uses (i.e., agriculture), but also identify a broader class of compounds, which includes fertilizers and other products used to promote plant's growth. In this context, the use of the term 'pesticides', although sometimes considered obsolete, is justified, even because further classifications based on the target pest or organism(s) and on the modes of action are available. In addition, many national legislations and international institutions still refer to this group of chemical compounds as to 'pesticides'. From the functional point of view, pesticides can be classified into different categories, such as: acaricides, algicides, antifeedants, avicides, bactericides, bird repellents, chemosterilants, fungicides, herbicide safeners, herbicides, insect attractants, insect repellents, insecticides, mammal repellents, mating disrupters, molluscicides, nematicides, plant activators, plant growth regulators, rodenticides, synergists, virucides, and others. These major categories can be further sub-classified according to other criteria, such as the main functional groups present in the molecule (e.g. phenoxy herbicides) or the specific mechanisms of action (e.g. acetylcholinesterase inhibitors). Among the several categories of pesticides, the class of bio-pesticides includes compounds derived from natural sources, such as animals, plants, bacteria and some minerals. Individual pesticides can be identified with proprietary trademark or brand names that usually change over time and between countries. The active substances can be most easily identified by their chemical structures, according to the descriptive systematic nomenclature of the International Union of Pure and Applied Chemistry (IUPAC) and of the Chemical Abstract Service (CAS). To overcome the difficulty of identification for purposes of trade, registration, legislation, and use in scientific, technical, and popular publications, the International Organization for Standardization (ISO) assigns to each pesticide a short, distinctive, non-proprietary and widely accepted name. Pesticides are complex formulations usually containing one or two substances, whose purpose is to kill the target organisms (i.e., the active ingredients), and other substances essentially devoid of specific toxic activity, which are added to tailor the final product to the desired need (i.e., co-formulants). Co-formulants include solvents, emulsifiers, surfactants, or preservative, colouring, and vomiting agents. The presence of co-formulants can modify the bio-availability of the active substance and thus its toxicity in a specific exposure condition. There are several unofficial database collections of pesticide properties, which include approved substances, substances considered obsolete or banned, new substances, as well as compounds and mixtures used as co-formulants.
Occupational exposures	Pesticides are primarily used: • In agriculture, to protect food crops and industrial commodities of agricultural origin (e.g. natural fibres, wood) from spoilage by moulds, insects, weeds, and other organisms that may reduce the agricultural yield or deteriorate the goods during all phases of their production. • In public health, for example in mosquito control or hospital disinfection; and, in tropical countries, for the prevention of vector-borne diseases: this is the case for the so-called 'indoor residual application', which consists of the periodic treatment of the internal walls and surfaces of houses and mosquitos nets in tropical and subtropical houses. Another example of pesticides use for management of public health issues is 'aircraft disinsection', consisting of the treatment of aircraft flying from tropical countries to areas where vector-borne diseases are not endemic, in order to prevent long-range migration of vectors and diseases. • In the treatment of ships' hulls with anti-vegetative agents, for the double purpose of preventing the unwanted migration of marine organisms among oceans and across the hemispheres, and of preventing excessive drag, which is increased by the natural growth of marine vegetation.

1.1.36 Diseases caused by pesticides	ICD Code T60 +Z57
Occupational exposures	• In the international trade for the treatment of goods and vectors (ships, freight containers, wood pallets, boxes, etc.) to protect the receiving countries from infestation by foreign (usually tropical) parasites, such as insects, beetles, moulds, and other undesired organisms. • In the protection of any kind of material and plants from biological degradation, as is the case for paints and formulations for wood treatment, and in paper production, leather tanning, and boat production and maintenance. Several categories of workers can be exposed to pesticides, and for each of them there are specific classes of products used, circumstances, routes and related levels of exposure. For the purposes of studying occupational risk, a set of conditions of pesticide use is usually called the 'exposure scenario'; and to identify whether any significant exposures are likely to occur, broad levels of pesticide exposure may be calculated without strict reference to a single product. Among workers who manipulate pesticides the following categories can be identified. • Industrial workers engaged in the production and formulation of commercial pesticides. • Applicators of pesticides in agriculture and in management of public health issues, together with their assistants. • Agricultural workers who enter cultivated fields that have been treated with pesticides. • Industrial workers who use materials or products treated with pesticides. • Non-industrial workers who enter enclosed spaces treated with pesticides or manipulate items that have been treated with pesticides. Each exposure scenario has its own properties and entails different risks of disease or poisoning by pesticides. In particular, chemical workers engaged in the in production and formulations of commercial pesticides share most of their exposure scenarios with the workers employed in manufacturing processes of other fine and specialty chemicals. Industrial workers who use materials or products treated with pesticides share most of their exposure scenarios with workers employed in other manufacturing activities, with an additional component represented by contact with treated or contaminated surfaces, which usually occurs following exposure to airborne vapours. The categories of workers for which specific scenarios exist for exposure to pesticides are agricultural farmers and pesticide applicators, both in the management of public health issues and whenever they are needed for anti-herbicide and vector control purposes (e.g. transport and logistics).
Toxicological profile, main health effects and diagnostic criteria	
Short toxicological profile	The mechanisms by which pesticides affect undesired organisms are in some cases the same ones that can induce toxic effects in exposed humans: an important role is played both by the doses reached in the subjects and by human sensitivity to perturbation of the biochemical mechanism(s) representing the active substance target. In general, a greater biochemical selectivity and a subsequent lower toxicity for non-target species, can be achieved to the degree that the target organism is phylogenetically separated from others. Therefore, in principle, herbicides that act by exploiting biochemical mechanisms that are not present in animals such as the photosynthesis or plant growth, are much less toxic to humans than those that exploit more general mechanisms, such as impairment of oxidative phosphorylation or inhibition of acetylcholinesterase (AChE) activity. In some cases, such as when pesticides are pro-drugs of the actual toxic molecule, a level of selective toxicity can be achieved by exploiting the lack of an activating biotransformation pathway in non-target species: this is the case, for example, of thione-phosphate esters, whose conversion into the corresponding (oxo)-phosphates is catalysed by a sulphur-oxidizing enzyme, which is abundantly expressed in insects but not in mammals. For this reason, insecticides such as malathion are much more toxic to insects than to humans. On the contrary, compounds such as rodenticides, which are designed to kill warm-blooded organisms, are also very toxic to humans.

1.1.36 Diseases caused by pesticides — ICD Code T60 +Z57

Short toxicological profile

The main chemical classes of pesticides for which there is a concern for workers' health are:

- carbamates (insecticides);
- conazoles (fungicides);
- coumarine derivatives (rodenticides);
- dithiocarbamates (fungicides);
- nicotinoid compounds (insecticides);
- organochlorine compounds (various uses);
- organophosphorus compounds (insecticides and herbicides);
- phenoxy acids derivatives (herbicides);
- pyrethroids (insecticides); and
- quaternary ammonium compounds (herbicides).

The following are the best known toxic mechanisms of insecticides, herbicides, fungicides and rodenticides:

- interference with axonal nerve conduction (dichlorodiphenyltrichloroethane – DDT (now banned), and pyrethroids);
- interference with synaptic transmission (organophosphate esters, carbamates);
- interference with mitochondrial respiration (paraquat and hexachlorobenzene (the use of both is usually restricted);
- interference with steroid biosynthesis (conazole fungicides); and
- interference with blood coagulation (coumarin rodenticides).

Other mechanisms for biocidal action, such as interference with photosynthesis or cell wall biosynthesis, exploited in the design of herbicides, or interference with chitin biosynthesis (exploited in the design of acaricides), are lacking in warm-blooded animals, thus hindering mechanism related toxicity in humans.

Diseases caused by pesticides are mostly acute and follow direct exposure to the compound, by either inhalation, contact, or much less frequently in occupational scenarios, ingestion. The main target organs are the skin, the eyes, the mucosae of the respiratory tract, the digestive apparatus, and the nervous system. Some disorders might entail long-term sequelae, such as pulmonary fibrosis following paraquat poisoning, or delayed polyneuropathy induced by organophosphates. Uncertainties remain regarding chronic effects following pesticide exposure, as there are reports suggesting a range of effects exerted by different compounds, including liver and kidney toxicity, as well as chronic effects on the skin, on immune, respiratory, and endocrine systems, on blood, and on peripheral and central nervous system (including behavioural impairment). As regard carcinogenic effects, evidence is consistent for pesticides containing arsenicals (almost globally banned), while being more limited for working activities related to pesticide application (e.g. spraying).

Name of the diseases and ICD code: **Diseases caused by pesticides** *(Specific disease code)* **+T60 +Z57**

Acute pesticide poisoning (T60): Acute mucous membranes irritation (respiratory inflammation) (J68), Allergic contact dermatitis (L23), Burns and corrosions of external body surface (T20-T25), Burns and corrosions of respiratory tract (T27), Burns of eye and adnexa (T26.0-T26.1), Chemical burns of mouth and pharynx, oesophagus and stomach (T28.0-T28.2), Conjunctivitis (H10.2), Corneal ulcer (H16.0), Irritant contact dermatitis (L24), Irritant-induced acute occupational asthma (J68.3), Pneumonitis and acute chemical bronchitis (J68.0), Pulmonary oedema (J68.1), Reactive airways dysfunction syndrome (RADS), Upper respiratory inflammation (J68.2)

Short description of the disease

The term "acute pesticide poisoning" refers to any health effect following an exposure to pesticide that occurred during the 48 hours preceding the clinical manifestation. This definition applies both to cases related to a single, high level exposure, and to cases attributable to repeated exposures to compounds with a prolonged half-life. In these cases, health effects are observed after the absorption of the "last" dose needed to reach the body burden that exceeds the threshold concentration for the effect. Exposure to pesticides, in particular if mixed with solvents, may cause irritation of the mucous membranes, the eyes and the skin, that can increase skin absorption. Exposure to pesticides can also increase the risk of atopy and asthma. Acute ingestion (relatively common in occupational scenarios related to suicide attempts, may cause burns to the lips, mouth, throat, oesophagus, and stomach.

1.1.36 Diseases caused by pesticides ICD Code T60 +Z57

Diagnostic criteria

Clinical manifestations

- Acute eye exposure causes stinging pain, photophobia, ulceration, conjunctivae irritation.
- Symptoms of skin sensitization or irritation may include redness, itching, swelling, pain, and blistering. For further details on allergic and irritant contact dermatitis, refer to items 2.2.1 and 2.2.2, respectively
- Acute exposure by inhalation in the nose and upper respiratory tract causes irritation, coughing, chest tightness, shortness of breathing, and may cause ulceration and choking. At higher concentrations, tachypnoea and chemical-induced asthma or reactive airways dysfunction syndrome (RADS) may be observed. In severe cases, pulmonary oedema may occur hours or days after exposure, characterized by a rapid onset of dyspnoea at rest, tachypnoea, tachycardia and severe hypoxemia.
- Ingestion of paraquat causes severe burns of oesophagus and digestive tract.
- Other nonspecific symptoms may include salivation, dysphagia, intense thirst, nausea, vomiting, haemorrhage, diarrhoea, and abdominal pain.

Exposure assessment

- History of occupational exposure: evidence of occupational exposure to the pesticide (liquid, dust, aerosol or vapours).
- Minimum duration of exposure: few minutes.
- Maximum latent period: 48 hours from the last dose.

Acute cholinergic crisis (T60.0)

Short description of the disease

Acute cholinergic crisis may occur following exposure to organophosphorous or carbamate compounds; it is caused by the inhibition of acetylcholinesterase activity in the nervous system, with subsequent accumulation of acetylcholine in the muscarinic and nicotinic synapses. Several studies have shown that another serine esterase, butyrylcholinesterase, is effectively inhibited by certain organophosphorous or carbamate pesticides, and butyrylcholinesterase inhibition is considered a sensitive biological marker of exposure to these chemicals (N.B. the physiological function of butyrylcholinesterase is not known). The typical signs of cholinesterase inhibition usually occur for levels of inhibition exceeding 50%, but acetylcholinesterase inhibition of 20% after exposure may be considered a hallmark of excessive exposure.

Since the inhibition caused by carbamate is less severe than the one caused by organophosphates and with a shorter inhibition time, carbamate poisoning is usually less serious than organophosphate poisoning, although clinical manifestations tend to be similar. If treated on time and properly, the syndrome is reversible and without sequelae. Nonetheless, from 24 to 96 hours after the acute cholinergic crisis, a second phase of organophosphorous insecticide poisoning can be observed, the so called 'intermediate syndrome', a condition consisting of neurological signs, affecting mainly muscles innervated by cranial nerves.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms:
  - Early or mild poisoning may be difficult to diagnose because signs and symptoms of cholinergic toxicity are not specific. These may include: headache, fatigue, giddiness, anxiety, mental confusion, nausea, sweating, lacrimation and blurred vision, tightness in the chest, abdominal cramps, vomiting, and diarrhoea.
  - In more advanced poisoning, difficult breathing, bronchial hypersecretion, bronchoconstriction, agitation, tremors, convulsions, brady- or tachycardia, arrhythmia, hypo- or hyper-tension, shock, collapse, coma, pulmonary oedema and respiratory failure follow.
- Examinations: physical examination may reveal typical signs of cholinesterase inhibition, which include pinpoint pupils, excessive sweating, excessive salivation, and muscle fasciculation. Miosis is an important sign of cholinergic toxicity but may represent a local reaction to direct pesticide contact rather than a systemic effect.

Exposure assessment

- History of occupational exposure: confirmed occupational exposure to organophosphorous or carbamate compounds (taking into account the possibility of skin absorption); a significant inhibition of red blood cell acetylcholinesterase or plasma butyrylcholinesterase may be detected.
- Minimum duration of exposure: few minutes.
- Maximum latent period: three days for organophosphates (note that, especially with thiophosphates, the onset of the cholinergic crisis may occur several hours after the exposure, after full metabolisation of the compound to its toxic metabolite, or when a slowly metabolized compound reaches critical concentration in the body); 24 hours for carbamates.

1.1.36 Diseases caused by pesticides — ICD Code T60 +Z57

Organophosphate-induced delayed neuropathy (OPIDN) (G62.2+T60.0)

Short description of the disease

Organophosphate-induced delayed neuropathy (OPIDN), also known as organophosphate-induced delayed polyneuropathy (OPIDP), is caused by those organophosphorus compounds that are able to undergo "aging" (i.e., capable of losing one of the alkyl lateral chains of the molecules). Only certain organophosphate pesticides are associated with OPIDN, e.g, phosphates, phosphonates, and phosphoramidates. Neuropathy target esterase (NTE) inhibition is a biomarker for OPIDN, and the condition is believed to occur when more than 70% of NTE has been inhibited. However, aging of the esterase, rather than inhibition of esteratic activity appears to be the key step in the development of OPIDN, and the precise mechanism is unclear. OPIDN results in the death of the peripheral motor neurons in the brainstem and spinal cord, which leads to denervation and consequent atrophy of the corresponding muscle fibres. OPIDN is seen after severe poisoning and an acute cholinergic crisis. In this case, typical symptoms and signs of OPIDN occur 20-25 days after recovery from an acute organophosphate poisoning. The neuropathic signs occur peripherally and progress centrally. The symptoms continue to worsen for 3-6 months. Recovery is usually observed, but is very often incomplete. In the interval between the end of the cholinergic crisis and the onset of OPIDN, the intermediate syndrome might appear.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms:
  - Early symptoms include cramping muscle pain in the legs accompanied by distal paraesthesias.
  - Progressive weakness of the legs with decreased deep tendon reflexes follows.
  - Initial motor neuropathy is characterized by a flaccid paralysis affecting the lower extremities (lower motor neuron impairment) which can ascend to affect the upper extremities in severe cases. High stepping gait associated with bilateral foot drop may be observed.
  - In some cases, after recovery from the flaccid neuropathy, a spastic paralysis may occur, which is indicative of an upper motor neuron impairment at the level of the spinal cord.
- Examinations:
  - Electromyography may show fasciculation or fibrillation.
  - Electroneurography usually documents reduction (up to complete abolition) of nerve conduction.
  - Muscle biopsy can show a picture of muscle atrophy.
  - Peripheral nerve biopsy may demonstrate Wallerian degeneration of distal axons.

Exposure assessment

- History of occupational exposure: evidence of a previous acute poisoning, in particular if caused by dichlorvos, isofenphos, methamidophos, mevinphos, mipafox, trichlorfon, trichlornat, phosphamidon.
- Minimum duration of exposure: evidence of a previous acute poisoning is necessary.
- Maximum latent period: up to six weeks from acute poisoning.

Acute neurologic effects caused by organochlorinated compounds (T60.1)

Short description of the disease

Aldrin, endrin, dieldrin and toxaphene are most frequently involved in acute poisoning from organochlorinated compounds. Target organs belong to the nervous system and the digestive apparatus.

Diagnostic criteria

Clinical manifestations

- The basic syndrome is cerebral, characterized by headache, dizziness, ataxia and paraesthesia, and is accompanied by gastrointestinal symptoms: nausea, vomiting, diarrhoea, and stomach pains.
- In addition, acute poisoning may lead to bulbar paralysis of the respiratory and vasomotor centres, which causes acute respiratory deficiency or apnoea, up to severe collapse.

Exposure assessment

- History of occupational exposure: evidence of occupational exposure to organochlorinated compounds (liquid, dust, aerosol or vapours).
- Minimum duration of exposure: few minutes.
- Maximum latent period: 24 hours.

1.1.36 Diseases caused by pesticides ICD Code T60 +Z57

Acute poisoning from chlorophenoxy herbicides (T60.3)

Short description of the disease

The acute toxicity of chlorophenoxy derivatives tends to be low and major toxic effects can be observed only after exposure to very high doses (usually through ingestion). Toxic effects, especially neuropathy, can be at least partly attributed to organic solvents which are often present in the formulation. Nonetheless, direct effects of chlorophenoxy herbicides on plasma membranes and cellular metabolic pathways have been observed. In the past, phenoxy herbicides were contaminated by dioxins and furans.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms:
  - In cases of intense poisoning from chlorophenoxy derivatives, symptoms include: hypertonia, hyperreflexia, ataxia, nystagmus, miosis, hallucinations, convulsions, fasciculation, and paralysis. Myopathic symptoms, including limb muscle weakness, loss of tendon reflexes, and myotonia, have been described.
  - In case of less severe exposures, gastrointestinal (e.g. nausea, vomiting, diarrhoea) and peripheral neuromuscular (e.g. paraesthesiae, muscle pain and weakness) manifestations have been reported.
- Examinations:
  - Electroneurography shows severe reduction of the nerve impulse transmission.

Exposure assessment

- History of occupational exposure: evidence of occupational exposure to chlorophenoxy herbicides (liquid, dust, aerosol or vapours) together with measurement of blood and urine chlorophenoxy herbicide concentration.
- Minimum duration of exposure: few minutes or one single ingestion.
- Maximum latent period: few hours.

Acute poisoning from paraquat (T60.3) and subsequent pulmonary fibrosis (T60.3+J68.4)

Short description of the disease

Paraquat is a very toxic bipyridyl compound, whose exposure usually occurs through ingestion, while exposure through inhalation or skin contact is less relevant: if ingested, it can cause severe burns of the buccal cavity, oesophagus and digestive tract. If the affected subject survives this phase, toxic effects in the lung can lead to pulmonary fibrosis, with dyspnoea and hypoxia occurring several days after ingestion. The main toxic mechanism is the formation of reactive oxygen species and free radicals, which damage type 1 and 2 alveolar epithelial cells, and Clara (i.e., bronchiolar exocrine) cells of the lungs.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms:
  - After paraquat ingestion, severe burns of buccal cavity, oesophagus and digestive tract occur. Mucosal lesions of the mouth and the tongue start appearing usually within two days from exposure, and may become ulcerated and bleed; mucosal lesions in the pharynx, oesophagus and stomach are common and may result in severe complications such as perforation, mediastinitis, and pneumomediastinum.
  - At pulmonary level, the disorder is usually biphasic: in about 1-3 days, an acute alveolitis may develop, followed by a secondary fibrosis, with increasing signs of respiratory involvement over the following days (usually 3-7 days). Severe anoxia due to rapidly progressive fibrosis can bring death in about 5 weeks.
- Examinations:
  - Gastroscopy (to be performed with caution to minimize the risk of oesophageal rupture) may show chemical burns of the digestive tract.
  - Chest X-ray may demonstrate infiltrates initially, and fibrosis later on.
  - Fibrosis might be observed on lung biopsy.

Exposure assessment

- History of occupational exposure: evidence of occupational exposure to paraquat, together with measurement of plasma paraquat concentrations, and urine and plasma dithionite tests (in an alkaline medium, sodium dithionite reduces paraquat to a blue radical).
- Minimum duration of exposure: one single ingestion.
- Maximum latent period: 15 days for pulmonary fibrosis following paraquat poisoning.

1.1.36 Diseases caused by pesticides — ICD Code T60 +Z57

Anti-coagulation syndrome due to exposure to coumarin derivatives (T60.4)

Short description of the disease

Exposure to coumarin derivatives, both as first-generation (warfarin, coumachlor) or second-generation (brodifacoum, difenacoum, focoumafen) compounds, may alter coagulation: resulting signs may vary from localized to generalised bleeding, depending on the level of inhibition of coagulation factor synthesis. Acute anticoagulant rodenticide toxicosis is usually caused by ingestion of the substance but can result from severe or prolonged occupational exposures to second-generation compounds. In cases of exposure to first generation compounds, effects are generally observed a few hours after the causal exposure, and usually within 15 days. Effects caused by second-generation compounds, more potent and long-acting than first generation ones, may persist even two years after poisoning and may arise in a delayed fashion, when the burden of the compound has reached the effective dose.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms:
  - Primary manifestations are haemorrhagic: unusual bruising, nosebleeds, bleeding gums, exaggerated bleeding from cuts, exaggerated and prolonged menstrual bleeding, anaemia, melaena, haemothorax, hyphaema, epistaxis, haemoptysis, and haematuria.
  - Following haemorrhage, other manifestations may develop, such as weakness, dizziness, ataxia, colic, gangrene, and polypnoea.
- Examinations: a prolonged prothrombin, partial thromboplastin, or thrombin time in the presence of normal fibrinogen, fibrin degradation products, and platelet counts is strongly suggestive of anticoagulant rodenticide poisoning, as is a positive therapeutic response to vitamin K1.

Exposure assessment

- History of occupational exposure: evidence of occupational exposure to coumarin derivatives and, when available, detection of the compound or its metabolites in biological fluids.
- Minimum duration of exposure: a single ingested dose or several months for second-generation compounds.
- Maximum latent period: 30 days for first generation compounds; one year for second generation compounds.

Toxic effects caused by pentachlorophenol (T60.1)

Short description of the disease

Pentachlorophenol (PCP) is a chlorinated hydrocarbon fungicide, rarely used nowadays. Contact with PCP (particularly in the form of vapour) can irritate the skin, eyes, and mouth. Short-term exposure to large amounts of PCP can affect the liver, kidneys, blood, lungs, nervous system, immune system, and gastrointestinal tract. The main systemic effect, mediated by uncoupling of oxidative phosphorylation that results in increased cellular oxidative metabolism, is increased body temperature and profuse sweating.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: primarily, increased body temperature and profuse sweating; other symptoms include tachycardia, tachypnoea, altered consciousness, convulsions, and irritation of skin and mucous membranes.
- Examinations: liver function enzymes can show alterations.

Exposure assessment

- History of occupational exposure: evidence of occupational exposure to PCP, and measurement of its concentration in plasma and urine.
- Minimum duration of exposure: few minutes.
- Maximum latent period: 48 hours.

1.1.36 Diseases caused by pesticides — ICD Code T60 +Z57

Name of the diseases and ICD code: **Carcinogenic effects of pesticides** *(Specific disease code)* **+T60 +Z57**

Studies evaluating the association between cancers and pesticide exposure have suggested an association with leukaemia and non-Hodgkin lymphoma. Solid tumours of the prostate, pancreas, kidney, and breast have been reported. However, methodological weaknesses especially regarding the lack of sufficient exposure information, still prevent firm conclusions.

The International Agency for Research on Cancer (IARC) has evaluated the cancer risk associated with non-arsenical insecticide spraying and has concluded that this activity is probably carcinogenic to humans (Group 2A), bringing about an increased risk of skin, lymphatic, lung and brain cancer.

Some compounds nowadays banned in most countries (for example, arsenical derivatives) have been associated with an increased risk of cancer and, in particular, lung, skin, liver (especially angiosarcoma) and, with a lower level of evidence, bladder, kidney, and prostate. Arsenic and inorganic arsenic compounds are classed as Group 1 carcinogens. For further details on carcinogenic effects of arsenic and its compounds, refer to item 3.1.15.

Key actions for prevention

Due to their inherent health and environment hazards, pesticides are regulated substances at the international level. Some countries have agencies and institutions in charge of authorizing a chemical entity (active substance) and the formulations based on it (products) for pesticide-specific marketing and use. Pesticides are usually authorized for limited periods of time (e.g. 5-10 years), and re-authorization is issued after a re-evaluation of the body of knowledge that has been produced over time. There is a framework of criteria that regulatory agencies commonly apply to decide whether a new chemical can be used as a pesticide or an active substance already in use can continue to be authorized, such as:

- The substance shall not belong to classes of compounds for which there are some specific risks for human health (e.g. it should not be carcinogenic, or teratogenic, nor can be its products of biotransformation and of environmental degradation) and for the environment it shall not persist in the environment nor have ozone depleting or greenhouse effects.
- Its use shall not entail unacceptable health risk for applicators and for the public, during application or as a consequence of its presence as residues in food, water and other environmental compartments likely to entail human exposure.
- It shall not unnecessarily threaten the viable existence of other non-target species (e.g. pollinating insects, the marine environment and the fish stock, cattle and pet animals, wild animals and birds that may feed on treated areas or on food sources that may be contaminated by the active substances).

The overall use of pesticides in agriculture and in public health is unlikely to be eliminated because of their importance to protect crops, to fight vector-borne diseases, and to avoid uncontrolled diffusion of undesirable plants and animals. The main interventions to mitigate the impact of pesticides on workers' health, on the public, and on the environment; are substitution of toxic and persistent active substances with less active, more selective and less persistent ones (in this context, an example of successful international intervention is the ban of persistent organochlorine pesticides as a class of persistent organic pollutants through the 2001 Stockholm Convention).

Enclosure of pesticide dispersal is often impossible because of their mode of use as crop treatments etc. However, mitigation can be applied to some modes of pesticide application. In particular, pesticides are frequently sprayed from airplanes on extended flatlands, especially in the plains of North and South America, Russia, Siberia, Central Asia, and Australia. Helicopters are typically used to spray in hilly landscapes, such as vineyards in California. In both cases, pesticide clouds can drift and expose farmers and the public. In several countries, this practice is limited or forbidden.

Exposure control includes elimination, substitution, and least effectively personal protective equipment. The application of pesticides in open fields, in enclosed environments such as warehouses, on commercial freighters and airplanes, and the preventive treatment of items in trans-continental trade are sources of exposure for applicators and for other classes of workers. Where elimination and substitution are not possible, the use of suitable personal protective equipment, such as protective clothing and respirators, and the availability of facilities for personal hygiene, washing and decontamination can, with appropriate training, be effective measures to avoid excessive and health-threatening exposures.

1.1.36 Diseases caused by pesticides — ICD Code T60 +Z57

Key actions for prevention

In some areas of the world, however, farmers spread pesticides in the fields with little training, or using improvised tools and methods. For example by dipping green branches in pesticide solutions of undetermined nature, purity and strength, and agitating the branches to spread the liquid. This mode of application obviously poses a threat to the safety and health of applicators, and even more to vulnerable groups such as females and children who often participate in subsistence agriculture and family farming.

Risk assessment of the exposure to pesticides of the general population and of workers is accomplished by comparing the measured or estimated systemic dose with the maximum allowable daily dose relevant to each. These values are usually stated in regulatory authorizations and are based on the results of toxicological studies evaluated by boards of experts. For each active substance, the following health-based exposure limits are often available:

- Acceptable daily intake (ADI) is defined as the *"estimated maximum amount of an agent, expressed on a body mass basis, to which an individual in a (sub)population may be exposed daily over his or her lifetime without appreciable health risk"*.
- Acute reference dose (ARfD) is defined as: *"an estimate of the amount of a substance in food and drinking-water, normally expressed on a body-weight basis, that can be ingested in a period of 24 h or less, without appreciable health risk to the consumer, on the basis of all the known facts at the time of the evaluation"*.
- Acceptable operator exposure level (AOEL) is defined as: *"the maximum amount of active substance to which the operator may be exposed without any adverse health effects. The AOEL is expressed as milligrams of the chemical per kilogram body weight of the operator"*.

The assessment of likely exposure for risk evaluation can be accomplished both empirically, workplace and biological monitoring, and with the use of calculations (modelling). The former approach is well established in internationally agreed protocols, but cost and technical demands tend to limit its general use, although they are often employed in studies required for pesticide authorization or for research purposes. To overcome this limitation, some countries allow the use of calculations in the authorization phase of new products (e.g. pre-marketing models). However, the reliability of these devices to forecast occupational exposure and risk should be thoroughly assessed, especially in relation to different working and meteorological conditions which are difficult to model accurately.

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For the chemical entities listed below an entry exists in the collection of International Chemical Safety Cards (ICSC) hosted in the ILO website

Name	Synonyms	ICSC
Parathion	O,O-Diethyl-O-(4-nitrophenyl)phosphorothioate; Phosphorothioic acid O,O-diethyl O-(4-nitrophenyl) ester; Ethyl parathion	0006
2,4-D	2,4-Dichlorophenoxyacetic acid; 2,4-D acid	0033
DDT	p,p'-DDT; Dichlorodiphenyltrichloroethane; 1,1,1-Trichloro-2,2-bis(p-chlorophenyl)ethane; 2,2-bis(p-Chlorophenyl)-1,1,1-trichloroethane; 1,1'-(2,2,2-Trichloroethylidene)bis(4-chlorobenzene)	0034
Dichlorprop	2-(2,4-Dichlorophenoxy)propionic acid; 2,4-DP; Dichloroprop	0038
Lindane	gamma-1,2,3,4,5,6-Hexachlorocyclohexane; gamma-BHC; gamma-HCH	0053
MCPA	4-Chloro-o-tolyloxyacetic acid; 2-Methyl-4-chlorophenoxyacetic acid; 4-Chloro-2-methylphenoxyacetic acid	0054
Mecoprop	2-(4-Chloro-o-tolyloxy)propionic acid; 2-(4-Chloro-2-methylphenoxy)propanoic acid; MCPP	0055
p-Nitrophenol	4-Nitrophenol; 4-Hydroxynitrobenzene	0066
Pentachlorophenol;		0069
2,2'-Dipyridyl	2,2'-Bipyridine alpha,alpha'-Bipyridyl; 2,2'-Bipyridyl; 2-(2-Pyridyl)pyridine	0093
Aldicarb	2-Methyl-2-(methylthio)propionaldehyde O-(methylcarbamoyl)oxime; 2-Methyl-2-(methylthio)propanal O-((methylamino)carbonyl)oxime	0094
Aminocarb	4-Dimethylamino-m-tolyl N-methylcarbamate; 4-Dimethylamine m-cresyl methylcarbamate	0097
Amitraz	N-Methylbis(2,4-xylyliminomethyl)amine; N,N'-(Methyliminodimethylidyne)bis-2,4-xylidine	0098
Atrazine	2-Chloro-4-ethylamino-6-isopropylamino-1,3,5-triazine; 6-Chloro-N-ethyl-N'-(1-methylethyl)-1,3,5-triazine-2,4-diamine; 2-Chloro-4-ethylamino-6-isopropylamino-s-triazine	0099
Captafol	N-(1,1,2,2-Tetrachloroethylthio)cyclohex-4-ene-1,2-dicarboximide; 3a,4,7,7a-Tetrahydro-N-(1,1,2,2-tetrachloroethanesulphenyl)phthalimide	0119
Captan	1,2,3,6-Tetrahydro-N-(trichloromethylthio)phthalimide; 3a,4,7,7a-Tetrahydro-2-((trichloromethyl)thio)-1H-isoindole-1,3(2H)-dione	0120
Carbaryl	1-Naphthalenol methylcarbamate; 1-Naphthyl methylcarbamate; Methyl carbamic acid 1-naphthyl ester; 1-Naphthalenyl methylcarbamate	0121
Carbofuran	2,3-Dihydro-2,2-dimethylbenzofuran-7-yl methylcarbamate; 2,3-Dihydro-2,2-dimethyl-7-benzofuranyl methylcarbamate; 2,2-Dimethyl-2,3-dihydro-7-benzofuranyl-N-methylcarbamate	0122
Chlordimeform	Chlorphenamidine; N'-(4-Chloro-o-tolyl)-N,N-dimethylformamidine N'-(4-Chloro-2-methylphenyl)-N,N-dimethylmethanimidamide	0124
Chlordimeform hydrochloride	N'-(4-Chloro-o-tolyl)-N,N-dimethylformamidine hydrochloride; N'-(4-Chloro-2-methylphenyl)-N,N-dimethylmethanimidamide hydrochloride	0125
Chlorothalonil	Tetrachloroisophthalonitrile; 2,4,5,6-Tetrachloro-1,3-benzenedicarbonitrile; 2,4,5,6-Tetrachloro-3-cyanobenzonitrile	0134
Diazinon	O,O-Diethyl-O-(2-isopropyl-6-methylpyrimidin-4-yl) phosphorothioate; Phosphorothioic acid O,O-diethyl O-(6-methyl-2-(1-methylethyl)-4-pyrimidinyl) ester; O,O-diethyl O-[6-methyl-2-(propan-2-yl)pyrimidin-4-yl]phosphorothioate	0137

Name	Synonyms	ICSC
Dicamba	3,6-Dichloro-o-anisic acid; 3,6-Dichloro-2-methoxybenzoic acid	0139
Dinoseb	2,4-Dinitro-6-sec-butylphenol; 2-sec-Butyl-4,6-dinitrophenol; 2-(1-Methylpropyl)-4,6-dinitrophenol; 2,4-Dinitro-6-(1-methylpropyl)phenol	0149
Folpet	N-(Trichloromethylthio)phthalimide; 2-{(Trichloromethyl)thio}-1H-isoindole-1,3(2H)-dione	0156
Glyphosate	N-(Phosphonomethyl)glycine	0160
Hexachlorophene	2,2'-Methylenebis(3,4,6-trichlorophenol); HCP	0161
Malathion	Diethyl(dimethoxythiophosphorylthio)succinate; S-1,2-bis(Ethoxycarbonyl)ethyl O,O-dimethylphosphorodithioate; Butanedioic acid, {(dimethoxyphosphinothioyl)thio}-, diethyl ester; Diethyl 2-dimethoxyphosphinothioylsulfanylbutanedioate	0172
Maneb	Manganese, ethylenebis(dithiocarbamato);	0173
Methamidophos	O,S-Dimethyl phosphoramidothioate; Phosphoramidothioic acid, O,S-dimethyl ester	0176
Methomyl	S-Methyl-N-(methylcarbamoyloxy)thioacetimidate; Ethanimidothioic acid, N-{{(methylamino)carbonyl}oxy}-, methyl ester; Methyl N-{(methylamino)carbonyloxy}ethanimidothioate	0177
Monocrotophos	Dimethyl (E)-1-methyl-2-(methylcarbamoyl) vinyl phosphate; trans-Monocrotophos; (E)-Phosphoric acid dimethyl [1-methyl-3-(methylamino)-3-oxo-1-propenyl] ester	0181
Potassium nitrate	Saltpeter	0184
Sodium nitrate	Chile saltpetre	0185
Phosphamidon	2-Chloro-2-diethylcarbamoyl-1-methylvinyl dimethyl phosphate; 2-Chloro-3-(diethylamino)-1-methyl-3-oxo-1-propenyl dimethyl phosphate; Dimethyl phosphate ester 2-chloro-N,N-diethyl-3-hydroxycrotonamide; O,O-Dimethyl-O-(2-chloro-2-diethylcarbamoyl-1-methylvinyl) phosphate	0189
Propoxur	2-Isopropoxyphenyl methylcarbamate; Phenol, 2-(1-methylethoxy)-,methylcarbamate; 2-(1-Methylethoxy)phenyl methylcarbamate; PHC	0191
Temephos	O,O,O',O'-Tetramethyl O,O'-thiodi-p-phenylene bis(phosphorothioate); O,O'-(Thiodi-4,1-phenylene) bis(O,O-dimethylphosphorothioate); Phosphorothioic acid, O,O'-(thiodi-4,1-phenylene) O,O,O',O'-tetramethyl ester	0199
Trietazine	2-Chloro-4-(diethylamino)-6-(ethylamino)-s-triazine; 1,3,5-Triazine-2,4-diamine, 6-chloro-N,N,N'-triethyl-	0202
Trifluralin	alpha, alpha, alpha-Trifluoro-2,6-dinitro-N,N-dipropyl-p-toluidine 2,6-Dinitro-N,N-dipropyl-4-(trifluoromethyl)benzenamine	0205
Allethrin	(RS)-3-Allyl-2-methyl-4-oxocyclopent-2-enyl (1RS)-cis-trans-chrysanthemate; 2-Methyl-4-oxo-3-(2-propenyl)-2-cyclopenten-1-yl 2,2-dimethyl-3-(2-methyl-1-propenyl)cyclopropanecarboxylate	0212
d-Allethrin	(RS)-3-Allyl-2-methyl-4-oxocyclopent-2-enyl (1R)-cis-trans-chrysanthemate; 2-Methyl-4-oxo-3-(2-propenyl)-2-cyclopenten-1-yl 2,2-dimethyl-3-(2-methyl-1-propenyl)cyclopropanecarboxylate	0213
Bioallethrin	(RS)-3-Allyl-2-methyl-4-oxocyclopent-2-enyl (1R)-trans-chrysanthemate; 2-Methyl-4-oxo-3-(2-propenyl)-2-cyclopenten-1-yl 2,2-dimethyl-3-(2-methyl-1-propenyl)cyclopropanecarboxylate	0227

Name	Synonyms	ICSC
s-Bioallethrin	(S)-3-Allyl-2-methyl-4-oxocyclopent-2-enyl (1R)-trans-chrysanthemate; 2-Methyl-4-oxo-3-(2-propenyl)-2-cyclopenten-1-yl 2,2-dimethyl-3-(2-methyl-1-propenyl)cyclopropanecarboxylate	0228
Bioresmethrin	(5-Benzyl-3-furyl)methyl (1R)-trans-chrysanthemate; (5-(Phenylmethyl)-3-furanyl)methyl 2,2-dimethyl-3-(2-methyl-1-propenyl) cyclopropanecarboxylate	0229
Cismethrin	(5-Benzyl-3-furyl)methyl (1R)-cis-chrysanthemate; (5-(Phenylmethyl)-3-furanyl)methyl 2,2-dimethyl-3-(2-methyl-1-propenyl) cyclopropanecarboxylate	0239
Cypermethrin	(RS)-alpha-Cyano-3-phenoxybenzyl (1RS)-cis-trans-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate; Cyano(3-phenoxyphenyl)methyl 3-(2,2-dichloroethenyl)-2,2-dimethylcy-clopropanecarboxylate	0246
Deltamethrin	(S)-alpha-Cyano-3-phenoxybenzyl (1R)-cis-3-(2,2-dibromovinyl)-2,2-dimethylcyclopropanecarboxylate	0247
Dimethyl phthalate	Dimethyl 1,2-benzenedicarboxylate; Phthalic acid dimethyl ester; 1,2-Benzenedicarboxylic acid, dimethyl ester; DMP	0261
Fenvalerate	(RS)-alpha-Cyano-3-phenoxybenzyl (RS)-2-(4-chlorophenyl)-3-methylbutyrate; Cyano(3-phenoxyphenyl)methyl 4-chloro-alpha-(1-methylethyl) benzeneacetate	0273
Fluoroacetic acid	Monofluoroacetic acid; FAA; alpha-Fluoroacetic acid	0274
Permethrin	3-Phenoxybenzyl (1RS)-cis-trans-3-(2,2-dichlorovinyl)-2,2-dimethylcyclop ropanecarboxylate; (3-Phenoxyphenyl)methyl 3-(2,2-dichloroethenyl)-2,2-dimethylcyclopro-panecarboxylate	0312
d-Phenothrin	3-Phenoxybenzyl (1R)-cis-trans-chrysanthemate; (3-Phenoxyphenyl)methyl 2,2-dimethyl-3-(2-methyl-1-propenyl)cyclopro-panecarboxylate; Sumithrin	0313
Pyridine	Azine; Azabenzene	0323
Resmethrin	(5-Benzyl-3-furyl)methyl (1RS)-cis-trans-chrysanthemate; (5-(Phenylmethyl)-3-furanyl)methyl 2,2-dimethyl-3-(2-methyl-1-propenyl) cyclopropanecarboxylate	0324
Strychnine sulfate	Strychnidin-10-one sulfate (2:1)	0327
Sulfamic acid	Amidosulfonic acid; Amidosulfuric acid; Sulfamidic acid	0328
Tetramethrin	3,4,5,6-Tetrahydrophthalimidomethyl (1RS)-cis-trans-chrysanthemate; (1,3,4,5,6,7-Hexahydro-1,3-dioxo-2H-isoindol-2-yl)methyl 2,2-dimethyl-3-(2-methyl-1-propenyl)cyclopropanecarboxylate	0334
d-Tetramethrin	3,4,5,6-Tetrahydrophthalimidomethyl (1R)-cis-trans-chrysanthemate; (1,3,4,5,6,7-Hexahydro-1,3-dioxo-2H-isoindol-2-yl)methyl 2,2-dimethyl-3-(2-methyl-1-propenyl)cyclopropanecarboxylate	0335
Ziram	Zinc dimethyldithiocarbamate; (T-4)-bis(Dimethylcarbamodithioato-S,S')zinc	0348
Zineb	Zinc ethylenebis(dithiocarbamate); ((1,2-Ethanediylbis(carbamodithioato))(2-))zinc; Zinc ethane-1,2-diylbis(dithiocarbamate); Zinc ethylenebis(dithiocarbamate) (polymeric)	0350
Alachlor	2-Chloro-2',6'-diethyl-N-(methoxymethyl)acetanilide; 2-chloro-N-(2,6-diethyl)phenyl-N-methoxymethyl acetamide; Acetanilide,2-chlor-2',6'-diethyl-N-(methoxymethyl)-	0371

Name	Synonyms	ICSC
Benomyl	Methyl 1-(butylcarbamoyl)benzimidazol-2-ylcarbamate; Carbamic acid, ((1-(butylamino)carbonyl)-1H-benzimidazol-2-yl), methyl ester; 1-(Butylcarbamoyl)-2-benzimidazol-methylcarbamat; Methyl 1-(butylcarbamoyl)benzimidazol-2-ylcarbamate	0382
Bensulide	O,O-Diisopropyl S-2-phenylsulfonylaminoethyl phosphorodithioate; Phosphorodithioic acid, O,O-bis(1-methylethyl)S-(2-((phenylsulfonyl) amino) ethyl)ester; O,O-bis(propan-2-yl) [(2-benzenesulfonamidoethyl) sulfanyl] phosphonothioate; N-[2-di(propan-2-yloxy)phosphinothioylsulfanylethyl]benzenesulfonamide	0383
Cyanazine	2-Chloro-4-(1-cyano-1-methylethylamino)-6-ethylamino-1,3,5-triazine	0391
Carbophenothion	S-4-Chlorophenylthiomethyl O,O-diethyl phosphorodithioate; Phosphorodithioic acid, S-(((4-chlorophenyl)thio)methyl) O,O-diethyl ester	0410
Chloramine-T	Sodium N-chloro-p-toluenesulfonamide; Sodium N-chloro-4-toluenesulfonamide; Sodium N-chloro 4-methylbenzenesulfonamide; Tosyl chloramide sodium	0413
Coumaphos	O-3-Chloro-4-methyl-2-oxo-2H-chromen-7-yl O,O-diethyl phosphorothioate; Phosphorothioic acid O-(3-chloro-4-methyl-2-oxo-2H-1-benzopyran-7-yl) O,O-diethyl ester; O,O-Diethyl O-(3-chloro-4-methyl-7-coumarinyl)phosphorothioate; O,O-Diethyl 3-chloro-4-methyl-7-umbelliferone thiophosphate	0422
Demeton-O-methyl	O-2-Ethylthioethyl O,O-dimethyl phosphorothioate	0429
Clopyralid	3,6-Dichloropyridine-2-carboxylic acid; 3,6-Dichloropicolinic acid; 3,6-DCP	0443
Sodium n,n-diethyldithiocarbamate	Dithiocarb sodium; Sodium N,N-diethylcarbamodithioate	0446
Diethylthiophosphoryl chloride	Phosphorochloridothioic acid O,O-diethyl ester; Diethyl chlorothiophosphate; Diethyl phosphochloridothionate	0448
2,4-Xylenol	2,4-Dimethylphenol m-Xylenol 1-Hydroxy-2.4-dimethylbenzene	0458
EPTC	S-Ethyl dipropylthiocarbamate; Carbamothioic acid, dipropyl-, S-ethyl ester; S-Ethyl dipropylcarbamothioate; S-Ethyl-N,N-dipropylthiocarbamate	0469
Fenamiphos	Phenamiphos; Ethyl-3-methyl-4-(methylthio)phenyl(1-methylethyl)phosphoramidate	0483
Sodium fluoroacetate	Sodium fluoroacetic acid; Fluoroacetic acid, sodium salt	0484
Hexachlorocyclohexane	1,2,3,4,5,6-Hexachlorocyclohexane (mixed isomers); BHC/HCH (mixture of isomers); 1,2,3,4,5,6-Benzenehexachloride (mixed isomers)	0487
Metribuzin	4-Amino-6-tert-butyl-3-methylthio-as-triazin-5-one; 4-Amino-6-(1,1-dimethylethyl)-3-(methylthio)-1,2,4-triazin-5(4H)-one	0516
Nicotine	(S)-3-(1-Methylpyrrolidin-2-yl)pyridine; 3-(1-Methyl-2-pyrrolidinyl) pyridine; beta-Pyridyl-alpha-N-methylpyrrolidine; 1-Methyl-2-(3-pyridyl)pyrrolidine	0519
Nicotine sulfate	(-)-1-Methyl-2-(3-pyridyl)-pyrrolidine sulfate; (S)-3-(1-Methyl-2-pyrrolidinyl)-pyridine sulfate; 3-(1-Methyl-2-pyrrolidinyl)-pyridine sulfate	0520
Nicotine tartrate	Nicotine acid tartrate; Nicotine bitartrate	0521

Name	Synonyms	ICSC
Pentachlorophenol, sodium salt	Sodium pentachlorophenate; Sodium pentachlorophenol; Sodium pentachlorophenolate; Sodium pentachlorophenoxide	0532
Phenylmercuric acetate	Mercuriphenyl acetate; Merphenyl acetate; PMA	0540
Phosmet	O,O-Dimethyl S-phthalimidomethyl phosphorodithioate; Phosphorodithioic acid, S-((1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)methyl) O,O-dimethyl ester; O,O-Dimethyl phosphorodithioate S-ester with N-(mercaptomethyl) phthalimide	0543
Potassium chlorate	Potassium oxymuriate	0548
Propanil	3',4'-Dichloropropionanilide; Propanamide, N-(3,4-dichlorophenyl)-	0552
Thiometon	S-2-Ethylthioethyl O,O-dimethyl phosphorodithioate; Phosphorodithioic acid, S-(2-(ethylthio)ethyl)O,O-dimethyl ester; Dithiomethon	0580
Thiophosphoryl chloride	Phosphorothionic trichloride; Trichlorophosphine sulphide; Phosphorous sulfochloride; Phosphorothioic trichloride	0581
Trichlorphon	Dimethyl-2,2,2-trichloro-1-hydroxyethylphosphonate; Trichlorphene; (2,2,2-Trichloro-1-hydroxyethyl) phosphonic acid dimethyl ester; Chlorofos	0585
Zinc phosphide	Trizinc diphosphide	0602
Fenitrothion	O,O-Dimethyl O-4-nitro-m-tolyl phosphorothioate; O,O-Dimethyl O-(3-methyl-4-nitrophenyl) phosphorothioate; O,O-Dimethyl O-4-nitro-m-tolyl thiophosphate; Sumithion	0622
Methyl parathion	O,O-Dimethyl O-4-nitrophenyl phosphorothioate; O,O-Dimethyl-p-nitrophenylthionophosphate; Phosphorothioic acid, O,O-dimethyl O-(4-nitrophenyl) ester	0626
Amitrole	1,2,4-Triazol-3-ylamine; 3-Amino-1H-1,2,4-triazole; Aminotriazole	0631
Copper (II) orthoarsenate	Arsenic acid, copper salt; Copper arsenate	0648
Fenthion	Phosphorothioic acid, O,O-dimethyl O-(3-methyl-4-(methylthio)phenyl) ester; O,O-Dimethyl-O-(4-methylthio-m-tolyl) phosphorothioate	0655
o-Phenylphenol	1,1'-Biphenyl-2-ol; 2-Biphenylol; 2-Hydroxybiphenyl; 2-Phenylphenol	0669
Tetrahydrothiophene	Tetramethylene sulfide; Thiolane; Thiophane; Thiocyclopentane	0677
1,2,4-Triazole	Pyrrodiazole; 1H-1,2,4-Triazole; s-Triazole	0682

Name	Synonyms	ICSC
Dichlorvos	2,2-Dichlorovinyl dimethyl phosphate; Phosphoric acid, 2,2-dichloroethenyl dimethyl ester; DDVP	0690
Phosphine	Phosphorus trihydride; Hydrogen phosphide	0694
Phosphorus trichloride	Trichlorophosphine; Phosphorous chloride	0696
Propazine	2,4-Bis(isopropylamino)-6-chloro-1,3,5-triazine; 2-Chloro-4,6-bis(isopropylamino)-S-triazine; 1,3,5-Triazine-2,4-diamine, 6-chloro-N,N'-bis(1-methylethyl) 2-Chloro-4,6-bis(isopropylamino)-1,3,5-triazine	0697
Simazine	6-Chloro-N,N-diethyl-1,3,5-triazine-2,4-diamine; 2,4-Bis(ethylamino)-6-chloro-S-triazine; S-Triazine, 2-chloro-4,6-bis(ethylamino)-	0699
Demeton-S-methyl	S-2-Ethylthioethyl O,O-dimethyl phosphorothioate; Phosphorothioic acid, S-(2-(ethylthio)ethyl)O,O-dimethyl ester	0705
Fonofos	O-Ethyl S-phenylethylphosphonodithioate	0708
Sodium perchlorate	Perchloric acid, sodium salt; Inenat	0715
Chlordane	1,2,4,5,6,7,8,8-Octachloro-2,3,3a,4,7,7a-hexahydro-4,7-methanoindene; 1,2,4,5,6,7,8,8-Octachloro-2,3,3a,4,7,7a-hexahydro-4,7-methano-1H-indene	0740
Dimethoate	O,O-Dimethyl S-methylcarbamoylmethyl phosphorodithioate; Phosphorodithioic acid, O,O-dimethyl S-(2-(methylamino)- 2-oxoethyl) ester; O,O-Dimethyl S-(2-(methylamino)-2-oxoethyl)phosphorodithioate	0741
Endosulfan	(1,4,5,6,7,7-Hexachloro-8,9,10-trinorborn-5-en- 2,3-ylenebismethylene) sulfite; 6,9-Methano-2,4,3-benzodioxathiepin, 6,7,8,9,10,10-hexachloro-1,5,5a,6,9,9a-hexahydro-, 3-oxide	0742
Heptachlor	1,4,5,6,7,8,8-Heptachloro-3a,4,7,7a-tetrahydro-4,7-methanoindene; 1,4,5,6,7,8,8-Heptachloro-3a,4,7,7a-tetrahydro-4,7-methano-1H-indene; 3,4,5,6,8,8a-Heptachlorodicyclopentadiene	0743
Quintozene	Pentachloronitrobenzene; PCNB	0745
Tetradifon	4-Chlorophenyl 2,4,5-trichlorophenyl sulfone; 1,2,4-Trichloro-5-((4-chlorophenyl)sulfonyl)-benzene; 2,4,4',5-Tetrachlorodiphenyl sulfone	0747
Acephate	O,S-Dimethyl acetylphosphoramidothioate; Phosphoramidothioic acid, acetyl-, O,S-dimethyl ester; N-(Methoxy(methylthio)phosphinoyl)acetamide	0748
Chlorobenzilate	Ethyl 4,4'-dichlorobenzilate; Benzilic acid, 4,4'-dichloro-, ethyl ester; Ethyl 2-hydroxy-2,2-bis(4-chlorophenyl)acetate	0749
Trichloronitromethane	Chloropicrin; Nitrochloroform; Nitrotrichloromethane	0750
Copper sulfate	Cupric sulphate; Sulfuric acid, copper(2+) salt	0751
Dicofol	2,2,2-Trichloro-1,1-bis(4-chlorophenyl)ethanol; 4,4'-Dichloro-alpha-(trichloromethyl)benzhydrol	0752
EPN	Phosphonothioic acid, phenyl-, O-ethyl O-(4-nitrophenyl) ester; O-Ethyl O-4-nitrophenyl phenyl phosphonothioate	0753

Name	Synonyms	ICSC
Mancozeb	Manganese ethylenebis(dithiocarbamate)(polymeric)complex with zinc salt; Manzeb; Manganese-zinc ethylenebis(dithiocarbamate)	0754
Copper 8-quinolate	Copper-8-hydroxyquinoline; Oxine-copper; 8-Quinolinol, copper(II) chelate; Bis(8-oxyquinoline) copper	0756
Thiram	Tetramethylthiuram disulfide; Bis (dimethylthiocarbamoyl) disulfide; TMTD; Tetramethylthioperoxydicarbonic diamide (((H2N)C(S))2S2)	0757
Vamidothion	O,O-Dimethyl S-(2-(1-methylcarbamoylethylthio)ethyl) phosphorothioate; O,O-Dimethyl S-2-(1-N-methylcarbamoylethylmercapto)ethyl thiophosphate; N-Methyl O,O-dimethylthiolophosphoryl-5-thia-3-methyl-2-valeramide	0758
Paraformaldehyde	Polyoxymethylene; Formagen; Polymerised formaldehyde; Formaldehyde polymer; Paraform	0767
Aldrin	1,2,3,4,10,10-Hexachloro-1,4,4a,5,8,8a-hexahydro-exo-1,4-endo-5,8-dimethanonaphthalene; 1,4:5,8-Dimethanonaphthalene, 1,2,3,4,10,10-hexachloro-1,4,4a,5,8,8a-hexahydro-,(1alpha,4alpha,4aß,5alpha,8alpha,8aß); HHDN	0774
Chlormequat chloride	(2-Chloroethyl)trimethylammonium chloride; Chlorocholine chloride; 2-Chloro-N,N,N-trimethylethanaminium chloride	0781
Dazomet	Dimethylformocarbothialdine; Tetrahydro-3,5-dimethyl-2H-1,3,5-thiadiazine-2-thione	0786
Dieldrin	1,2,3,4,10,10-Hexachloro-6,7-epoxy-1,4,4a,5,6,7,8,8a-octahydro-endo-1,4-exo- 5,8-dimethanonaphthalene; 3,4,5,6,9,9-Hexachloro-1a,2,2a,3,6,6a,7,7a-octahydro-, (1aalpha,2&,2aalpha,3&,6&,6aalpha,7&,7aalpha)-2,7:3,6-dimethanonaphth(2,3-b)oxirene HEOD	0787
Ferbam	Ferric dimethyldithiocarbamate; Iron tris(dimethyldithiocarbamate)	0792
alpha-Hexachlorocyclohexane	alpha-1,2,3,4,5,6-Hexachlorocyclohexane; alpha-Benzenehexachloride (alpha-BHC); alpha-Hexachloran	0795
beta-Hexachlorocyclohexane	1-alpha,2-beta,3-alpha,4-beta,5-alpha,6-beta-Hexachlorocyclohexane; beta-1,2,3,4,5,6-Hexachlorocyclohexane; beta-Benzenehexachloride (beta-BHC)	0796
Phosalone	S-6-chloro-2,3-dihydro-2-oxobenzoxazol-3-ylmethyl O,Odiethyl phosphorodithioate; Benzphos	0797
Azinphos-methyl	Phosphorodithioic acid 0,0-dimethyl S-((4-oxo-11,2,3-benzotriazin-3-(4H)-yl)methyl) ester; S-3,4-Dihydro-4-oxo-1,2,3-benzotriazin-3-ylmethyl) O,O-dimethyl phosphorodithioate	0826
Bentazone	3-Isopropyl-1H-2,1,3-benzothiadiazin-4(3H)-one 2,2-dioxide; 1H-2,1,3-Benzothiadiazin-4(3H)-one, 3-(1-methylethyl)-, 2,2-dioxide; Bendioxide	0828

Name	Synonyms	ICSC
Binapacryl	2-(1-Methylpropyl)-4,6-dinitrophenyl 3-methyl-2-butenoate; 2-(1-Methylpropyl)-4,6-dinitrophenyl 3,3-dimethylacrylate; Dinoseb methacrylate	0835
Camphechlor	Toxaphene; Chlorinated camphene (60%); Polychlorocamphene	0843
p-Nitrochlorobenzene	1-Chloro-4-nitrobenzene; PCNB; PNCB	0846
Chlorpyrifos	O,O-Diethyl-O-(3,5,6-trichloro-2-pyridyl)phosphorothioate; O,O-Diethyl O-(3,5,6-trichloro-2-pyridinyl) phosphorothioic acid ester; Chlorpyrifos-ethyl	0851
Chlorthiamid	2,6-Dichlorothiobenzamide; 2,6-Dichlorobenzenecarbothioamide; DCBN	0852
Cyhalothrin	(RS)-alpha-Cyano-3-phenoxybenzyl (Z)-(1RS,3RS)-(2-chloro-3,3,3-trifluoropropenyl)-2,2-dimethylcyclopropanecarboxylate; Cyclopropanecarboxylic acid, 3-(2-chloro-3,3,3-trifluoro-1-propenyl)-2,2-dimethyl-, cyano(3-phenoxyphenyl)methyl ester	0858
Lambda-cyhalothrin	alpha-Cyano-3-phenoxybenzyl 3-(2-chloro-3,3,3-trifluoropropenyl)-2,2-dimethylcyclopropanecarboxylate; a 1:1 reaction mixture of the (Z)-(1R,3R), (S) ester and (Z)-(1S,3S), (R) ester	0859
Demeton		0861
Demeton-methyl	S-2-Ethylthioethyl O,O-dimethyl phosphorothioate; S (and O)-2-Ethylthioethyl O,O-dimethyl phosphorothioate	0862
Demeton-S	O,O-Diethyl S-2-ethylthioethyl phosphorothioate; Demethonthiol	0864
Dichlobenil	2,6-Dichlorobenzonitrile; DBN; 2,6-Dichlorophenylcyanide	0867
Dicloran	2,6-Dichloro-4-nitroaniline; 2,6-Dichloro-4-nitrobenzenamine; DCNA	0871
Dicrotophos	(E)-3 (dimethyloamino)-1-methyl-3-oxoprop-1-enyl dimethyl phosphate; Dimethyl cis-2-dimethylcarbamoyl-1-methylvinyl phosphate	0872
2,4,5-Trichlorophenol	2,4,5-TCP; 1-Hydroxy-2,4,5-trichlorobenzene	0879
Dinocap	2,4-Dinitro-6-(2-octyl)phenyl crotonate; 2-Butenoic acid, 2(or 4)-isooctyl-4,6(or 2,6)dinitrophenyl ester; 2,6(or 2,4)-Dinitro-4(or 6)octylphenyl crotonates in which octyl is a mixture of 1-methylheptyl, 1-ethylhexyl and 1-propylpentyl groups; DPC	0881
Dinoseb acetate	2-sec-Butyl-4,6-dinitrophenyl acetate; 2-(1-Methylpropyl)-4,6-dinitrophenyl acetate (ester); DNBPA	0882
Dioxathion	S,S'-(1,4-Dioxane-2,3-diyl) O,O,O',O'-tetraethyl-bis-(phosphorodithioate)	0883
Ethion	Diethion; O,O,O',O'-Tetraethyl S,S'-methylene-bis-phosphorodithioate	0888
Hexachlorobenzene	Perchlorobenzene; HCB; Pentachlorophenylchloride; Phenyl perchloryl	0895
Hexachlorobutadiene	1,1,2,3,4,4-Hexachloro-1,3-butadiene; Perchlorobutadiene	0896
Ioxynil	3,5-Diiodo-4-hydroxybenzonitrile; 4-Hydroxy-3,5-diiodobenzonitrile; 4-Cyano-2,6-diiodophenol	0900

Name	Synonyms	ICSC
Mevinphos	Methyl 3-(dimethoxyphosphinoyloxy)but-2-enoate	0924
Naled	1,2-Dibromo-2,2-dichloroethyl dimethyl phosphate	0925
Nitrofen	2,4-Dichloro-1-(4-nitrophenoxy) benzene; 2,4-Dichlorophenyl p-nitrophenyl ether	0929
Phenothiazine	Dibenzothiazine; Thiodiphenylamine; Dibenzo-1,4-thiazine	0937
Polychlorinated biphenyl	Chlorobiphenyl (54% chlorine); Chlorodiphenyl (54% chlorine); PCB	0939
Rotenone	Tubotoxine; Derris powder	0944
Sulfur monochloride	Sulfur chloride; Disulfur dichloride; Sulfur subchloride	0958
Triclopyr-2-butoxyethylester	2-Butoxyethyl [(3,5,6-trichloropyridin-2-yl)oxy]; Triclopyr-butotyl; Acetic acid, ((3,5,6-trichloro-2-pyridinyl)oxy)-,2-butoxyethylester; Triclopyr BEE Ester	0963
alpha-Naphthylthiourea	Antu; 1-(1-Naphthyl)-2-thiourea; 1-Naphtylthiourea	0973
Fenchlorphos	O,O-Dimethyl-O-(2,4,5-trichlorophenyl) phosphorothioate; Ronnel	0975
Sulfotep	Thiodiphosphoric acid tetraethyl ester; Ethyl thiopyrophosphate; Tetraethyl dithiopyrophosphate (TEDP)	0985
Endrin		1023
Piperazine	Antiren; 1,4-Diazacyclohexane; 1,4-Diethylenediamine; Diethyleneimine; Hexahydropirazine	1032
Ammonium chloride	Sal ammoniac	1051
Phorate	O,O-Diethyl-S-(ethylthio)methyl phosphorodithioate	1060
Potassium nitrite	Nitrous acid potassium salt	1069
2,3,4,6-Tetrachlorophenol	2,4,5,6-Tetrachlorophenol; Phenol, 2,3,4,6-tetrachloro	1089
Hexachlorocyclopentadiene	1,2,3,4,5,5-Hexachloro-1,3-cyclopentadiene; Perchlorocyclopentadiene	1096
Triclopyr	3,5,6-Trichloro-2-pyridyloxyacetic acid	1100
2,4,6-Trichlorophenol	2,4,6-TCP	1122
Disul-sodium	2-(2,4-Dichlorophenoxy)ethyl hydrogen sulphate sodium salt; Sesone; Sodium 2,4-dichlorophenoxyethylsulfate	1142
Crufomate	4-tert-Butyl-2-chlorophenyl methyl methylphosphoramidate; Amidophos	1143
Tetraethyl pyrophosphate	TEPP; Diphosphoric acid, tetraethyl ester; Tetraethyl diphosphate	1158

Name	Synonyms	ICSC
Sulfur	Flowers of sulfur; Flour sulfur; Brimstone; Sulphur	1166
Sodium dodecylbenzene sulphonate		1189
Thallium carbonate	Carbonic acid, dithallium(1+) salt; Dithallium carbonate; Thallous carbonate	1221
Picloram	4-Amino-3,5,6-trichloro-2-pyridinecarboxylic acid; 4-Amino-3,5,6-trichloropicolinic acid	1246
Sulprofos	O-Ethyl O-4-(methylthio)phenyl S-propyl phosphorodithioate; O-Ethyl O-4-(methylthio)phenyl S-propyl dithiophosphate; O-Ethyl O-4-(methylthio)phenyl phosphorodithioic acid S-propyl ester	1248
Triflumizole	(E)-4-Chloro-alpha,alpha,alpha-trifluoro-N-(1-imidazol-1-yl-2-propoxyethylidene)-o-toluidine; 1-[(1E)-1-[[4-chloro-2-(trifluoromethyl)phenyl]imino]-2-propoxyethyl]-1H-imidazole; (1E)-N-[4-chloro-2-(trifluoromethyl)phenyl]-1-(1H-imidazol-1-yl)-2-propoxyethanimine	1252
Bromuconazole	1-((2RS,4RS:2RS,4SR)-4-Bromo-2-(2,4-dichlorophenyl) tetrahydrofurfuryl)-1H-1,2,4-triazole; 1-((4-Bromo-2-(2,4-dichlorophenyl)tetrahydro-2-furanyl)methyl)-1H-1,2,4-triazole	1264
Flutolanil	alpha,alpha,alpha-Trifluoro-3'-isopropoxy-o-toluanilide; N-(3-(1-Methylethoxy)phenyl)-2-(trifluoromethyl)benzamide	1265
Hexaflumuron	N-(((3,5-dichloro-4-(1,1,2,2-tetrafluoroethoxy)phenyl)amino)carbonyl)-2,6-difluorobenzamide; 1-(3,5-Dichloro-4-(1,1,2,2-tetrafluoroethoxy)phenyl)-3-(2,6-difluorobenzoyl)urea	1266
Flocoumafen	4-Hydroxy-3-(1,2,3,4-tetrahydro-3-(4-(4-trifluoromethylbenzyloxy) phenyl) -1naphthyl)coumarin; 4-Hydroxy-3-(1,2,3,4-tetrahydro-3-(4-((4-(trifluoromethyl)phenyl) methoxy)phenyl)- 1-naphthalenyl)-2H-1-benzopyran-2-one	1267
Trinexapac-ethyl	Ethyl 4-cyclopropyl(hydroxy)methylene-3,5-dioxocyclohexanecarboxylate	1268
Pyriproxyfen	2-(1-Methyl-2-(4-phenoxy)ethoxy)pyridine; 4-Phenoxyphenyl (RS)-2-(2-pyridyloxy)propyl ether	1269
Propaquizafop	2-Isopropylideneamino-oxyethyl (R)-2-(4-(6-chloroquinoxalin- 2-yloxy) phenoxy)propionate; (R)-2-(((1-Methylethylidene)amino)oxy)ethyl 2-(4-((6-chloro-2-quinoxalinyl) oxy)phenoxy)propanoate	1271
Monolinuron	3-(4-Chlorophenyl)-1-methoxy-1-methylurea; Urea, N'-(4-chlorophenyl)-N-methoxy-N-methyl-; 3-(p-Chlorophenyl)-1-methoxy-1-methylurea	1273
Carbendazim	Methyl benzimidazole-2-ylcarbamate; Methyl (1H-benzimidazol-2-yl)carbamate; Carbendazol; 1H-Benzimidazol-2-ylcarbamic acid methyl ester	1277
Tributyltin oxide	Hexabutyldistannoxane; Tri-n-butyltin oxide; TBTO	1282
Triphenyltin hydroxide	Hydroxytriphenylstannane; Hydroxytriphenylstannate; Fentin hydroxide	1283

Name	Synonyms	ICSC
Methylene bis(thiocyanate)	Thiocyanic acid, methylene ester; Methylene dithiocyanate	1287
Linuron	3-(3,4-Dichlorophenyl)-1-methoxy-1-methylurea; Urea, N'-(3,4-dichlorophenyl)-N-methoxy-N-methyl-; Methoxydiuron	1300
Imazalil	Allyl 1-(2,4-dichlorophenyl)-2-imidazol-1-ylethyl ether; 1-(2-(2,4-Dichlorophenyl)-2-(2-propenyloxy)ethyl)-1H-imidazole; Enilconazole	1303
Chlorfenvinphos	O,O-Diethyl-O-{2-chloro-1-(2,4-dichlorophenyl)vinyl}phosphate; 2-Chloro-1-(2,4-dichlorophenyl)vinyldiethyl phosphate	1305
Methoxychlor	1,1-(2,2,2-Trichloroethylidene)bis(4-methoxybenzene); 1,1,1-Trichloro-2,2-bis(p-methoxyphenyl)ethane; Dimethoxy-DDT	1306
Chlorotoluron	3-(3-Chloro-p-tolyl)-1,1-dimethylurea	1327
Piperonyl butoxide	5-2-(2-Butoxyethoxy)ethoxymethyl-6-propyl-1,3-benzodioxole; 2-(2-Butoxyethoxy)ethyl 6-propylpiperonyl ether; alpha-2-(2-Butoxyethoxy)-ethoxy-4,5-methylenedioxy-2-propyltoluene; [3,4-(Methylenedioxy)-6-propylbenzyl]butyl diethyleneglycol ether	1347
Tribenuron-methyl	Methyl 2-((((N-(4-methoxy-6-methyl-1,3,5-triazin-2-yl)methylamino) carbonyl)amino)sulfonyl)benzoate; 2-(4-Methoxy-6-methyl-1,3,5-triazin-2-yl(methyl)carbomoylsulfamoyl) benzoic acid, methyl ester	1359
Metolachlor	2-Chloro-6'-ethyl-N-(2-methoxy-1-methylethyl)aceto-o-toluidide; 2-Chloro-N-(2-ethyl-6-methylphenyl)-N-(2-methoxy-1-methylethyl) acetamide	1360
Metamitron	4-Amino-3-methyl-6-phenyl-1,2,4-triazin-5(4H)-one	1361
Diquat dibromide	1,1'-Ethylene-2,2'-bipyridyllium dibromide; 6,7-Dihydrodipyridol1,2-a:2',1-cpyrazinedium dibromide; 9,10-Dihydro-8a-10a-diazoniaphenanthrene dibromide	1363
Sulfuryl fluoride	Sulfuryl difluoride; Sulfuric oxyfluoride	1402
Fensulfothion	O,O-Diethyl O-(p-(methylsulfinyl)phenyl) phosphorothioate; O,O-Diethyl O-p-(methylsulfinyl)phenyl thiophosphate	1406
Disulfoton	Dithiodemeton; O,O-Diethyl S-(2-ethylmercaptoethyl) dithiophosphate; O,O-Diethyl S-2-(ethylthio)ethyl phosphorodithioate	1408
Chlordecone	1,1a,3,3a,4,5,5,5a,5b,6-Decachloro-octahydro-1,3,4-metheno-2H-cyclo buta(cd)pentalen-2-one; Kepone; Decachloroketone	1432
Fluoroacetamide	2-Fluoroacetamide; Monofluoroacetamide; Fluoroacetic acid amide	1434
Bromacil	5-Bromo-3-sec-butyl-6-methyl uracil; 5-Bromo-6-methyl-3-(1-methylpropyl) uracil; 5-Bromo-6-methyl-3-(1-methylpropyl)-2,4(1H,3H)-pyrimidinedione; 2,4(1H,3H)-Pyrimidinedione, 5-bromo-6-methyl-3-(1-methyl propyl)-	1448
Potassium chloride		1450
Potassium sulfate	Sulfuric acid dipotassium salt; Dipotassium sulfate	1451
Pyrethrum	Buhach; Pyrethrum extract; Pyrethrum oleoresin	1475

Name	Synonyms	ICSC
4-Dimethylamino-azobenzene	N,N-Dimethyl-4-phenylazobenzenamine; p-Dimethylaminoazobenzene; N,N-Dimethyl-p-(phenylazo)aniline;	1498
Chlorpropham	Isopropyl 3-chlorocarbanilate; 1-Methylethyl (3-chlorophenyl) carbamate; Isopropyl 3-chlorophenylcarbamate	1500
Imidacloprid	1-(6-Chloro-3-pyridylmethyl)-N-nitroimidazolidin-2-ylideneamine; 1-((6-Chloro-3-pyridinyl)methyl)-N-nitro-2-imidazolidinimine; 1-(6-Chloro-3-pyridinylmethyl)-N-nitroimidazolidin-2-ylideneamine; 1H-Imidazol-2-amine, 1-((6-chloro-3-pyridinyl)methyl)-4,5-dihydro-N-nitro	1501
Spinosad		1502
Fipronil	5-Amino-3-cyano-1-(2,6-dichloro-4-trifluoro-methylphenyl)-4-trifluoromethylsulfinylpyrazole	1503
2,2-Dichloropropionic acid	Dalapon; alpha,alpha-Dichloropropionic acid	1509
Carbadox	2-Formylquinoxaline-1,4-dioxide carbomethoxyhydrazone; 2-(Methoxycarbonylhydrazonomethyl)quinoxaline 1,4-dioxide; Methyl 3-(quinoxalin-2-ylmethylene)carbazate 1,4-dioxide	1510
Pindone	2-Pivaloylindan-1,3-dione; 2-(2,2-Dimethyl-1-oxopropyl)-1H-indene-1,3 (2H)-dione; 2-Pivaloyl-1,3-indandione	1515
Esfenvalerate	(S)-alpha-Cyano-3-phenoxybenzyl-(S)-2-(4-chlorophenyl)-3-methylbutyrate; (S)-(R*,R*)-Cyano (3-phenoxyphenyl) methyl-4-chloro-alpha-(1-methylethyl) benzene acetate; (S-(R*,R*))-Benzeneacetic acid, 4-chloro-alpha-(1-methylethyl)-, cyano (3-phenoxyphenyl)methyl ester; (S)-alpha-Cyano-3-phenoxybenzyl-(S)-2-(4-chlorophenyl)isovalerate; S-Fenvalerate	1516
Ammonium sulfamate	Sulfamic acid, monoammonium salt; Ammonium amidosulfonate; Ammonium sulfamidate	1555
2,4,6-Tribromophenol	2,4,6-TBP	1563
Cryolite	Aluminium trisodium fluoride; Sodium fluoaluminate; Sodium aluminium fluoride; Sodium hexafluoroaluminate	1565
White mineral oil	Paraffinum liquidum; Paraffin oil	1597
Potassium dihydrogen phosphate	Potassium phosphate, monobasic; Phosphoric acid, monopotassium salt	1608
2-Chloro-6-trichloromethylpyridine	Nitrapyrin; alpha,alpha,alpha,6-Tetrachloro-2-picoline; 2-Chloro-6-(trichloromethyl)pyridine	1658
Methidathion	O,O-Dimethyl S-(2,3-dihydro-5-methoxy-2-oxo-1,3,4-thiadiazol-3-ylmethyl) phosphorodithioate; O,O-Dimethyl-S-(5-methoxy-1,3,4-thiadiazolinyl-3-methyl) dithiophosphate	1659
Ethoprophos	O-ethyl-S,S-dipropyl phosphorodithioate; Phosphorodithioic acid, O-ethyl S,S-dipropyl ester; Ethoprop	1660
Chlorethoxyfos	Phosphorothioic acid, O,O-diethyl O-(1,2,2,2-tetrachloroethyl) ester; O,O-Diethyl O-(1,2,2,2-tetrachloroethyl) phosphorothioate	1681

Name	Synonyms	ICSC
Chlormephos	Clormethylphos; S-(Chloromethy) O,O-diethyl phosphorodithioate; Phosphorodithioic acid, S-(chloromethyl) O,O-diethyl ester	1682
Zinc sulfate	Sulfuric acid, zinc salt (1:1); Zinc sulfate (anhydrous); Zinc sulphate	1698

▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
1.1.36	Diseases caused by pesticides	T60	NE61&XM7D46
1.1.36	Acute pesticide poisoning	T60	NE61&XM7D46
1.1.36	Acute mucous membranes irritation	J68	CA81.Z
1.1.36	Allergic contact dermatitis	L23	EK00
1.1.36	Burns and corrosions of external body surface	T20-T25	ND9Z
1.1.36	Burns and corrosions of respiratory tract	T27	NE01
1.1.36	Burns of eye and adnexa	T26.0-T26.1	NE00
1.1.36	Chemical burns of mouth and pharynx, oesophagus and stomach	T28.0-T28.2	NE02
1.1.36	Conjunctivitis	H10.2	9A60.Z
1.1.36	Corneal ulcer	H16.0	9A76
1.1.36	Irritant contact dermatitis	L24	EK02
1.1.36	Irritant-induced acute occupational asthma	J68.3	CA81.Y
1.1.36	Pneumonitis and acute chemical bronchitis	J68.0	CA81.0
1.1.36	Pulmonary oedema	J68.1	CA81.1
1.1.36	Reactive airways dysfunction syndrome (RADS)	J68.3	CA81.Y
1.1.36	Upper respiratory inflammation	J68.2	CA81.2
1.1.36	Acute cholinergic crisis	T60.0	NE61& XM7154
1.1.36	Organophosphate-induced delayed neuropathy (OPIDN)	T60.0+G62.2	NE61& XM7154&8D43.Y
1.1.36	Acute neurologic effects caused by organochlorinated compounds	T60.1	NE61& XM5E09
1.1.36	Acute poisoning from chlorophenoxy herbicides	T60.3	B33, NE61, PH53
1.1.36	Acute poisoning from paraquat and subsequent pulmonary fibrosis	T60.3+J68.4	NE61& XM88B4
1.1.36	Anticoagulation syndrome due to exposure to coumarin derivative	T60.4	NE61&XM4SL8& CA26.Z
1.1.36	Toxic effects caused by pentachlorophenol	T60.1	NE61& XM6000
	Occupational exposure to risk factors	Z57	NE61& XM32P2

1.1.37 Diseases caused by sulphur oxides	ICD Code T59.1, T59.8 +Z57
General characteristics of the causal agent	Sulphur oxides (SO_x) are the binary compounds formed by sulphur and oxygen. They react with water to yield corrosive acidic solutions. One of them (sulphur dioxide, SO_2) is an important airborne environmental contaminant and yields sulphur trioxide (SO_3) by radical oxidation in the upper atmosphere. The latter sulphur oxide reacts with water vapour to yield sulphuric acid, which is in turn responsible for acid rain. *Sulphur dioxide* is a colourless, heavier-than-air, non-flammable gas with a characteristic pungent off-smell, odour of 'burnt matches', or sometimes 'devilish', with an olfactory threshold of 0.67 to 4.75 ppm. The gas can be easily converted by moderate compression and cooling to a volatile liquid, which has itself some industrial applications. Both the vapours and the liquid are corrosive towards many metals and alloys and other structural materials such as wood, cellulose fibres, most polymeric materials, and rubbers. In nature, sulphur dioxide is mostly emitted by volcanos, while its most common anthropogenic source is the combustion of fossil fuels, which makes it a common pollutant of urban air. Sulphur dioxide reacts with water to yield the mildly irritating and weakly acid sulphurous acid. Sulphur dioxide also reacts with some biological structures, and in particular with the double bond of unsaturated lipids, and generates highly acidic alkyl sulphonic acids. Sulphur dioxide is also used as a preserving food additive. *Sulphur trioxide* exists in three forms: condensable gas, fuming hygroscopic colourless volatile liquid, and crystalline white solid substance. Nowadays, the main industrial source of sulphur trioxide is the desulphuration of crude oil. This substance is mainly used in the production of sulphuric acid. Other uses are as sulphating or sulphonating agents in the manufacture of detergents and in the synthesis of chemicals such as dyestuffs, drugs, and insecticides. *Sulphuric acid* is a major product of the chemical industry, which is treated in item 1.1.22 dedicated to mineral acids.
Occupational exposures	Sulphur oxides are always produced when sulphur-containing organic substances burn in the presence of air or oxygen. Air oxidation of sulphur dioxide to sulphur trioxide under ambient conditions is very slow, and sulphur dioxide predominates in the combustion fumes of coal and oil. The inorganic sulphate salts of most metals may decompose at sufficiently high temperatures, releasing sulphur oxide fumes. Occupational exposure to sulphur dioxide occurs whenever workers are exposed to combustion fumes of coal and oil, although the real determinants of the true exposure to dangerous concentrations of sulphur dioxide are the source and nature of the fuel, and the extent of the post-combustion treatment of gaseous effluents. Current industrial uses of sulphur dioxide are mainly in rubber vulcanization, while its use as a refrigerant fluid in industrial cooling units has been largely superseded by other chemical compounds. Sulphur dioxide is an authorized food preserving agent and is added (e.g. to wine) either as such, bubbling gas from a cylinder, or as solid sodium metabisulphite salt. Occupational exposure can take place through inhalation, eye contact and only occasionally through contact with the skin. Occupational exposure to sulphur trioxide typically occurs in the chemical industry, in the manufacture of sulphuric acid and oleum, and in chemical processes such as the sulphonation of organic acids with sulphur trioxide. Absorption can take place through inhalation, eye contact and only occasionally through contact with the skin.
Toxicological profile, main health effects and diagnostic criteria	
Short toxicological profile	Occupational exposure to the oxides of sulphur mainly affects workers' respiratory tract, mucous membranes and skin. The main acute effects following inhalation include irritation and inflammation of the upper respiratory tract, acute chemical bronchitis, bronchitis, chemical pneumonia, and pulmonary oedema. Chronic effects of exposure to sulphur dioxide include chronic skin and mucous membrane irritation, ulceration of the nasal septum, asthma, chronic obstructive pulmonary disease, emphysema, chronic *bronchiolitis obliterans*, as well as pulmonary fibrosis. Continued exposure to acidic gases, such as sulphur dioxide and trioxide, can give rise to mottling of tooth enamel.

1.1.37 Diseases caused by sulphur oxides ICD Code T59.1, T59.8 +Z57

Name of the diseases and ICD code: **Acute diseases caused by sulphur oxides**
(Specific disease code) **T59.1, T59.8 +Z57**

Mucous membranes irritation (J68), Acute chemical pneumonitis and bronchitis (J68.0), Upper respiratory inflammation (J68.2), Pulmonary oedema (J68.1), Reactive airways dysfunction syndrome (RADS) (J68.3), Irritant-induced acute occupational asthma (J68.3), Burns and corrosions of eye and adnexa (T26.0-T26.1, T26.5-T26.6), Conjunctivitis (H10.2), Keratoconjunctivitis (H16.2), Corneal ulcer (H16.0), Burns and corrosion of respiratory tract (T27), Burns and corrosions of other internal organs (T28), Burns and corrosions of external body surface (T20-T25), Acute irritant contact dermatitis (L24), Darkroom disease (J68.2, H16.2)

Short description of the disease

Being moderately soluble in water, SO_2 easily dissolves in the layer of fluid on the surface of the mucous membranes (eyes and respiratory tract). The main targets of its effects are, therefore, the upper respiratory tract and bronchi; however, the lower respiratory tract and the lungs can be affected. After an acute respiratory syndrome caused by sulphur dioxide, a reactive airways dysfunction syndrome may appear. The term '*Darkroom disease*' has been described in subjects engaged in X-ray film processing in poorly ventilated conditions. Sufferers complain of upper respiratory and eye irritation, but the precise exposures and pathology are poorly defined. The causal agents may be sulphur dioxide and acetic acid at concentrations of about 0.1 ppm, as well as glutaraldehyde. Clinical features of irritant contact dermatitis have been thoroughly addressed in dedicated item 2.2.2, which should be referred to for further details. Irritation symptoms arising within seconds to minutes have been reported for workplace air concentrations > 1 ppm (or 2.7 mg/m^3) of SO_2. Exposures higher than 400 ppm (1,040 mg/m^3) of SO_2 can be fatal in few minutes.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms:
  - Symptoms of respiratory irritation such as coughing, chest tightness, shortness of breath, and choking. At higher concentrations, tachypnoea and a chemical-induced type of nonallergic asthma (reactive airways dysfunction syndrome, RADS) can be observed. In high exposure scenarios, bronchospasm, laryngospasm and acute pneumonitis can be observed, up to pulmonary oedema.
  - Acute eye exposure causes stinging pain, photophobia, blurred vision, ulceration, and conjunctival irritation.
- Examinations:
  - Evidence of various degrees of irritation and burns of skin and mucous membranes at physical examination.
  - Pulmonary auscultation may document signs of respiratory impairment (e.g. crackles).
  - Chest X-ray may show a picture of bronchitis, pneumonitis or even pulmonary oedema.
  - Respiratory function tests (when feasible) may show an acute obstructive picture, together with evidence of bronchodilator responsiveness and bronchial hyperresponsiveness (on methacholine challenge testing).

Exposure assessment

- History of occupational exposure: evidence of occupational exposure to sulphur oxides (liquid, dust, aerosol or vapours).
- Minimum duration of exposure: few minutes.
- Maximum latent period: few hours. Pulmonary oedema due to sulphuric acids is typically observed with a latent period of 6 to 24 hours (in any case, less than 72 hours) after exposure.

1.1.37 Diseases caused by sulphur oxides — ICD Code T59.1, T59.8 +Z57

Name of the diseases and ICD code: **Chronic diseases caused by sulphur oxides**
(Specific disease code) **+T59.1, T59.8 +Z57**

Chronic skin and mucous membranes irritation (L24)

Short description of the disease

The prolonged contact of sulphur oxides with mucous membranes and skin can cause chronic irritation with different levels of severity.

Diagnostic criteria

Clinical manifestations

Redness and burning of skin and eyes, cough, dysphonia, and dyspnoea can be observed. Clinical features of irritant contact dermatitis have been thoroughly addressed in dedicated item 2.2.2, which should be referred to for further details.

Exposure assessment

- History of occupational exposure: evidence of prolonged/repeated exposure to sulphur oxides, in particular in poor occupational hygiene conditions.
- Minimum duration of exposure: few months.
- Maximum latent period: few months.

Nose septal ulceration (J34.8)

Short description of the disease

The disease consists of erosion, ulceration or perforation of mucosal membrane of the nasal septum, observed in case of repeated/continuous high nasal exposures to sulphur oxides gas or mist.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: nasal pain and bleeding, rhinorrhoea.
- Examinations: rhinoscopy may show nasal mucosae ulceration and perforation of the nasal septum.

Exposure assessment

- History of occupational exposure: chronic inhalation exposure to sulphuric acid mist or sulphur oxides.
- Minimum duration of exposure: few months.
- Maximum latent period: few months.

Chronic obstructive pulmonary disease (COPD), Chronic bronchiolitis obliterans, Emphysema, Pulmonary fibrosis (J68.4)

Short description of the disease

Progressive deterioration of the lower respiratory tract involving bronchial, bronchiolar, alveolar, and interstitial regions have been observed in subjects chronically exposed to sulphur oxides or as a consequence of a single high exposure. In the most severe cases permanent respiratory disability can occur.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: the presence of persistent respiratory symptoms and not fully reversible airflow limitation, worsening dyspnoea, productive cough, asthenia, cyanosis.
- Examinations:
  - Wheezing and chest tightness on auscultation.
  - Peribronchial thickening at chest X-ray and computed tomography (CT).
  - Airflow obstruction at pulmonary function tests; in addition, impaired CO diffusion can be observed.
  - Increase in the arterial CO_2 concentration at arterial blood gas test.

Exposure assessment

- History of occupational exposure: evidence of chronic inhalation of (or a single high exposure to) sulphuric acid mist or sulphur oxides.
- Minimum duration of exposure: one year.
- Maximum latent period: 18 months.

1.1.37 Diseases caused by sulphur oxides — ICD Code T59.1, T59.8 +Z57

Key actions for prevention

Sulphur oxides are common industrial and environmental pollutants, and the use of sulphur dioxide and sulphur trioxide cannot be easily replaced in most of their current applications.

The use of sulphur dioxide as a refrigerant in industrial cooling, such as in food processing, has been largely superseded by other non toxic compounds, despite the fact that its offensive and well recognizable smell flags leaks in the circuits. The use of sulphur dioxide as a vulcanization accelerant for natural rubber has been mostly superseded by that of synthetic chemicals.

Since most of the occupational exposure occurs through contact of mainly the eye, the respiratory tract and the skin with airborne sulphur oxides, most of the preventive measures are aimed at capturing emissions at the source; the use of personal protective devices such as goggles and respirators is indicated only as a last resort. The group of experts considered that the following limits of exposure of workplace atmospheric concentrations have been observed to provide a reasonable level of protection for workers' health and to be used in a number of countries:

- Sulphur dioxide: 0.25 ppm as STEL.
- Sulfuric acid: 0.2 mg/m^3 as 8hr TWA.

Further reading

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3. Balmes JR; Frank E. Speizer FE. Chapter 256. Occupational and Environmental Lung Disease. Outdoor Air pollution. In: Harrison's Principles of Internal Medicine.18th Edition.
4. Baxter PJ. Gases. Chapter 39 in Hunter's Diseases of Occupations. Editors Baxter PJ, Aw T-C, Cockcroft A, Durrington P, Harrington JM. Tenth Edition, London: Hodder Arnold, 2010, P 258, 263- 4, 287- 8.
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6. European Commission: Information notices on occupational diseases: a guide to diagnosis (2009). Office for official publication for the European communities, Luxemburg. Annex I 113.01 and 113.02, Sulphuric acid and sulphur oxides. P 58-60.
7. Glazer CS. Section IX. Occupational & Environmental Lung Disease. Chapter 35. Acute Inhalational Injury. In: Hanley ME, Welsh CH, eds. CURRENT Diagnosis & Treatment in Pulmonary Medicine. New York: McGraw-Hill; 2003.
8. ILO Encyclopaedia of occupational health and safety, 4th edition; available at: https://iloencyclopaedia.org/. Last accessed: October 2021.
9. Al Zabadi H, Nazzal Y. Evaluation of Darkroom disease's symptoms among radiographers in the West Bank hospitals: a cross-sectional study in Palestine. J Occup Med Toxicol. 2014;9:15. doi: 10.1186/1745-6673-9-15.

For the chemical entities listed below an entry exists in the collection of International Chemical Safety Cards (ICSC) hosted in the ILO website

Name	Synonyms	ICSC
Nickel (II) sulphate	Nickelous sulphate; Nickel(2+)	0063
Sulphur dioxide	Sulfurous oxide; Sulfurous anhydride; Sulfur oxide	0074
Dimethyl sulfate	Sulfuric acid dimethyl ester; Dimethyl monosulfate; DMS	0148
Sulphuryl chloride	Sulfuric oxychloride; Sulphuryl dichloride; Sulfonyl chloride; Sulfur chloride oxide	0198
Manganese sulphate monohydrate	Manganous sulphate monohydrate	0290
Sulfamic acid	Amidosulfonic acid; midosulfuric acid; Sulfamidic acid	0328
Thallium sulfate	Thallium (I) sulphate; Dithallium sulphate; Thallous sulphate	0336
Sulfuric acid , concentrated (> 51% and < 100%)	Sulfuric acid; Oil of vitriol	0362
Diethyl sulfate	Sulfuric acid diethyl ester; DES	0570
Copper sulfate (anhydrous)	Cupric sulphate; Sulfuric acid, copper(2+) salt(1:1)	0751

Name	Synonyms	ICSC
p-Toluenesulfonic acid (max. 5% Sulfuric acid)	4-Methylbenzenesulfonic acid; p-Methylphenylsulfonic acid; Tosic acid; Toluene-4-sulfonic acid	0773
Barium sulfate	Barium sulphate; Blanc fixe; Artificial barite	0827
Hydroxylamine hydrosulphate	Hydroxylammonium hydrogensulfate; Di(hydroxylamine)sulphate; Hydroxylamine sulfate (1:1); Hydroxylamine sulfate	0897
Bis(hydroxylamine) sulfate	Oxammoniumsulphate	0898
Sodium sulfate	Sodium sulfate anhydrous; Disodium sulfate, Sulfuric acid disodium salt	0952
Mercuric sulfate	Mercury (II) sulphate; Mercuric bisulphate	0982
Chlorosulfonic acid	Sulfuric chlorohydrin; Chlorosulfuric acid	1039
Cobalt sulfate	Cobaltous sulphate; Cobalt (II) sulphate; Sulfuric acid, cobalt (2+) salt	1127
Sodium dodecylbenzene sulphonate		1189
Aluminium sulfate	Aluminium sulphate; Aluminium trisulfate; Dialuminium trisulfate; Alum	1191
Magnesium sulfate	Magnesium sulphate	1197
Sodium sulfite	Sodium sulphite; Sulfurous acid, disodium salt; Disodium sulfite	1200
Sulfur trioxide	Sulphuric (acid) anhydride; Sulfuric oxide	1202
Gypsum	Calcium sulfate dihydrate	1215
Ammmonium bisulfite	Sulfurous acid, monoammonium salt; Ammonium hydrogen sulphite	1254
4,4'-Oxybis(benzenesulphonyl hydrazide)	Benzenesulfonic acid, 4,4’-oxybis-, dihydrazide; 4,4’-Oxydi(benzenesulphonohydrazide); Diphenyloxide 4,4’-sulphonylhydrazide; p,p’-Oxybisbenzenesulphonyl hydrazide	1285
Chromium hydroxide sulfate	Basic Chrome Sulphate; Monobasic chromium sulphate	1309
Cadmium sulfate	Cadmium sulphate	1318
Beryllium sulfate	Beryllium sulphate	1351
Cobalt (II) sulfate heptahydrate		1396
Sulfuryl fluoride	Sulfuryl difluoride; Sulfuric oxyfluoride	1402
Copper (II) sulfate, pentahydrate	Sulfuric acid, copper(2+) salt, pentahydrate	1416
Oleum	Sulfuric acid, fuming; Disulphuric acid; Dithionic acid; Pyrosulfuric acid; Mixture of sulfuric acid and sulfur trioxide	1447
Potassium sulfate	Sulfuric acid dipotassium salt; Dipotassium sulfate	1451
Dodecyl benzenesulfonic acid	Benzenesulfonic acid, dodecyl; Laurylbenzenesulfonic acid	1470
p-(Methylamino)phenol sulfate	bis(4-Hydroxy-N-methylanilinium) sulfate; Metol; 4-(Methylamino) phenol sulfate	1528
2,5-Toluenediamine sulfate (1:1)	2-Methyl-p-phenylenediamine sulfate; 2,5-Diaminotoluene sulfate	1544
Ammonium sulfamate	Sulfamic acid, monoammonium salt; Ammonium amidosulfonate; Ammonium sulfamidate	1555
Potassium hydrogen sulfate	Potassium acid sulfate; Sulfuric acid monopotassium salt; Monopotassium sulfate; Potassium bisulfate	1585
Calcium sulfate (anhydrous)	Sulfuric acid, calcium salt (1:1)	1589
Petroleum sulfonate, sodium salt	Sodium petroleum sulfonate; Sulfonic acids, petroleum, sodium salt; Petroleum sulfonic acid, sodium salt	1598
C10-13 Alkylbenzenesulfonic acid, sodium salt	Sodium alkylbenzene sulfonate; Linear alkylbenzene sulfonic acid sodium salt; Linear alkylbenzene sodium sulfonate; LAS	1602
Strontium sulfate	Celestite; Sulfuric acid, strontium salt (1:1); Celestine; Strontium sulphate	1696
Zinc sulfate	Zinc sulfate (anhydrous); Sulfuric acid, zinc salt (1:1); Zinc sulphate	1698

▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
1.1.37	Acute/chronic diseases caused by sulphur oxides	T59.1, T59.8	NE61&XM2598
1.1.37	Mucous membranes irritation	J68	CA81.Y
1.1.37	Acute chemical pneumonitis and bronchitis	J68.0	CA81.0
1.1.37	Upper respiratory inflammation	J68.2	CA81.2
1.1.37	Pulmonary oedema	J68.1	CA81.1
1.1.37	Reactive airways dysfunction syndrome (RADS)	J68.3	CA81.Y
1.1.37	Irritant-induced acute occupational asthma	J68.3	CA81.Y
1.1.37	Burns and corrosions of eye and adnexa	T26.0-T26.1, T26.5-T26.6	NE00
1.1.37	Conjunctivitis	H10.2	9A60.Z
1.1.37	Keratoconjunctivitis	H16.2	9A7Y, 9A60.Y
1.1.37	Corneal ulcer	H16.0	9A78.8
1.1.37	Burns and corrosion of respiratory tract	T27	NE01
1.1.37	Burns and corrosions of other internal organs	T28	NE02
1.1.37	Burns and corrosions of external body surface	T20-T25	ND9Z
1.1.37	Acute irritant contact dermatitis	L24	EK02
1.1.37	Darkroom disease	J68.2, H16.2	CA81.2, 9A7Z
1.1.37	Chronic skin and mucous membranes irritation	L24	EK02
1.1.37	Nose septal ulceration	J34.0	CA0K.Y
1.1.37	Chronic obstructive pulmonary disease (COPD), Chronic bronchiolitis obliterans, Emphysema, Pulmonary fibrosis	J68.4	CA22.Z
	Occupational exposure to risk factors	Z57	QD84.Y

1.1.38 Diseases caused by organic solvents	ICD Code T52 +Z57
General characteristics of the causal agent	Organic solvents are a common designation for a large group of more than 200 chemical compounds capable of dissolving fats, oils, waxes, resins, rubber, asphalt, cellulose filaments, plastic materials and organic polymers. Many solvents are used as chemical intermediates, fuels, and as components of a wide range of products. Technical solvents are often complex mixtures of chemical substances of a similar (e.g. white or mineral spirit, kerosene, and naphtha) or of a different nature. At room temperature, technical solvents are usually fluid (i.e., liquids with different rheological properties) with boiling points below 200-250°C, and evaporate easily. From the point of view of their chemical nature, organic solvents include aliphatic, aromatic or chlorinated hydrocarbons, alcohols, ethers, esters, ketones, and other compounds such as carbon disulphide and nitro-aliphatic compounds. Common examples of solvents include: • acetone • petroleum spirits • dichloromethane • 1,1,1 trichloroethane • hexane • toluene • methanol • trichloroethylene • methyl ethyl ketone • xylene • perchloroethylene • white spirit Industrial solvents are often mixtures of several individual substances and can be found under a variety of trade names.
Occupational exposures	The main technological role of organic solvents is to disperse useful substances (solutes, such as colouring, waterproofing, adhesive materials) so that they can be deposited onto large amounts, by surface or volume, of substrate materials such as metals, wood, and other structural materials and items, textiles, or elastomers, to impart some desirable properties, such as colour, water resistance, and adhesiveness. Another major role of solvents is to remove selectively from materials and items some undesired deposited substance such as dirt, debris, residues of technical processing by solubilisation or by easing mechanical removal. Solvents are widely used in chemical synthesis and manufacturing. Therefore, large groups of workers in a great variety of professions are exposed daily or frequently to organic solvents. In general, the main activities are the production of paints, lacquers, adhesives and printing inks; the production and lamination of reinforced plastic; rubber and plastics manufacturing; the production of footwear; industrial painting, glueing (of metal, wood, polymer items, brick and mortar buildings), floor laying and lacquering; cleaning and degreasing, paint removal; dry cleaning; industrial printing; production, maintenance cleaning and repairing of vehicles and machines; laboratory and cleaning work; pesticides and toiletries. Hence, industries where solvents are most likely used are: • Engineering • Construction • Chemicals • Printing • Rubber • Plastics • Footwear • Textiles • Foodstuff • Woodworking • Dry cleaning • Ink manufacture • Pharmaceutical manufacture • Paint manufacture

1.1.38 Diseases caused by organic solvents	ICD Code T52 +Z57
	Examples of industrial activities where some organic solvents are widely used are summarised in Table 1 at the end of the item. Some classes of chemical compounds are used as solvents because of specific properties. For example, chlorinated hydrocarbon solvents do not ignite and are therefore used where a fire hazard exists; on the other hand, some oxygenated solvents, such as alcohols and alkyl ethers, are miscible with water and are useful to enhance the compatibility of organic substances with wettable substrates. A class of compounds with similar properties to solvents are plasticizers, which are used to impart useful technological properties to industrial polymers. Gasoline and diesel fuel share several properties and risks of occupational exposure with hydrocarbon solvents. The presence of organic solvents in products for household use and for personal body care, e.g., nail lacquers and lacquer solvents, gives a risk of dermal exposure in hairdressers and beauticians, who often work in the informal sector, and may work during pregnancy and breastfeeding. In industrial and developing countries, organic solvents are a major hygiene problem at many workplaces, even though the quantities and the hazard profiles of the materials used have declined in some occupations, as a consequence of increasing regulation, hygiene improvements and substitution of work practices.
Toxicological profile, main health effects and diagnostic criteria	
Short toxicological profile	Since solvents are volatile, the main route of intake is usually inhalation, especially when the workplace is poorly ventilated and warm. An increase in physical activity increases the respiratory uptake of solvents. Absorption through the skin may contribute significantly to exposure, particularly when the skin is not intact due to lesions (e.g. eczema). This is especially the case for solvents such as glycol ethers, as their vapour pressure is low. Eye contact with liquid solvents and their vapours represents a possible route of exposure, with subsequent irritation and inflammation. Exposure via ingestion of contaminated food and drinks, as well as through contaminated cigarettes, is also possible. People have accidentally drunk solvents that have been kept in old, unlabelled drinking containers. Most organic solvents accumulate in the fatty organs of the body, such as in body fat, bone marrow, liver, and brain. The mechanisms of toxicity of the different solvents are as diverse as their chemical identities. For many organic solvents, the toxicity can be linked to the physicochemical properties of the solvent molecule *per se*, to the toxicity of metabolic products, or to a combination of both mechanisms. Technical mixtures of industrial solvents can contain several different compounds, each showing its own toxic behaviour. Compounds can feature combined or synergistic effects with other components of the solvent mixture, with other chemical compounds introduced in the body (e.g. components of food, ethyl alcohol from drinks, pharmaceutical drugs), with other chemical agents present in the work environment, and with physical factors such as a high workload, extreme temperatures, high or low air pressure, or underlying clinical conditions of the exposed workers (especially liver and kidney disorders). In general, the following mechanisms are most likely involved in the pathogenesis of health effects due to organic solvents: • Blocking of key enzymes in several metabolic pathways, such as in the catabolism of glucose, with subsequent reduction of the energy available for cellular needs. • Impairment or reduction of the efficiency of metabolic energy generation at mitochondrial level. • Alteration of the structure and permeability of cellular membranes, leading to impairment of ion channel function and neurotransmitter cascades, and to slowing of axonal flow. The main effects of solvents are irritation of the skin, eyes and lungs, headache, nausea, dizziness and lightheadedness. Exposure can impair coordination, and this can make people more prone to accidents. People may lose concentration for important or difficult tasks and they may react more slowly to dangerous situations. The effect can vary from person to person and will generally be made worse by drinking alcohol. Very high exposures can cause unconsciousness and even death, for instance, where adhesives are used in unventilated confined spaces or where there are serious spillages. Other possible effects on health vary according to which solvent workers are exposed to. Long-term health effects from repeated lowlevel exposure to particular solvents may include dermatitis, damage to the central nervous system, the kidneys, the liver or the blood, or, in the case of benzene, even cancer. Further information on the chemical and biochemical features that characterise the toxicity of specific classes of organic solvents are reported in dedicated items, viz: carbon disulphide (1.1.10), halogen derivatives of aliphatic or aromatic hydrocarbons (1.1.11), benzene or its homologues (1.1.12), alcohols, glycols or ketones (1.1.15), and hexane (1.1.21).

1.1.38 Diseases caused by organic solvents — ICD Code T52 +Z57

Name of the diseases and ICD code: **Acute diseases caused by organic solvents** *(Specific disease code)* **+T52 +Z57**

Respiratory tract irritation (J68), Acute chemical pneumonitis and bronchitis (J68.0), Upper respiratory inflammation (J68.2), Burns and corrosions of eye and adnexa (T26.0-T26.1, T26.5-T26.6), Conjunctivitis (H10.2), Corneal ulcer (H16.0), Irritant contact dermatitis (L24)

Short description of the disease

Irritant effects on the mucous membranes, eyes, skin and respiratory system are common to most solvents. Direct contact or exposure to vapours at high concentrations can cause irritation of conjunctivae and the respiratory tract. Prolonged or repeated skin contact may result in irritant dermatitis.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms:
  - Exposure to inhaled high concentrations of vapours of organic solvents can lead to symptoms of lung and upper respiratory tract irritation, including sneezing, rhinorrhoea, redness of the throat, epistaxis, nasal itching and soreness, coughing, wheezing, inspiratory pain, bronchitis, pneumonitis, decreased pulmonary function, bronchospasm, and asthmatic attacks which may recur on subsequent exposure.
  - Direct skin contact can produce dryness, erythema, fissuring, papules, scaling, small vesicles, and swelling. For further details on the clinical features of irritant contact dermatitis, refer to item 2.2.2.
  - In case of contact with the eyes and adnexa, solvents (or their vapours) may produce a local inflammation (conjunctivitis) up to corneal ulcers, with alteration, reduction or loss of vision.
- Examinations:
  - Chest X-rays may reveal a picture of pneumonitis or bronchitis, with increased bronchovascular markings.
  - Pulmonary function tests may show an acute obstructive picture.
  - An ophthalmic examination should be performed, including visual acuity and slit lamp inspection of the cornea. Corneal ulceration may be seen on corneal examination.

Exposure assessment

- History of occupational exposure: confirmed occupational exposure to high concentrations of organic solvents via inhalation or skin and eye contact and, when available, workplace air monitoring and detection of the compounds or their metabolites in biological fluids (some examples of target chemicals for biological monitoring are reported in Table 3 at the end of the item).
- Minimum duration of exposure: few minutes.
- Maximum latent period: 48 hours.

Narcotic syndrome (T52)

Short description of the disease

Mild exposure to solvent vapours may lead to central nervous system symptoms (i.e., headache, lightheadedness and disturbances of equilibrium at the end of a working day), which usually disappear during exposure free periods. Severe intoxications occur mainly in accidental situations with exposure to very high levels of solvent vapours.

Diagnostic criteria

Clinical manifestations

The symptoms of narcotic syndrome include headache, dizziness, nausea, drowsiness, weakness, confusion, unconsciousness, respiratory depression, memory loss, nausea, hearing and colour vision loss and, in the most severe cases, coma.

Exposure assessment

- History of occupational exposure: confirmed occupational exposure to high concentrations of organic solvents via inhalation or skin and eye contact and, when available, workplace air monitoring and detection of the compounds or their metabolites in biological fluids (some examples of target chemicals for biological monitoring are reported in Table 3 at the end of the item).
- Minimum duration of exposure: few minutes.
- Maximum latent period: 48 hours.

1.1.38 Diseases caused by organic solvents ICD Code T52 +Z57

Allergic contact dermatitis (L23)

Formulations of some organic solvents may contain potential sensitizers, and can cause allergic contact dermatitis. This is the case, for example, with solvents containing oil of turpentine, used in the perfume industry and ceramic decoration. In general, solvents damage the skin barrier and enhance the absorption presentation of haptens that can trigger sensitization.

For further details on clinical features and exposure assessment criteria of allergic contact dermatitis, refer to item 2.2.1.

Name of the diseases and ICD code: **Chronic diseases caused by organic solvents**
(Specific disease code) **+T52 +Z57**

Toxic encephalopathy (G92)

Short description of the disease

Exposure to organic solvents may cause acute and chronic adverse effects in the central nervous system. Acute solvent-induced encephalopathy with permanent morbidity may develop after massive intoxication. On the other hand, chronic solvent-induced encephalopathy, also known as chronic toxic encephalopathy or organic brain syndrome due to chronic exposure to solvents, may develop, usually insidiously after long-term exposure, often decades, even at not particularly high exposure levels. Chronic solvent encephalopathy is characterized by irreversible impairment of memory, concentration, and mood, accompanied by fatigue and loss of initiative. Attention, learning, psychomotor performance and verbal and non-verbal reasoning, as well as concept formation, can be affected. Loss of colour vision and alterations in visual perception may be part of the effects related to chronic exposure to organic solvents, despite eyes and other visual functions being normal in these subjects.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms:
  - Acute encephalopathy is characterised by narcosis (i.e., headache, lightheadedness and disturbances of equilibrium at the end of a working day), followed by convulsions and coma in the most severe cases.
  - If exposure is not avoided, the disease progresses through three levels of increasing severity: from *organic affective syndrome* (characterized by depression, irritability, loss of interest in daily activities), to *mild chronic toxic encephalopathy* (characterized by fatigue, mood disturbances, memory and attention deficits, together with impairment of psychomotor functions such as speed and dexterity), up to *severe chronic toxic encephalopathy* (characterized by loss of intellectual ability interfering with occupational or social functioning, as well as by impairment of memory, abstract thinking and judgment). Third-level lesions become permanent, although the exposure ceases, and the affected person usually remains severely disabled.
- Examinations:
  - Neuropsychological assessment may show neurobehavioral impairment and should be conducted through the use of tests exploring the following functions: verbal and visual memory, attention, psychomotor speed, visual analysis, construction, abstraction, and primary intellectual abilities (some examples of specialized behavioural tests to measure neurotoxicity are reported in Table 2 at the end of the item).
  - Electroencephalography may show non specific abnormalities (such as diffuse slowing).
  - Neuroimaging investigations may show mild cerebral atrophy.

Differential diagnosis

Depression and other psychiatric disorders, sleep and neurodegenerative disorders, vascular disorders of the brain, neoplasms such as brain tumours, metabolic causes such as thyroid disorders and avitaminosis, or even traumatic brain disorders.

Exposure assessment

- History of occupational exposure: confirmed occupational exposure to organic solvents via inhalation or skin contact and, when available, workplace air monitoring and detection of the compounds or their metabolites in biological fluids.
- Minimum duration of exposure: 10 years.
- Maximum latent period: not applicable.

1.1.38 Diseases caused by organic solvents — ICD Code T52 +Z57

Acute toxic renal failure with tubular necrosis (N17.0), Chronic toxic renal failure (N18.9)

Short description of the disease

Long-term exposure to organic solvents can cause progressive renal fibrosis and renal failure as well as glomerulonephritis, in particular of membranous type. Among solvents often associated with nephrotoxicity are halogenated hydrocarbons, i.e., carbon tetrachloride, chloroform, trichloroethylene and tetrachloroethylene (see also item 1.1.11). Pre-existing conditions potentially affecting the urinary system such as IgA nephropathy and diabetes cause increased vulnerability to nephrotoxic effects of organic solvents.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms:
  - When present, symptoms are often due to uraemia, which can cause nausea, vomiting, malaise, and altered sensorium.
  - In chronic, more insidious onset, general symptoms of uraemia may include fatigue and weakness, anorexia, nausea, vomiting, and a metallic taste in the mouth are common. Other features may include irritability, memory impairment, insomnia, restless legs, paresthaesias, and twitching. Generalized pruritus without rash may occur.
  - Decreased libido and menstrual irregularities are common, as are hypertension and altered fluid homeostasis.
- Examinations:
  - Elevated blood urea nitrogen and serum creatinine levels are present; creatinine clearance is usually reduced.
  - At the beginning of the disease, presence in the urine of low molecular weight proteins such as beta-2-microglobulin and retinol binding proteins can be detected (tubular proteinuria), as well as N-acetylglucosaminidase (NAG) and gamma-glutamyl transpeptidase (GGT) (enzymuria).
  - When the disease progresses, red blood cells, white/tubular epithelial cells and albumin can be found in urine, while high circulating anti-laminin antibodies are detected in serum.
  - Ultrasound evaluation may show renal atrophy.
  - Renal biopsy may uncover a histopathological picture of glomerulonephritis.

Exposure assessment

- History of occupational exposure: confirmed occupational exposure to organic solvents via inhalation or skin contact and, when available, workplace air monitoring and detection of the compounds or their metabolites in biological fluids.
- Minimum duration of exposure: one year.
- Maximum latent period: 24 months.

Toxic liver disease (K71), Liver toxicity (impairment, functional) (K72.9)

Short description of the disease

Exposure to organic solvents such as halogenated derivatives of hydrocarbons (i.e., carbon tetrachloride, trichloromethane, trichloroethane, tetrachloroethane, trichloroethylene, tetrachloroethylene), or N,N-dimethyl formamide may cause acute and chronic hepatic diseases.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: patients usually complain of digestive disturbances, abdominal pain, and fatigue.
- Examinations:
  - At earlier stages, serum transaminase concentration increases; when the disease progresses, an increase of alkaline phosphatase and serum bilirubin can be observed.
  - Ultrasound examination may show steatosis.
  - At liver biopsy, a variety of histological changes can be observed, including acute inflammation (hepatitis), steatosis (fatty liver), fibrosis, and centrilobular necrosis.

Exposure assessment

- History of occupational exposure: confirmed occupational exposure to organic solvents via inhalation or skin contact and, when available, workplace air monitoring and detection of the compounds or their metabolites in biological fluids (some examples of target chemicals for biological monitoring are reported in Table 3 at the end of the item).
- Minimum duration of exposure: few days.
- Maximum latent period: one year.

1.1.38 Diseases caused by organic solvents ICD Code T52 +Z57

Bone marrow depression (aplastic anaemia) (D61.9)

Short description of the disease

Aplastic anaemia can occur following high exposure to benzene. Prolonged exposure to ethylene glycol ethers and benzene may cause macrocytic anaemia and granulocytopaenia. Chronic exposure to some alkoxyalcohols causes haemolysis. For a detailed description of non-carcinogenic and carcinogenic haematopoietic effects of benzene, refer to items 1.1.12 and 3.1.8, respectively.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: main complaints are dyspnoea on exertion, pallor, and increased frequency of infections.
- Examinations:
  - At physical examination, skin and mucous pallor, sometimes with jaundice, and lymphadenopathy can be observed.
  - Ultrasound examination may show splenomegaly.
  - Full blood count may show anaemia and increased concentration of reticulocytes.
  - Bone marrow aspiration can show aplasia.

Exposure assessment

- History of occupational exposure: confirmed prolonged or repeated occupational exposure to organic solvents via inhalation or skin contact and, when available, workplace air monitoring and detection of the compounds or their metabolites in biological fluids (some examples of target chemicals for biological monitoring are reported in Table 3 at the end of the item).
- Minimum duration of exposure: weeks.
- Maximum latent period: three years.

Infertility (N46, N97.0), Congenital malformation syndromes (Q86.8)

Short description of the disease

High-level exposure to organic solvents in the workplace may cause reduced semen quality and disruption of endocrine homeostasis. In addition, reports have suggested that compounds such as carbon disulfide and some of the alkoxyalcohols might represent a hazard for pregnant workers.

Exposure to ethylene glycol monomethyl and monoethyl ethers may affect fertility by inhibiting spermatogenesis. Female fertility can also be affected. Both ethers have been associated with increased risk of miscarriage and exposure to the monomethyl ether has been related to increased risk of congenital malformations (for further details, refer to item 1.1.10).

Diagnostic criteria

Clinical manifestations

- Signs and symptoms:
  - Azoospermia or hypospermia in workers exposed to carbon disulfide, alkoxyalcohols, ethylene glycol monomethyl and monoethyl ethers.
  - Evidence of malformations affecting children born to pregnant workers exposed to ethylene glycol monomethyl ether during pregnancy.
- Examinations: azoospermia, hypospermia or spermatocyte abnormalities.

Exposure assessment

- History of occupational exposure: confirmed prolonged or repeated occupational exposure to organic solvents via inhalation or skin contact and, when available, workplace air monitoring and detection of the compounds or their metabolites in biological fluids (some examples of target chemicals for biological monitoring are reported in Table 3 at the end of the item).
- Minimum duration of exposure: prolonged and repeated exposure (occurring during pregnancy in case of congenital malformations).
- Maximum latent period: nine months for birth defects; 12 months for other effects.

1.1.38 Diseases caused by organic solvents ICD Code T52 +Z57

Ototoxic hearing loss (H91.0)

Short description of the disease

Prolonged exposure to organic solvents can induce ototoxicity. Noise-induced hearing loss may be potentiated and the incidence of the disease can be higher than expected in workers that are exposed to both noise and solvents.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: the main symptom reported by the workers is hearing loss. Other symptoms include difficulties in following conversations in noisy environments (so called "cocktail effect") and headache.
- Examinations:
  - Otoscopy: in neuronal hearing loss, otoscopy is usually normal.
  - Rinne test: negative (i.e., neuronal rather than conductive hearing loss).
  - Weber test: does not lateralise and indicates bilateral hearing loss.
  - Audiometry: sensorineural bilateral deficit in the frequency range 4,000-6,000 Hz and subsequently involving other frequencies.

Exposure assessment

- History of occupational exposure: confirmed prolonged or repeated occupational exposure to organic solvents via inhalation or skin contact (with common concurrent exposure to noise) and, when available, workplace air monitoring and detection of the compounds or their metabolites in biological fluids (some examples of target chemicals for biological monitoring are reported in Table 3 at the end of the item).
- Minimum duration of exposure: few months.
- Maximum latent period: one year.

Peripheral polyneuropathy (G62.2)

Short description of the disease

Exposure to n-hexane and methyl n-butyl ketone may lead to polyneuropathy. The two solvents share a common neurotoxic metabolic compound, 2,5-hexanedione. Carbon disulfide has been associated with polyneuropathy. The clinical picture is usually characterized by symmetrical sensory or sensory-motor lesions involving distal parts of the extremities (legs in particular). The severity of the lesions increases with the dose of exposure (sometimes continuing even some months after cessation of exposure); then a slow and often incomplete recovery starts. Small myelinated and non-myelinated fibres, as well as large myelinated fibres, can be affected. High levels of exposure to trichloroethylene have been reported to be associated with cranial nerve outcomes, especially in the form of affected sensory functioning of the trigeminal nerve.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: at the beginning the worker reports weakness of the limbs and altered sensation; if the disease progresses, overt flaccid paralysis appears (typical of lower motor neuron syndrome). Symptoms of possible trigeminal nerve damage include sensation deficits, jaw weakness, and increased blink reflex latency.
- Examinations:
  - Electromyography may show different degrees of denervation.
  - Electroneurography may show impairment of nerve conduction up to denervation.
  - Nerve biopsy may show nerve lesions and denervation.

Exposure assessment

- History of occupational exposure: confirmed prolonged or repeated occupational exposure to n-hexane, methyl-n-butyl ketone, carbon disulphide, or trichloroethylene via inhalation or skin contact and, when available, workplace air monitoring and detection of the compounds or their metabolites in biological fluids, such as: n-hexane in blood and exhaled air, urinary 2-hexanol and 2,5-hexanedione; presence of carbon disulfide in blood and urine analyses, of 2-thiothiazolidine-4-carboxylic acid (TTCA) in urine and of carbon disulfide itself in the exhaled air can confirm exposure to this specific compound.
- Minimum duration of exposure: one month.
- Maximum latent period: three years.

1.1.38 Diseases caused by organic solvents — ICD Code T52 +Z57

Name of the diseases and ICD code: **Carcinogenic effects of benzene** *(Specific disease code)* **+T52.1 +Z57**

Acute myeloblastic leukaemia (C92.0)

There is sufficient evidence in humans for the carcinogenicity of benzene, which causes acute myeloid leukaemia in adults. Positive associations have been observed for non-Hodgkin lymphoma, chronic lymphoid leukaemia, multiple myeloma, chronic myeloid leukaemia, acute myeloid leukaemia in children, and cancer of the lung. There is strong evidence that benzene metabolites, acting alone or in concert, produce multiple genotoxic effects at the level of the pluripotent haematopoietic stem cell, and chromosomal changes consistent with those seen in haematopoietic cancer. IARC classified benzene as carcinogenic to humans (Group 1). For further details on the carcinogenic effects of benzene, refer to item 3.1.8.

Key actions for prevention	At workplaces, exposure to organic solvents mostly occurs through inhalation and dermal absorption. The physical (fire and explosion) and toxicological hazards posed by some industrial solvents, as well as increasing environmental regulation, has encouraged substitution with less toxic alternatives. For example, the more volatile chlorinated solvents are powerful depletors of stratospheric ozone and have been gradually phased out through international agreements. The toxicological hazards posed by industrial hydrocarbon solvents both aromatic and aliphatic, used in printing and cleaning, has encouraged substitution with substances such as limonene, which can be cheaply extracted from bulk waste material from the food and drink industry (orange peels) using environmental friendly processes. The toxicity of several industrial solvents has prompted the substitution of oil-based paints which need hydrocarbon solvents as thinners, with those formulated with polyether solvents and dispersants, which can be thinned and sprayed with water. Substitution has been encouraged in some countries, by restricting the market availability of solvents posing the greatest hazard. Enclosure of equipment and recycling of solvents in closed-circuit plants have reduced exposure. Regulation of informal workplaces can also be an important control measure. For example, dry cleaning clothes in urban environments has traditionally been a small family enterprise, with potential exposure of childbearing and breastfeeding mothers, and of children. Spent chlorinated solvents were often dumped in municipal sewage and infiltrated the ground, causing exposure through drinking groundwater and evaporation from contaminated urban soil. Restrictions on the use of solvents have encouraged centralisation of dry-cleaning facilities, that employ more efficient control measures, the nearly complete recovery of spent solvents and environmentally correct disposal of final waste. If solvent-based products are used, the following general preventive actions should be implemented: • Make sure the work area is well ventilated. • Open doors, windows, roof lights, etc. to increase ventilation and make sure that they are kept open. Local exhaust (mechanical) ventilation may be necessary in some cases. • If possible, avoid spraying solvent-based products, as this causes more vapour to get into the air than using a brush. • Store solvents in properly labelled, suitable containers. Use dispensers where possible to keep evaporation to a minimum and reduce spillage. Keep lids on containers unless contents are being poured or dipped, etc. Use sealed containers for solvent waste. Dispose of solvent-soaked rags in closed containers. • Provide workers with Safety Data Sheets - SDS (also referred to as Material Safety Data Sheets [MSDS]) for solvents. • Train workers in the handling and use of specific solvents. Training should include (but not be limited to) physical properties, health effects, routes of exposure, how to minimize exposure, personal protective equipment (PPE), first aid, prevention of spillages, and disposal. • Many solvents are flammable: take precautions to avoid fire and explosion risks; in particular, do not smoke in areas where solvents are used. Post “No Smoking” and “No Naked Flame” signs where solvents are stored. Store products containing solvents in a secure and well-ventilated area.

1.1.38 Diseases caused by organic solvents	ICD Code T52 +Z57
Key actions for prevention	If exposure cannot be adequately controlled in any other way, workers should wear personal protective equipment (PPE). They may need to wear one or more of the following: • protective overalls; • appropriate gloves that have been specially selected for use with solvents; • face shields; and • respiratory protective equipment, where ventilation does not provide adequate control. Half mask respirators fitted with the appropriate cartridge may be sufficient in many instances, but compressed airline breathing apparatus may be necessary where solvents are sprayed or when working in a confined space. Those who need to wear PPE should be trained in its proper use and in its limitations. Store the PPE in clean, dry conditions away from chemicals - a locker would be suitable. PPE should be maintained and kept clean and fit for wear. The use of PPE is the most frequently applied prevention procedure, especially when the manufacturing process involves the use of solvents for degreasing, painting and paint removal, application of glues and adhesives, and assembling of degreased mechanical parts by workers who need to act very close to the working surfaces. An important factor in the efficiency of respiratory protective equipment employing absorptive filters (such as activated carbon) is the saturation of the filters during use, that allows break through of solvent. Perception of the smell of the solvent by the user is not a reliable means of knowing whether the filter has been saturated. The relationship between safe airborne concentrations of solvents, and olfactory thresholds of detection is at best tenuous, even under controlled laboratory conditions. The sensory fatigue which occurs in real life exposures can prevent the detection of solvents, even at levels well above reported olfactory thresholds. Clothes that become heavily contaminated with solvent should be removed immediately. Overalls and contaminated personal clothing should be laundered before being re-worn. It may be necessary to first air them in a safe place to let the solvent evaporate. Good personal hygiene is very important. Facilities for washing and changing should be provided, and workers should wash their hands before eating, drinking, smoking and going to the toilet. Eating, drinking and smoking should take place away from the work area. Areas where solvents are used should be smoke-free, not only for fire and explosion risks, but also because solvents passing through a cigarette can break down to even more harmful substances such as phosgene from chlorinated hydrocarbon vapours. Industrial solvents should not be used to remove paint or grease from the skin, as this can cause the skin to become dry and inflamed. Proper cleaning materials, e.g. soap or other cleansers, should be provided and used. Anyone who appears to have been affected by solvents should be taken to fresh air immediately and given appropriate first aid treatment. Heavily contaminated clothing should be removed as soon as possible. Solvent splashes should be washed off the skin with plenty of water, and any wounds should be covered with a suitable dressings. Splashes of solvent in the eye should be treated by washing the eye with water for at least 10 minutes. In serious cases, the worker must be taken to the hospital. For most pure compounds used as industrial solvents, most industrial countries have suggested or enforced occupational exposure limits, typically expressed as time-weighted average (TWA) airborne concentrations. Only a few solvents have short-term (STEL) or ceiling limits. For exposure limits of single compounds, refer to the specific items.

1.1.38 Diseases caused by organic solvents ICD Code T52 +Z57

Further reading

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3. ILO Encyclopaedia of occupational health and safety, 4th edition; available at: https://iloencyclopaedia.org/. Last accessed: October 2021.
4. European Commission: Information notices on occupational diseases: a guide to diagnosis (2009). Office for official publication for the European communities, Luxemburg.
   a. Annex I 113.03. Carbon disulphide. P61-2.
   b. Annex I 116. Aliphatic or alicyclic hydrocarbons derived from petroleum spirit or petrol. P73-6.
   c. Annex 117. Halogenated derivates of the aliphatic or alicyclic hydrocarbons. P77-89.
   d. Annex I 119. Ethylene glycol, diethylene glycol, 1,4-butanediol and the nitrated derivatives of the glycols and of glycerol. P92-3.
   e. Annex I 121. Acetone,chloroacetone, bromoacetone, hexafluoroacetone, methyl ethyl ketone, methyl n-butyl ketone, methyl isobutyl ketone, diacetone alcohol, mesityl oxide, 2-methyl cyclohexanone. P100.
   f. Annex I 123. Organic Acids. P105-7.
   g. Annex I 126.01. Benzene or counterparts thereof (the counterparts of benzene are defined by the formula: CnH2n-6). P112-6.
   h. Annex I 126.03. Vinylbenzene and divinylbenzene. P119-120.
   i. Annex I 127. Halogenated derivatives of the aromatic hydrocarbons. P121-4.
   j. Annex I 135. Encephalopathies due to organic solvents which do not come under other headings.
   k. P150-2.
   l. Annex I 136. Polyneuropathies due to organic solvents which do not come under other headings. P153.
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▶ Table 1. Organic solvents associated with neurotoxicity

Chemical	Examples of source of exposure	Selected industries at risk	Effects*
Chlorinated hydrocarbons: trichloroethylene (TRI); 1,1,1-trichloroethane; tetra-chloroethylene	Degreasing; electroplating; painting; printing; cleaning; general and light anaesthesia	Metal industry; graphic industry; electronic industry; dry cleaners; anaesthetists	M: Unknown A: Prenarcotic symptoms C: Encephalopathy; polyneuropathy; trigeminal affection (TRI); hearing loss
Methylene chloride	Extraction, including extraction of caffeine; paint remover	Food industry; painters; graphic industry	M: Metabolism –> CO A: Prenarcotic symptoms; coma C: Encephalopathy
Methyl chloride	Refrigerator production and repair	Refrigerator production; rubber industry; plastic industry	M: Unknown A: Prenarcotic symptoms; loss of consciousness; death C: Encephalopathy
Toluene	Printing; cleaning; degreasing; electroplating; painting; spray painting	Graphic industry; electronic industry	M: Unknown A: Prenarcotic symptoms C: Encephalopathy; cerebellar dysfunction; polyneuropathy; hearing loss; visual disturbance
Xylene	Printing; synthesis of phthalic anhydride; painting; histology laboratory procedures	Graphic industry; plastic industry; histology laboratories	M: Unknown A: Prenarcotic symptoms C: Encephalopathy; visual disturbance; hearing loss
Styrene	Polymerization; moulding	Plastic industry; fibre glass production	M: Unknown A: Prenarcotic symptoms C: Encephalopathy; polyneuropathy; hearing loss
Hexacarbons: n-hexane; methyl butyl ketone (MBK); methyl ethyl ketone (MEK)	Gluing; printing; plastic coating; painting; extraction	Leather and shoe industry; graphic industry; painter; laboratories	M: Impairment of axonal transport A: Prenarcotic C: Polyneuropathy; encephalopathy
Various solvents: Freon 113	Refrigerator production and repair; dry cleaning; degreasing	Refrigerator production; metal industry; electronic industry; dry cleaning	M: Unknown A: Mild prenarcotic symptoms C: Encephalopathy
Diethylether; halothane	General anaesthetics (nurses; doctors)	Hospitals; clinics	M: Unknown A: Prenarcotic symptoms C: Encephalopathy
Carbon disulphide	Production of rubber and viscose rayon	Rubber and viscose rayon industries	M: Impaired axonal transport and enzyme activity is likely C: Peripheral neuropathy; encephalopathy; headache; vertigo; gastrointestinal disturbances
Mixtures: white spirit and thinner	Painting; degreasing; cleaning; printing; impregnation; surface treatment	Metal industry; graphic industry; wood industry; painters	M: Unknown A: Prenarcotic symptoms C: Encephalopathy

* M: mechanism; A: acute effects; C: chronic effects. Neuropathy: dysfunction of motor and sensory peripheral nerve fibres. Encephalopathy: brain dysfunction due to generalized impairment of the brain.

Adapted from the ILO Encylopaedia of occupational health and safety, 4th edition.

▶ Table 2. Examples of specialized behavioural tests to measure neurotoxicity

Function	Procedure	Representative agents
Motor		
Weakness	Grip strength, Swimming endurance, Suspension rod, Discriminative motor function, Hind limb splay	n-Hexane, Methylbutylketone
Sensory		
Auditory	Discriminant conditioning, reflex modification	Toluene
Cognitive		
Instrumental conditioning	One-way avoidance, Two-way avoidance, Y-maze avoidance, Biel water maze, Morris water maze, Radial arm maze, Delayed matching to sample, Repeated acquisition, Visual discrimination learning	Styrene

Adapted from: EPA 1998. https://goo.gl/exheFR (Many of these tests in animals have been designed to assess neural functions in humans using similar testing procedures.)

▶ Table 3. Some examples of target chemicals for biological monitoring and sampling time

Solvent	Target chemical	Urine/blood	Sampling time*
Carbon disulphide	2-Thiothiazolidine-4-carboxylicacid	Urine	Th F
N,N-Dimethyl-formamide	N-Methylformamide	Urine	M Tu W Th F
2-Ethoxyethanol and its acetate	Ethoxyacetic acid	Urine	Th F (end of last work-shift)
Hexane	2,4-Hexanedione Hexane	Urine Blood	M Tu W Th F confirmation of exposure
Methanol	Methanol	Urine	M Tu W Th F
Styrene	Mandelic acid Phenylglyoxylic acid Styrene	Urine Urine Blood	Th F Th F confirmation of exposure
Toluene	Hippuric acid o-Cresol Toluene Toluene	Urine Urine Blood Urine	Tu W Th F Tu W Th F confirmation of exposure Tu W Th F
Trichloroethylene	Trichloroacetic acid (TCA) Total trichloro compounds (sum of TCA and free and conjugated trichloroethanol) Trichloroethylene	Urine Urine Blood	Th F Th F confirmation of exposure
Xylenes**	Methylhippuric acids Xylenes	Urine Blood	Tu W Th F Tu W Th F

* End of workshift unless otherwise noted: days of week indicate preferred sampling days assuming a traditional 5 day work week.

** Three isomers, either separately or in any combination.

Adapted from: WHO, Biological Monitoring of Chemical Exposure in the Workplace – Guidelines, 1996 (https://goo.gl/4dmuuh).

For the chemical entities listed below an entry exists in the collection of International Chemical Safety Cards (ICSC) hosted in the ILO website

Name	Synonyms	ICSC
Aniline	Benzeneamine; Aminobenzene; Phenylamine	0011
Benzene	Cyclohexatriene; Benzol	0015
Carbon tetrachloride	Tetrachloromethane; Tetrachlorocarbon; Tetra	0024
Chloroform	Trichloromethane; Methane trichloride; Formyl trichloride	0027
1,4-Dioxane	1,4-Diethylene dioxide; 1,4-Diethyleneoxide	0041
Ethanol	Ethyl alcohol	0044
Methanol	Methyl alcohol; Carbinol Wood alcohol	0057
Dichloromethane	Methylene chloride; DCM	0058
Ethylene glycol monoethyl ether	Cellosolve, EGEE, 2-Ethoxyethanol; Monoethyl glycol ether; Oxitol	0060
Ethylene glycol monomethyl ether	2-Methoxyethanol; Monomethyl glycol ether; Methyl oxitol; EGME; Methyl cellosolve	0061
Toluene	Methylbenzene; Toluol; Phenylmethane	0078
1,1,1-Trichloroethane	Methyl chloroform; Methyltrichloromethane; alpha-Trichloroethane	0079
1,1,2-Trichloroethane	Vinyl trichloride; beta-Trichloroethane	0080
m-Xylene	meta-Xylene; 1,3-Dimethylbenzene; m-Xylol	0085
Acetone	2-Propanone; Dimethyl ketone; Methyl ketone	0087
Acetonitrile	Methyl cyanide; Cyanomethane; Ethanenitrile; Methanecarbonitrile	0088
1-Butanol	n-Butanol, n-Butyl alcohol, Propyl carbinol, Butan-1-ol, Butyl alcohol	0111
Cyclohexane	Hexahydrobenzene; Hexamethylene; Hexanaphthene	0242
n-Hexane	Hexyl hydride	0279
Hydrazine	Diamide, Diamine; Nitrogen hydride	0281
Piperidine	Hexahydropyridine; Azacyclohexane; Pentameth yleneimine	0317
Pyridine	Azine; Azabenzene	0323
Diethyl ether	Ethyl ether; Ethyl oxide; Ether	0355
Stoddard solvent	White spirit	0361
Acetic acid	Glacial acetic acid; Ethanoic acid; Ethylic acid; Methanecarboxylic acid	0363
Ethyl acetate	Acetic acid; Ethyl ester Acetic ether	0367
Dimethyl ether	Methyl ether; Oxybismethane; Wood ether; Methoxymethane	0454
n,n-Dimethylformamide	Dimethylformamide; DMF; DMFA; N-Formyldimethylamine	0457
Dimethyl sulphoxide	Methyl sulphoxide; DMSO	0459
Formic acid	Hydrogen carboxylic acid; Methanoic acid; Aminic acid; Formylic acid	0485
Isobutyl acetate	2-Methylpropyl acetate; 2-Methyl-1-propyl acetate; Acetic acid; 2-methylpropyl ester; beta-Methylpropyl ethanoate	0494
n-Pentane	Amyl hydride	0534
1-Propanol	Propyl alcohol; Propan-1-ol	0553
Isopropyl alcohol	2-Propanol; Propan-2-ol; Isopropanol; Dimethyl carbinol	0554
Tetrahydrofuran	Tetramethylene oxide; Diethylene oxide; 4-Epoxybutane; Oxacyclopentane	0578
Isoheptane	2-Methylhexane	0658
sec-Butyl acetate	1-Methylpropyl acetate; Acetic acid; 2-butyl ester	0840
Hexachlorobutadiene	1,1,2,3,4,4-Hexachloro-1,3-butadiene; Perchloro-butadiene	0896
Diisopropyl ether	Isopropyl ether, 2,2'-Oxybispropane, 2-Isopropoxypropane	0906
1,2,4-Trichlorobenzene	1,2,4-Trichlorobenzol; unsym-Trichlorobenzene	1049
1-Nitropropane	1-NP	1050
Turpentine	Turpentine, oil; Spirits of turpentine; Oil of turpentine; Steam distilled turpentine; Gum spirits; Wood turpentine	1063

Name	Synonyms	ICSC
Hexamethylenetetramine	1,3,5,7-Tetraazaadamantane; Methenamine; Hexamine; 1,3,5,7-Tetraazatricyclo(3.3.1.1(3,7))decane	1228
Thinner	Petroleum 50 thinner	1237
sec-Hexyl acetate	1,3-Dimethylbutyl acetate; Methylisoamyl acetate, Acetic acid; 1,3-dimethylbutyl ester; 4-Methyl-2-pentanol; acetate	1335
Naphtha	Low boiling point hydrogen treated naphtha; Catalytic Reformer Feed	1380
1,1,1,2-Tetrachloroethane	Hexabutyldistannoxane; Tri-n-butyltin oxide; TBTO	1486
Ethylene glycol dimethyl ether	1,2-Dimethoxyethane, 1,2-Ethanediol; dimethyl ether; Monoglyme; 2,5-Dioxahexane; EGDME	1568

▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
1.1.38	Acute/chronic diseases caused by organic solvents	T52	NE61&XM0W28
1.1.38	Respiratory tract irritation	J68	CA81.Z
1.1.38	Acute chemical pneumonitis and bronchitis	J68.0	CA81.0
1.1.38	Upper respiratory inflammation	J68.2	CA81.2
1.1.38	Burns and corrosions of eye and adnexa	T26.0-T26.1, T26.5-T26.6	NE00
1.1.38	Conjunctivitis	H10.2	9A60.Z
1.1.38	Corneal ulcer	H16.0	9A76
1.1.38	Irritant contact dermatitis	L24	EK02
1.1.38	Narcotic syndrome consequent to poisoning by organic solvents	T52	NE61&XM0W28
1.1.38	Allergic contact dermatitis	L23	EK00
1.1.38	Toxic encephalopathy	G92	8D43.0Z
1.1.38	Acute toxic renal failure with tubular necrosis	N17.0	GB60.Z
1.1.38	Chronic toxic renal failure	N18.9	GB61.Z
1.1.38	Toxic liver disease	K71	DB95.Y
1.1.38	Liver toxicity (impairment, functional)	K72.9	DB9.7
1.1.38	Bone marrow depression (aplastic anaemia)	D61.9	3A70.Z
1.1.38	Infertility	N46, N97.0	GB04.Z, GA31.Z
1.1.38	Congenital malformation syndromes	Q86.8	LD2F.Y
1.1.38	Ototoxic hearing loss	H91.0	AB53
1.1.38	Peripheral polyneuropathy	G62.2	8C0Z
1.1.38	Acute myeloblastic leukemia	C92.0	2A60.3Z
	Occupational exposure to risk factors	Z57	QD84.Y

1.1.39 Diseases caused by latex or latex-containing products ICD Code T65.8, L50.6, L50.0, L23, J30.4, H10.1, J45.0, T78.2, L24, +Z57	
General characteristics of the causal agent	'Latex' (natural rubber latex, NRL) identifies a colloidal suspension of natural origin, consisting of the milky white liquid emulsion of flowering plants, such as the Pará rubber tree (Hevea brasiliensis). This complex natural product is a high molecular weight polymeric mixture of isoprene and contains a mixture of gum resins, fats, and waxes, suspended in a watery medium with sugars, salts, enzymes, tannins, alkaloids, and other natural substances. The term "latex" is in some cases improperly used for other emulsions of synthetic rubber or elastomers. This item is dedicated to the natural product, which is used in manufacturing items for various consumer uses, such as: • Articles for the health care sector (surgical gloves, catheters, anaesthesiology bags and masks, tracheal devices, intravenous devices, adhesive bandages, inter dental barriers). • Objects for children (balls and other toys, pacifiers). • Objects for sport (fins, underwater masks, accessories for the sail, balls), contraceptives (condoms, diaphragm). • Clothes (rubber shoes, elastic bands). • Furniture and manufactured articles for domestic use (gloves, curtains for the shower, adhesive, insulating materials). • Office articles (rubber bands, erasers, postage stamps). Although for many bulk applications such as the manufacturing of car tyres, natural rubber has been largely superseded by engineered speciality industrial polymers, NRL is still a high volume chemical commodity, which is extracted from trees grown in extensive commercial plantations in tropical countries. The sap is collected by scarification of trees and undergoes multiple physical and chemical processes before being converted into marketed items. Manufactured NRL items still contain several chemical constituents of the natural mixture, some of which such as specific small-sized proteins, can cause allergic sensitization in exposed subjects (see below). Other chemical products capable of eliciting allergic sensitization are some small organic compounds containing sulphur, nitrogen, and metals that are added to processed latex to achieve rubber vulcanization.
Occupational exposures	Workers employed in rubber production plants and in the manufacture of latex-containing objects may be exposed via inhalation and through skin contact to airborne rubber dust. Occupational exposure to NRL is common in all classes of workers who need to wear gloves as personal protective equipment, particularly: • Health care professionals: physicians, surgeons, dentists, ambulance attendants. • Staff of chemical and biological laboratories. • Workers in the food industry, catering personnel. • Workers in personal care and hygiene, hairdressers, aestheticians, masseurs. • Workers in industrial and household cleaning. • Workers who manipulate chemical substances: chemical industry, industrial manufacturing and maintenance, painting and covering, pesticide application in agriculture and public health. • Agricultural workers and breeders, cow and goat milkers, etc. Due to the large use of NRL in professional and household products and objects, almost everyone may be exposed to this material. Exposure of child entertainers and kindergarten workers may occur through hand and lip contact with flexible toys and rubber balloons.
Toxicological profile, main health effects and diagnostic criteria	
Short toxicological profile	Exudates from the laticifer layer of the Hevea brasilinesis tree contain ~200 proteins: fourteen allergens have been identified, which may cause sensitization in several risk groups through various routes of exposure: • Hev b 1 and 3 (main allergens in patients with spina bifida). • Hev b 5 and 6 (main allergens among health care workers). • Hev b 2, 4, 7, and 13 (secondary but still relevant allergens among health care workers). • Hev b 6.02 and 7 (have a verified cross-reactivity with fruits). • Hev b 8, 11, and 12 (panallergens with unknown cross-reactivity with fruits). • Hev b 14 (whose clinical relevance remains to be determined).

1.1.39 Diseases caused by latex or latex-containing products
ICD Code T65.8, L50.6, L50.0, L23, J30.4, H10.1, J45.0, T78.2, L24, +Z57

Short toxicological profile	Hev b 5 and Hev b 6.02 are the proteins most commonly associated with latex sensitivity in humans. Clinical features following exposure to the different allergens may vary, although some degree of overlap is common. People that have prolonged contact with latex, such as workers or surgical patients, are considered at high risk for developing NRL sensitivity. In addition, patients who need to undergo multiple surgical procedures, especially in their childhood (e.g. those born with congenital anomalies such as spina bifida and urogenital abnormalities) or at any age as the consequence of disease or trauma are typically at higher risk. Life-threatening allergic reactions may occur in already sensitized patients when, e.g. injection needles used to administer medications pick up traces of NRL proteins as they are pushed through the rubber caps of the vials of the drugs. There are reports about the association between allergic reactions in humans and exposure to latex. Three main clinical manifestations may be observed following exposure to NRL: irritant contact dermatitis (direct tissue damage on the exposed areas of skin), allergic contact dermatitis (type IV delayed hypersensitivity reactions to latex additives), and IgE-mediated latex allergy (i.e., type I allergic response that can range from contact urticaria, rhino-conjunctivitis, and asthma up to anaphylaxis). It has been noted that there may be a progression of symptoms over time, from distal/hand skin localization to more generalized allergic responses. Cross-reactive foods (e.g. kiwi fruit, chestnuts, pineapples, potatoes) may trigger an allergic reaction in patients with NRL sensitivity even without direct contact with natural rubber products.

Name of the diseases and ICD code: **Acute and chronic diseases caused by latex or latex-containing products**
(Specific disease code) **+T65.8 +Z57**

Contact urticaria (L50.6), Allergic angioedema with urticaria (T78.3)

Short description of the disease

Skin exposure to latex may cause a wheal eruption 20-30 minutes after the contact of sensitized individuals. Atopic sensitivity (Type I allergic reaction) is caused by a NRL antigen which, through a series of events involving B and T cells, eventually brings about the production of antigen-specific immunoglobulin E (IgE) antibodies that can then bind to high-affinity IgE receptors located on the surfaces of mast cells and basophils. This reaction triggers the release of histamine and other mediators from the mast cells and basophils and initiates the systemic allergic cascade in sensitized individuals. It is important to recall that cross-reactive proteins are present in many fruits and vegetables (avocado, banana, pineapple, mango, strawberry, passion fruit, chestnut, sweet pepper, potato, kiwi fruit, tomato, soy, etc.), and subjects sensitized against these antigens can be allergic to latex proteins too.

The clinical signs range from contact urticaria to generalized urticaria to angioedema, localized oedema of the deeper and subcutaneous layers. Recurrent episodes of urticaria and angioedema of fewer than six weeks duration are considered acute, whereas attacks persisting beyond this period are designated as chronic.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms:
  - History of itching and burning. Urticaria presents as itchy and fleeting wheals and appears in crops with variable duration (from minutes up to 24 hours) in exposed contact areas while donning gloves, undergoing surgical, medical, and dental procedures, or following any exposure to NRL containing devices. Generalized whole body urticaria or anaphylaxis can be observed under the same conditions of exposure.
  - In angioedema, the deep tissues and mucous membranes are affected, resulting in the manifestation of respiratory difficulties when the oropharyngeal region is affected. Symptoms may result from direct contact of normal or inflamed skin with gloves or inhalation of aerosolized NRL proteins or other latex-containing materials, such as dust from some types of surgical gloves (e.g. latex gloves with powder).
- Examinations: The diagnosis of urticaria or angioedema is clinical, and specific tests may help to clarify the aetiology of the event:
  - Skin prick tests (SPT) are considered the method of choice to confirm or rule out latex allergy. Standardized extracts can provide a sensitivity of 93% with a specificity of 100% and are considered safe, although isolated cases of anaphylaxis have been reported.
  - Blood tests such as radioallergosorbent test (RAST) which is no longer widely used, or the current ImmunoCAP ISAC test should be conducted to reach the diagnosis of immunological contact urticaria and angioedema. These tests can be used in conjunction with SPT or when SPT cannot be performed to increase diagnostic accuracy. Determination of recombinant allergens using CAP may confirm the diagnosis in cases where sensitization has not been proven by other techniques and is useful for establishing profiles of sensitization to different allergens in different groups of patients and with cross-reactions.
  - Immunoblotting can be used to detect specific IgE, but always as a complement to another diagnostic technique.

1.1.39 Diseases caused by latex or latex-containing products
ICD Code T65.8, L50.6, L50.0, L23, J30.4, H10.1, J45.0, T78.2, L24, +Z57

Exposure assessment

- History of occupational exposure: evidence of direct contact with medical devices, such as surgical latex gloves, elastic bandages, rubber inner shoe soles, surgical drains containing high levels of NRL proteins, or other latex-containing materials, or mucosal contact with, or inhalation of, aerosolized NRL proteins, or talcum or powder particles to which NRL proteins have adhered.
- Minimum duration of exposure: for sensitization, several contacts with the allergen are needed. In sensitized subjects, few minutes are sufficient for eliciting the symptoms.
- Maximum latent period: in sensitized subjects, any further exposure to the agent causes the onset of clinical signs, usually within hours, not longer than one day.

Allergic contact dermatitis (L23)

Short description of the disease

Acute allergic contact dermatitis (ACD) to NRL is a type IV eczematous skin reaction against contaminants such as rubber accelerators and antioxidants. Nearly 80% of "latex glove allergy" is actually a Type IV reaction to the accelerators. Pre-existing skin irritation promotes the development of ACD. Even though sensitization can be induced even by a single contact with the compound, in occupational settings, usually it takes place after some months of repeated contact, and in some cases, even after many years.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: ACD presents as pruritic eczema, characterized by redness, swelling, vesicles, oozing, and crusting (acute eczematous reaction) of the skin, which develops within 24-48 hours from exposure at the site of hapten penetration in sensitized individuals. Skin lesions may also extend to areas that are not in direct contact with the allergen. Repeated contact with both weak and moderate allergens/haptens can cause a sub-acute form of contact dermatitis characterized by dry, red plaques. ACD may become chronic if the exposure is not interrupted. Features of chronic allergic contact dermatitis generally include dry, thickened and scaly skin, cracking and fissuring of the fingers and palms, chronic nail dystrophy (chronic eczematous reaction). Itch (pruritus) is usually present.
- Examinations:
  - Lesions are localized at allergen contact sites but often spread in the surrounding area or even to other body sites. Occupational ACD is mainly found on the hands. Upon exposure to volatile allergens or by transference from the hands, it may occur at the face, neck, arms. The involved areas must be carefully examined. Note should be taken of the severity and stage of dermatitis, of its precise distribution and of its degree of interference with function. A complete skin examination must be performed, looking for tell-tale stigmata of psoriasis, atopic dermatitis, lichen planus, tinea, etc., which may signify that the dermatitis is not of occupational origin.
  - Patch tests should be performed by a specialized physician, according to relevant guidelines (such as those listed in the 'further reading'), taking account of the suspected agent of skin sensitization. This diagnostic approach might bring about sensitization, and the testing concentration should be defined according to specific recommendations.

Exposure assessment

- History of occupational exposure: evidence of direct contact with medical devices, such as surgical latex gloves, elastic bandages, rubber inner shoe soles, surgical drains containing high levels of NRL proteins, or other latex-containing materials, or mucosal contact with (or inhalation of) aerosolized NRL proteins, or talcum or powder particles to which NRL proteins have adhered.
- Minimum duration of exposure: usually, several instances of exposure are required over long periods for sensitization, but in exceptional cases, even a single contact might be sufficient. For elicitation of ACD in sensitized individuals, skin contact with the allergen for a few minutes to several hours may give rise to skin reactions.
- Maximum latent period: in sensitized subjects, any further exposure to the agent causes the onset of clinical signs, usually within 12-72 hours or even later (up to 1-2 weeks).

Allergic rhinitis (J30.4), Allergic conjunctivitis (H10.1)

Short description of the disease

Inhalation exposure to NRL proteins can cause allergic rhinitis and conjunctivitis, characterized by a plethora of symptoms due to the release of histamine and other active substances by mast cells (Type I allergic reaction), which stimulate dilation of blood vessels, irritate nerve endings and increase secretion of tears. The use of powder-containing gloves in health care facilities may facilitate the transport of the latex proteins to the mucous membranes of the workers.

1.1.39 Diseases caused by latex or latex-containing products
ICD Code T65.8, L50.6, L50.0, L23, J30.4, H10.1, J45.0, T78.2, L24, +Z57

Diagnostic criteria

Clinical manifestations

- Signs and symptoms:
  - Rhinorrhoea, sneezing, lacrimation, red eyes, itchy eyes, nose and throat, nasal cavity obstruction, watery and pale nasal mucosae, congested conjunctivae.
  - Nasal polyps are often present; if this is the case, the risk of evolution into asthma increases.
- Examinations:
  - Eosinophils can be found in the nasal secretions of the affected subjects, as well as modest peripheral eosinophilia and elevation of serum IgE. The skin prick test represents an in vivo examination aimed at identifying specific IgE antibodies.
  - Anterior rhinoscopy should be used to examine the nasal mucosae.
  - Rhinomanometric measurements can be used to measure nasal obstruction.

Exposure assessment

- History of occupational exposure: evidence of direct contact with medical devices, such as surgical latex gloves, elastic bandages, rubber inner shoe soles, surgical drains containing high levels of NRL proteins, or other latex-containing materials, or mucosal contact with (or inhalation of) aerosolized NRL proteins, or talcum or powder particles to which NRL proteins have adhered.
- Minimum duration of exposure: usually a few weeks, since occupational allergic upper airways disorders require a sensitization period. In exceptional cases, the minimum duration of exposure may be as short as a few days.
- Maximum latent period: in sensitized individuals, usually no more than 48 hours, but recall that the exposure following sensitization (and thus producing the symptoms) may occur even years after sensitization itself.

Occupational asthma (J68.3)

Short description of the disease

Inhalation exposure to latex proteins can cause sensitized-induced (Type I allergic reaction) occupational asthma.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: cough, dyspnoea, wheezes.
- Examinations:
  - Lung function testing may show evidence of airway obstruction. The absence of airway obstruction does not exclude a diagnosis of asthma (or occupational asthma). Bronchodilator response may be seen in certain workers with occupational asthma when given β2 agonists.
  - Skin prick tests (SPT) are considered the method of choice to confirm or rule out latex allergy. Standardized extracts can provide a sensitivity of 93% with a specificity of 100% and are considered safe, although isolated cases of anaphylaxis have been reported.
  - Blood tests such as radioallergosorbent test (RAST) which is no longer widely used, or the current ImmunoCAP ISAC test should be conducted to reach the diagnosis of immunological contact urticaria and angioedema. These tests can be used in conjunction with SPT or when SPT cannot be performed to increase diagnostic accuracy. Determination of recombinant allergens using CAP may confirm the diagnosis in cases where sensitization has not been proven by other techniques and is useful for establishing profiles of sensitization to different allergens in different groups of patients and with cross-reactions.
  - Immunoblotting can be used to detect specific IgE, but always as a complement to another diagnostic technique.
  - If the diagnosis remains doubtful in the presence of reported symptoms, but negative tests, finger or glove use test can be practised: the affected subject wears and manipulates only a wet finger of the latex glove and is immediately assessed for the appearance of symptoms and for evidence of bronchial obstruction on spirometry. This test, accompanied with intradermal skin testing, might bring about a risk for the patients and must be carried out with the availability of first aid devices and specific drugs and must be performed only by experienced medical personnel in a protected environment. Increased blood levels of eosinophilic cationic protein and increased expired fraction of nitric oxide may be observed after the exposure test.

1.1.39 Diseases caused by latex or latex-containing products
ICD Code T65.8, L50.6, L50.0, L23, J30.4, H10.1, J45.0, T78.2, L24, +Z57

Exposure assessment

- History of occupational exposure: evidence of direct contact with medical devices, such as surgical latex gloves, elastic bandages, rubber inner shoe soles, surgical drains containing high levels of NRL proteins, or other latex-containing materials, or mucosal contact with (or inhalation of) aerosolized NRL proteins, or talcum or powder particles to which NRL proteins have adhered.
- Minimum duration of exposure: usually from weeks to years but, in some cases, this period may be as short as a few days.
- Maximum latent period: usually between 3 to 24 months but may be shorter in atopic subjects and in exceptional cases it may be as short as a few days. In sensitized subjects, the latency between exposure and onset of symptoms is usually no longer than 48 hours.

Allergic anaphylaxis (T78.2)

Short description of the disease

Exposure to latex proteins can rarely cause an allergic IgE mediated (Type I allergic reaction) anaphylaxis.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: the symptoms generally start at the skin with urticaria and or angioedema, and then evolve towards laryngeal oedema and intense bronchospasm with systemic involvement and shock (allergic march).
- Examinations:
  - Positive IgE blood test (Type I allergy, RAST) specific for latex positive.
  - Documented cross-reactivity with fruits or vegetables can be present.
  - When skin prick (epicutaneous) tests are performed, they should be conducted only in a protected environment and after a negative specific IgE blood test for latex.
  - Serum tryptase levels showing an elevation compared to baseline values for up to five hours after anaphylaxis can be helpful.

Exposure assessment

- History of occupational exposure: evidence of direct contact with medical devices, such as surgical latex gloves, elastic bandages, rubber inner shoe soles, surgical drains containing high levels of NRL proteins, or other latex-containing materials, or mucosal contact with (or inhalation of) aerosolized NRL proteins, or talcum or powder particles to which NRL proteins have adhered. Clinical manifestations of anaphylaxis should be confirmed from medical history and observations, and there should be pointed out a strong temporal association between exposure and onset of symptoms. Non-occupational risk factors should also be assessed.
- Minimum duration of exposure: for sensitization, several contacts with the allergen are usually necessary. In sensitized subjects, few minutes are sufficient for eliciting the symptoms.
- Maximum latent period: up to 60 minutes in already sensitized subjects.

Irritant contact dermatitis (L24)

Short description of the disease

A very common adverse effect of occupational exposure to latex is irritant dermatitis (most often of the hands). Dermatitis can be either acute or chronic and is characterized by dry, itchy, irritated areas on the skin. The disease is often consequent to improper use of gloves, in particular when they are worn continuously for prolonged periods. Incomplete drying of washed hands, exposure to hand sanitizers, and the talc-like powder coatings (zinc oxide, etc.) used with gloves can aggravate symptoms. Usually, recovery is observed after the introduction of good occupational hygiene practice (frequent change of gloves; avoidance of wearing gloves for prolonged periods).

1.1.39 Diseases caused by latex or latex-containing products
ICD Code T65.8, L50.6, L50.0, L23, J30.4, H10.1, J45.0, T78.2, L24, +Z57

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: they range from simple irritation (redness, itching, scaling, minor erythema) to severe (third-degree) chemical burns (corrosion), including erythema, swelling, blisters, oozing and crusting. If the disease evolves in chronic dermatitis, its main features are desquamation, thickening and lichenification of the skin with painful fissures. Lesions are confined to the areas exposed to the irritants (mainly the hands and arms). Volatile irritants may cause airborne lesions in uncovered skin areas, like the face and neck. Signs are usually accompanied by pain and burning sensations.
- Examinations: exclusion of allergy on appropriate patch testing.

Exposure assessment

- History of occupational exposure: evidence of exposure to latex through dermal contact (especially by wearing gloves) during work.
- Minimum duration of exposure: some days.
- Maximum latent period: the symptoms appear immediately or within 48 hours after the exposure.

Key actions for prevention	The primary objective is to eliminate NRL-containing dust from general working areas to avoid unnecessary exposure of non sensitized persons and possible development of sensitization to NRL and to avoid exposure in those who are already allergic to cross-reactive antigens (such as those of common food vegetables). Animal experiments and human observational studies consistently demonstrate an excess risk of sensitization or allergic reaction following repeated exposure to NRL. Skin exposure is an important risk factor and may be more important than respiratory exposure in predicting latex dermatitis and sensitization. It is very important that good quality gloves and devices of low protein content are used in the workplace. NRL-sensitive workers, should have minimal or no direct contact to potentially harmful latex-containing materials. To protect both NRL-sensitized patients and workers from consequences of exposure to latex (either airborne or settled on surfaces), in hospitals and outpatient clinics, suitable "latex safe" and "latex-free" paths can be organized by thorough cleaning and insulation of the rooms, removal of the NRL-containing material from the workplace, and appropriate labelling. Good occupational hygiene practices should be disseminated among users and latex materials substituted, when possible, with other products (example: vinyl/nitrile gloves instead of latex gloves, etc.). Selecting good quality materials and avoiding the use of latex devices, when unnecessary, may help in reducing the risk. The use of starch powder treated gloves should be discouraged. The group of experts considered that a limit of 0.0001 mg/m^3 of workplace atmospheric concentration (as 8hr TWA) of NRL (as inhalable allergenic proteins) has been observed to be used in a number of countries and to provide a reasonable level of protection for workers' health.

1.1.39 Diseases caused by latex or latex-containing products
ICD Code T65.8, L50.6, L50.0, L23, J30.4, H10.1, J45.0, T78.2, L24, +Z57

Further reading

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▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
1.1.39	Acute and chronic diseases caused by latex or latex-containing products	T65.8	NE61&XM7762
1.1.39	Contact urticaria	L50.6	EB01.3
1.1.39	Allergic angioedema with urticaria	L50.0	EB01.Y
1.1.39	Allergic contact dermatitis	L23	EK00
1.1.39	Allergic rhinitis	J30.4	CA08.0Z
1.1.39	Allergic conjunctivitis	H10.1	9A60.02
1.1.39	Occupational asthma	J45.0	CA23.0
1.1.39	Allergic anaphylaxis	T78.2	4A84.4
1.1.39	Irritant contact dermatitis	L24	EK02
	Occupational exposure to risk factors	Z57	QD84.Y

1.1.40 Diseases caused by chlorine	ICD Code T59.4 +Z57
General characteristics of the causal agent	Chlorine (Cl_2), CAS number 7782-50-5, is the chemical element with atomic number 17 in the periodic table of elements, has two stable isotopes (^{35}Cl and ^{37}Cl, in a 2:1 ratio), and its mean atomic mass is 35.5 Da. It is classified in Group 17 (VII-A; Main group, Halogens) and features all oxidation numbers between -I (chloride), 0 (elemental), and VII (perchlorate). Elemental chlorine is a heavier-than-air greenish-yellow gas with a typical pungent, suffocating smell. The solution in water is a strong corrosive acid. Reaction with bases is strongly exothermic and generates equimolecular amounts of chloride and hypochlorite, the latter being an oxidant and a chlorinating agent for several organic substances. Chlorine reacts exothermically with many inorganic compounds, such as ammonia and hydrogen, and with finely divided metals causing fire and explosion hazards. Chlorine reacts with plastic, rubber, coatings, and many metals in the presence of water. It reacts exothermically with organic compounds such as hydrocarbons. It is very soluble in water and even more in alkalis by forming oxidizing hypochlorous acid and hypochlorite solutions. Chlorine is one of the classical chemical warfare agents.
Occupational exposures	Chlorine is a principal bulk product of the chemical industry and the starting material for several products and uses. It is industrially produced by the electrochemical decomposition of concentrated sodium chloride solutions (brines). Once produced, it is usually used in plants immediately downstream instead of being transported to other production plants. In the rare cases in which it is transported, stringent precautions are necessary to ship or rail liquid chlorine in specialised cooled tanks. Chlorine has wide industrial uses as a chemical reagent in the production of hydrochloric acid, sodium and calcium hypochlorite bleaches; of organic chlorine compounds such as the polymer precursors vinyl chloride and chloroprene, chlorinated solvents such as methylene chloride, chloroform, and tri- and tetrachloro-ethylene; of speciality organic chemicals for the dye, pharmaceutical and pesticide industry. Other uses are as a bleaching agent for textiles and paper and as a disinfectant for drinking water. Although occupational exposure to elemental chlorine is theoretically possible in several production activities and during transport, the most frequent form of human exposure is to chlorine gas released when hypochlorite bleach is inadvertently mixed to industrial acids such as hydrochloric (muriatic) acid. This may occur when cleaning houses and workplaces, in water purification plants or in swimming pools. Toxic and explosive mixtures of gaseous chlorine and of chloramine are formed when hypochlorite bleach and ammonia solutions are inadvertently mixed. Occupational exposure is possible in the chemical industry during the synthesis of derivates such as hypochlorite, hydrochloric acid, organic chlorine compounds, and calcium and zinc chloride. It is used as a bleaching agent in the textile and paper industries. Exposure may occur in water purification where chlorine is used as a disinfectant, home cleaning, and paper pulp mill work.
Toxicological profile, main health effects and diagnostic criteria	
Short toxicological profile	Chlorine is a highly reactive gaseous element. Occupational exposure mainly occurs from inhalation and direct contact. Physiological effects are mostly local and involve the site of contact, resulting in irritation and corrosion of the skin and mucosae and in irritative respiratory effects. Systemic effects involve the respiratory system, and their severity depends on the intensity of exposure. Delayed, more serious, life-threatening respiratory effects are seen following high exposures.

1.1.40 Diseases caused by chlorine — ICD Code T59.4 +Z57

Name of the diseases and ICD code: **Acute diseases caused by chlorine** *(Specific disease code)* **+T59.4 +Z57**

Irritant contact dermatitis (L24), Chemical burns and corrosions of external body surface (T20-T25), Burns and corrosions of eyes and adnexa (T26.0-T26.1, T26.5-T26.6), Burns and corrosions of internal organs (T28.0-T28.2, T28.5-T28.7), Respiratory tract irritation (J68), Acute chemical pneumonitis and bronchitis (J68.0), Pulmonary oedema (J68.1), Upper respiratory inflammation (J68.2), Reactive airways dysfunction syndrome (RADS) (J68.3), Irritant-induced occupational asthma (J68.3)

Short description of the disease

Chlorine may cause severe irritation and burns of the skin and eyes. Direct contact with liquid chlorine produces severe ocular lesions and skin damage.

One of the principal targets of exposure to chlorine gas is the respiratory tract. Exposure to relatively low concentrations of chlorine (<5 ppm) are not expected to affect deep lung structures since most of the inhaled chlorine (>95%) is retained in the upper portion of the respiratory tract, whether breathing through the nose or the mouth. Subjects surviving the acute phase of exposure to high concentrations of chlorine may still be in danger of severe delayed effects such as bronchopneumonitis, pneumonia or subacute bronchiolitis. The location and severity of respiratory tract damage is a function of inhaled concentration and duration of exposure. Death at high exposures results from pulmonary oedema, caused by marked alveolar capillary congestion followed immediately by focal and confluent area of fluid with a high content of fibrinogen.

The complications of chlorine inhalation fit the histological condition known as diffuse alveolar damage that is associated with adult respiratory distress syndrome.

Diagnostic criteria

Clinical manifestations

In case of mild exposures, skin and ocular erythema and burns, cough, dyspnoea, substernal pain, and respiratory distress are observed. With the exception of cough, substernal pain, and respiratory distress, the symptoms occurring after exposure to moderate concentrations of chlorine generally subside within 24 hours.

High exposures cause skin and eye burns, acute dyspnoea, cough with frothy rosy sputum, asthenia, tachycardia, increased heart and respiratory rates. Respiratory symptoms can be delayed by up to 48 hours following exposure. Shock or coma may occur. Pulmonary oedema peaks between 12-24 hours, and the resulting hypoxia further increases capillary permeability, with hypoxaemia and later hypercapnia found on arterial blood gas analysis. Chest X-ray may show pneumonitis or bronchitis with increased bronchovascular markings, or pulmonary oedema. ECG could reveal pulmonary and cardiac involvement.

Exposure assessment

- History of occupational exposure: chemical industry workers may be accidentally exposed to high doses of chlorine in liquid form or in the form of vapours. Exposure to chlorine gas at concentrations in the order of 1-3 ppm produce mild irritation of the nose that can be tolerated for about one hour. Headache and throat irritation may occur at concentrations of 5-15 ppm; 30 ppm produce immediate chest pain, nausea and vomiting, dyspnoea, and cough; 40-60 ppm produces toxic pneumonitis and pulmonary oedema; 430 ppm usually cause death in 30 minutes, and 1,000 ppm are fatal within a few minutes. In most cases, death is the result of pulmonary oedema.
- Minimum duration of exposure: few seconds.
- Maximum latent period: minutes; 48 hours for pulmonary oedema.

Name of the diseases and ICD code: **Chronic diseases caused by chlorine** *(Specific disease code)* **+T59.4 +Z57**

Chronic obstructive pulmonary disease (COPD), Emphysema, Chronic bronchiolitis, Pulmonary fibrosis (J68.4), Chronic rhinitis (J31.0), Erosion of the teeth (K03.2)

Short description of the disease

Repeated and prolonged occupational exposure to chlorine via inhalation can cause chronic rhinitis, bronchiolitis, pulmonary fibrosis, emphysema, and asthma. Increased risk of COPD and asthma has been established in domestic cleaners and pulp mill workers, and repeated exposure to chlorine may be one of the causal agents.

Exposure to chlorinated water can irreversibly damage dental enamel, followed by further structural damage.

1.1.40 Diseases caused by chlorine — ICD Code T59.4 +Z57

Diagnostic criteria

Clinical manifestations

- Signs and symptoms:
  - Presence of persistent respiratory symptoms and incompletely reversible airflow obstruction, worsening dyspnoea, productive cough, asthenia, cyanosis.
  - Nasal symptoms include serous rhinorrhoea, sneezing, and nasal itching.
  - Dental erosions consist of loss of enamel: the teeth appear yellowed and may have roundings and splits, and become more sensitive to pain and more fragile.
- Examinations:
  - Wheezing and chest tightness at auscultation.
  - Peribronchial thickening at chest X-ray and computed tomography (CT).
  - Airflow obstruction on pulmonary function tests; in addition, impaired CO diffusion can be observed.
  - Arterial blood gas samples may demonstrate raised CO_2 concentrations.
  - Anterior rhinoscopy can be used to examine the nasal mucosa.
  - Rhinomanometric measurements can be used to measure nasal obstruction.

Exposure assessment

- History of occupational exposure: history of prolonged occupational exposure to chlorine gas.
- Minimum duration of exposure: some weeks.
- Maximum latent period: manifestations should appear during the period of employment causing exposure, or soon after.

Key actions for prevention	Chlorine can sometimes be replaced with safer chemicals or by alternative processes, but substitution is often not feasible. Chlorination is still the most effective technique for water sanitization, and most alternatives of comparable efficacy and cost rely on the use of substitutes such as chlorine dioxide and hypochlorous acid themselves prepared from chlorine gas, or of active oxygen based products such as peracetic acid and ozone. Industrial technologies employing elemental chlorine for chemical reactions often rely on the use of closed-circuit plants to control exposure. The recovery of chlorine from hydrochloric acid by catalytic combustion is not only less costly, but also avoids large scale environmental pollution. Workers who need to operate in chemical plants and in other applications where direct exposure to chlorine is likely to occur need to use protective equipment, including closed-circuit respirators. Respirators with specific filters are effective only for very short periods of exposure to chlorine-contaminated atmospheres. The group of experts considered that the following limits of exposure of workplace atmospheric concentrations have been observed to provide a reasonable level of protection for workers' health and to be used in a number of countries: • 0.1 ppm as 8hr TWA. • 0.4 ppm as STEL.

Further reading

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For the chemical entities listed below an entry exists in the collection of International Chemical Safety Cards (ICSC) hosted in the ILO website

Name	Synonyms	ICSC
Chlorine		0126

▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
1.1.40	Acute/chronic diseases caused by chlorine	T59.4	NE61&XM0GT6
1.1.40	Irritant contact dermatitis	L24.0	EK02
1.1.40	Chemical burns and corrosions of external body surface	T20-T25	ND9Z
1.1.40	Burns and corrosions of eyes and adnexa	T26.0-T26.1, T26.5-T26.6	NE00
1.1.40	Burns and corrosions of internal organs	T28.0-T28.2, T28.5-T28.7	NE0Z
1.1.40	Respiratory tract irritation	J68	CA81.Y
1.1.40	Acute chemical pneumonitis and bronchitis	J68.0	CA81.0
1.1.40	Pulmonary oedema	J68.1	CA81.2
1.1.40	Upper respiratory inflammation	J68.2	CA81.1
1.1.40	Reactive airways dysfunction syndrome (RADS)	J68.3	CA81.Y
1.1.40	Irritant-induced occupational asthma	J68.3	CA81.Y
1.1.40	Chronic obstructive pulmonary disease (COPD), Emphysema, Chronic bronchiolitis, Pulmonary fibrosis	J68.4	CA22.Z
1.1.40	Chronic rhinitis	J31.0	CA09.0
1.1.40	Erosion of the teeth	K03.2	DA08.12
	Occupational exposure to risk factors	Z57	QD84.Y

1.2. Diseases caused by physical agents

1.2.1 Hearing impairment caused by noise	ICD Code H83.3 +Z57.0
General characteristics of the causal agent	The term *noise* covers all unwanted and disturbing sound with unpleasant acoustic characteristics which can result in hearing impairment or be harmful to health or otherwise dangerous. Sound (or noise) is the result of pressure variations, or oscillations, in an elastic medium (e.g. air, water, solids) generated by a vibrating surface or turbulent fluid flow. The propagation of sound occurs in the form of longitudinal waves, as a series of compressions and rarefactions in the elastic medium. When a sound wave propagates in the air, which is the medium most commonly seen in the occupational exposure settings, the oscillations in pressure are above and below the ambient atmospheric pressure, appearing as compression and rarefaction waves which alternate (sound *frequency*) in the range of several (*hertz*, Hz) to several thousand (*kilohertz*, kHz) times per second. The interface of mechanical waves with the hearing system and its subsequent neural processing gives rise to the human perception of sound. One parameter of the acoustic wave that is generally used to assess sound exposure is the sound pressure level, expressed using a logarithmic scale in decibels (dB). Tones of equal sound pressure levels but different frequencies are perceived by the human ear with different levels of sensitivity. The magnitude of a sound perceived by an individual (i.e., its loudness) differs for different frequencies. Within the sound frequency range that can be heard by human beings (from 20 Hz to 20 kHz), the ear is most sensitive to the frequencies 3-4 kHz. For lower or higher frequencies, the ear becomes less sensitive. In this context, the aim of weighting scales currently used in sound-level meters is to mimic isoloudness curves over frequency under different conditions of sound intensities. In particular, • *A-weighting* adjusts measurements to conform to the frequency sensitivity of the human ear at low levels. This is the most commonly used weighting scale, as it predicts the risk of damage to the ear. Sound level meters using the A-weighting scale filter out much of the low frequency noise they measure, similar to the response of the human ear. Noise measurements made with the A-weighting scale are expressed as dB(A). • *C-weighting* adjusts measurements to conform to the frequency sensitivity of the human ear at very high noise levels and is usually used for peak measurements. Noise measurements made with the C-weighting scale are expressed as dB(C). Finally, noise may be classified as continuous and or impulsive, according to the temporal changes in sound pressure level. Continuous noise maintains a relatively stable level during a given time period. On the other hand, impulsive noise is a sound characterized by the development of energy during a very short time and through a very elastic (well-transmitting) medium, which results in a high shock frontal pressure. This is typical of energy transmission through solids (e.g. hammering a piece of metal) and of explosive bursts in the air.
Occupational exposures	Occupational exposure to noise is one of the most common occupational exposures in the world. It is estimated that 1-4% of workers are exposed to noise and that a significant proportion of the disabling hearing difficulties around the world (≈16%) results from excessive exposure to noise at the workplace. Developed countries are slowly bringing noise levels under control while developing nations tend to experience increasing levels of urban and industrial noise. Very large equipment for metalworking and for construction work, such as hammer presses, drills, and cutting blades, dissipate most energy as shock waves in the worked material, resulting in loud intermittent (hammer) or continuous (drills, cutters) noise. Moving parts of mechanical machinery employed in all branches of working activity generate friction and vibrations, which result in noise. Industrial printing is a traditional workplace where rotary presses produce loud and continuous noise. Noise is one of the commonest health problems in the textile industry and bottling plants are also typically noisy workplaces. In agriculture, sources of noise are represented by large assemblies of animals, especially as found in the intensive rearing of cattle, pigs and chicken, above all at times when animals wait for a feeding or need to be moved between different areas. Large agricultural machines – such as tractors and tractor-operated machinery – are powered by large engines, and their moving parts may be very noisy.

1.2.1 Hearing impairment caused by noise	ICD Code H83.3 +Z57.0
Occupational exposures	Lightweight equipment such as powered saws, drills, and cutters used in industry, in agriculture and in the informal sector of crafts and repair work create noise. Open space front offices and call centres can be noisy due to crowding and to the necessity for continuous conversation. The use of headphones and headsets in assistance and commercial call centres often lasts for several hours, and the actual level of voices heard can be comparable to noise in manufacturing factories. The use of headphones for personal music players can cause users to turn the volume up to dangerously high levels to compensate for noisy work environments. The noise of urban traffic that reaches the lower-floor offices can add to the one produced indoors.
Biological mechanisms, main health effects and diagnostic criteria	
Short profile of the biological mechanisms	Exposures capable of causing occupational acoustic trauma are those where very high levels of noise are produced in a short time, such as explosions (e.g. in mining, tunnel construction and building demolition) and any other source of loud noise (e.g. jet aeroplane take off). Consequent hearing loss is usually defined as 'conductive' since damage mostly occurs to the outer and middle ear sound-conducting structures. On the other hand, exposure to continuous or intermittent noise at workplaces can cause occupational noise-induced hearing loss (NIHL), slowly developing over several years and typically being defined as 'sensorineural', as damage mostly occurs to the nervous structures of the inner ear. The risk of noise-induced chronic hearing loss increases with the cumulative exposure to noise above an intensity threshold, expressed as the daily noise exposure level (including impulsive noise) and as the exposure time in years. Worldwide excessive exposure to noise is probably the most common cause of preventable hearing loss. Prolonged exposure to sound in excess of 80 dB(A) is potentially hazardous, owing to both the level and the duration of exposure (i.e., the noise dose). After prolonged exposure to a stimulating sound intensity such as a typical hazardous industrial sound, e.g. above 85 dB(A) for an 8-hour workday, a change in hearing threshold or temporary threshold shift (TTS) can occur that by definition recovers to pre-exposure levels over a short (minutes to hours) or longer (days to weeks) period. The pathophysiology relates to cochlear blood flow and biochemical changes in the sensorineural component of hearing involving the hair cells, stereocilia, organ of Corti and supporting stuctures as well as the auditory nerve. If TTS occurs repeatedly, the recovery becomes less complete, and after around three weeks post exposure a permanent threshold shift (PTS) supervenes due to hair cell damage. First to fail permanently are the outer hair cells in the basilar part of the cochlea, in the area which responds to 4 kHz and the adjacent areas of 3 and 6 kHz. This is where the ear is most sensitive, because of the harmonic resonance of the ear canal for wavelengths which are approximately 4 times the length of the canal and because of cochlear damage. Hair cells once they degenerate, do not recover, and a permanent noise-induced hearing loss develops. At this stage, social communication is affected, and the worker becomes increasingly aware of the diminished acuity in his or her hearing. NIHL is the most serious health effect resulting from irreversible damage to the hearing mechanisms of the inner ear. Classically, following noise exposure, hearing loss is shown as an audiometric notch, usually maximal at 4 kHz but within the range of 3 and 6 kHz. The loss extends into adjacent frequencies with continued noise exposure. Workers will usually notice reduced hearing when the speech frequencies of 2 and 3 kHz are affected. There may be individual susceptibility to noise induced hearing loss from comorbid conditions such as otosclerosis. Permanent NIHL from exposure to hazardous noise may arise soon after exposure depending on the nature of the noise exposure, such that an audiometric notch may be noticeable even within 6-12 months of starting a job. Usually, both ears are exposed to the same level of sound, and the hearing loss is thus symmetrical. Some noise exposures may be asymmetrical such as firearms use, and it is reported that "head shadowing" of the noise may contribute to asymmetric exposure. However there is also a suggested physiologic effect of lower hearing levels in the left ear even after accounting for hand dominance. Another important occupational consideration is the ototoxic effects of some chemical exposures with a synergistic effect. Organic solvents (e.g. styrene, toluene, xylene), carbon monoxide, and metal fumes, may hasten hearing loss through ototoxic effects. Finally, it should be kept in mind that excessive noise can cause adverse extra-auditory effects, including elevated blood pressure, reduced performance, sleeping difficulties, annoyance and stress.

1.2.1 Hearing impairment caused by noise — ICD Code H83.3 +Z57.0

Name of the diseases and ICD code: **Acute hearing impairment caused by noise (H83.3) +Z57.0**

Short description of the disease

'Acoustic trauma' is caused by a brief exposure to a single very loud noise, such as an explosion or any single sound blast, usually with an intensity in the order of at least 140 dB. The impact of the sound wave can damage the tympanic membrane, with immediate bleeding and subsequent hearing loss. Typically, hearing loss due to acute acoustic trauma is conductive or mixed (i.e., both conductive and sensorineural), asymmetric or symmetric (depending on exposure), and generally partly reversible depending on the energy of the sound wave.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: the symptoms usually appear immediately or at most within a few days after exposure and include hypoacusis, which can lead to dizziness, tinnitus, and perceived hearing loss with a reduction in the capacity for hearing acute sounds such as at the beginning of ringing tones or bells, up to total deafness. A period of weeks to months may be required for the hearing to stabilize. Tinnitus can accompany hearing loss and may be the most problematic and persisting symptom. Rupture of the tympanic membrane with bleeding and physical damage to the middle ear and cochlea can be detected.
- Examinations: in most cases, a conductive loss detected at the pure tone audiometry may be present if there is rupture of the tympanic membrane and damage to the ossicular chain. Bilateral and symmetrical sensorineural loss, starting in the 4-6 kHz range and then expanding to the lower frequencies can be observed. Other methods such as auditory brainstem or cortical evoked potentials may be useful in confirming the hearing loss.

Exposure assessment

- History of occupational exposure: confirmed occupational exposure to sudden and very loud noise (usually above 140 dB). The contribution of other non-occupational sources of noise should be considered.
- Minimum duration of exposure: a single exposure event is sufficient to cause the trauma.
- Maximum latent period: a few days after the noise exposure event.

Name of the diseases and ICD code: **Chronic hearing impairment caused by noise (H83.3) +Z57.0**

Short description of the disease

In the occupational setting, hearing impairment is generally defined as a pure-tone average threshold across frequencies 1,000, 2,000, 3,000 and 4,000 Hz of 25 dB or more in either ear. The WHO defines disabling hearing loss more broadly as a permanent unaided hearing impairment above 40 dB hearing level in the better ear for the four frequencies 500, 1000, 2000 and 4000 Hz. Most definitions of hearing impairment vary between countries and are often linked to compensation systems. The following table shows the classification adopted since 1991 by WHO.

	Grade of hearing impairment	Audiometric ISO value[a] (dB, better ear)	Performance
0	No impairment	≤25	No, or very slight, hearing problems. Able to hear whispers.
1	Slight impairment	26–40	Able to hear and repeat words spoken in normal voice at 1 m.
2	Moderate impairment	41–60	Able to hear and repeat words using raised voice at 1 m.
3	Severe impairment	61–80	Able to hear some words when shouted into better ear.
4	Profound impairment, including deafness	≥81	Unable to hear and understand even a shouted voice.

Chronic occupational noise-induced hearing loss is considered to be always sensorineural and there is typically bilateral and symmetric hearing loss. The first indication of hearing loss due to noise exposure is a "notching" of around 10dB in the audiogram, usually maximal at 4 kHz but within the range of 3 and 6 kHz, with recovery at 8,000 Hz. The exact location of the audiometric notch is dependent upon the frequency of the damaging noise and the length of the ear canal amongst other factors. Although a notch is not infrequently seen at 6 kHz it is considered variable and of limited importance. Additionally, the effects of ageing may obscure the usual "notch" showing a bulging away from the expected age-associated hearing loss. Noise exposure alone usually does not produce a loss greater than 75 dB in high frequencies and 40 dB in lower frequencies. However, individuals with superimposed age-related losses may have hearing threshold levels in excess of these values. The loss of hearing deteriorates most in the first 10-15 years of exposure but then decreases as hearing threshold increases. Following cessation of noise exposure the progression of hearing loss then follows the expected age-related rate.

1.2.1 Hearing impairment caused by noise ICD Code H83.3 +Z57.0

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: NIHL usually progresses through four phases:
  - Phase 1: in the first 10-20 days of exposure to noise, tinnitus arises at the end of the work shift, together with a sensation of fullness and pressure in the ear, mild headache, a feeling of fatigue and daze, and hearing loss that is, however, reversible as long as the individual withdraws from exposure.
  - Phase 2: in this phase, that can last from few months to many years, subjective symptoms are absent, except for tinnitus (that may be experienced occasionally), and alterations that can be highlighted only by an audiometric examination (e.g. a permanent threshold shift at 4 kHz).
  - Phase 3: the subject becomes aware that his/her hearing capacity is not normal, as he/she is unable to hear the ticking of a clock, or understand all the sentences in a conversation especially within a noisy environment. A phenomenon called "recruitment" might occur, characterized by sounds becoming rapidly louder with increasing sound level; threshold shift at 4 kHz worsens and involves other frequencies.
  - Phase 4: a clear sensation of hearing impairment and impaired speech discrimination occur.
- Examinations: in most cases, pure tone audiometry shows a bilateral and symmetrical neurosensory loss, starting in the 4-6 kHz range and then expanding to lower frequencies.

Differential diagnosis

- History of deafness since childhood (congenital deafness may be associated with maternal rubella, flu, or prenatal medication, birth trauma).
- Familial deafness.
- Childhood illnesses such as measles (which usually results in bilateral deafness) or mumps (which usually results in unilateral deafness), encephalitis, meningitis, cerebral abscesses.
- Prolonged use of ototoxic drugs, such as streptomycin, gentamycin, neomycin.
- History of head injury.
- History of radiotherapy, especially at the head and neck regions.
- Presbycusis (especially for those above 50 years of age).
- Infection of the ear (e.g. otitis media).
- Otosclerosis.
- Barotrauma.
- Meniere's disease.
- Brain tumours (e.g. acoustic neuroma).
- Excessive noise exposure from non-occupational sources (e.g. nightclubs, concerts or headphones regularly used with personal music devices).

Exposure assessment

- History of occupational exposure: confirmed personal history of occupational exposure to noise and evaluation of working conditions showing prolonged or repeated exposure to noise levels exceeding 85 dB(A) as 8hr TWA or to repeated peak noise levels of over 137 dB(C). Note that exposure to noise levels over 80 dB(A) as 8hr TWA and peak noise over 135 dB(C) might already represent a source of mild occupational hearing loss.
- Minimum duration of exposure: generally, five years at levels exceeding 85 dB(A) as 8hr TWA; nonetheless, six months at higher daily exposure levels might be sufficient for the most susceptible individuals. Every 3 dB increase in noise exposure doubles the intensity of exposure (given that dB measurements are in a logarithmic scale) and halves the time of onset of adverse effects.
- Maximum latent period: does not apply (hearing loss is gradual and increases with increasing levels of exposure).

1.2.1 Hearing impairment caused by noise	ICD Code H83.3 +Z57.0
Key actions for prevention	The prevention of occupational NIHL is based on the implementation of the principles of occupational prevention: elimination, substitution, engineering control, administrative controls, and personal protective equipment. Elimination is based on avoidance of noise production by changing technologies known to generate less noise whenever possible. As an example, in the manufacturing sector, the use of cast moulding has greatly reduced the necessity of pressing, drilling and cutting metal parts, and the substitution of high-strength organic polymers for metal has greatly reduced the energy requirements for production. These technologies led to a reduction of mechanical noise at the source. In office environments, the noisy mechanical typewriters and dot-matrix printers once used have been superseded by electronic keyboards and ink-jet or laser printers, which are virtually noise-free. The digital storage and transmission of information has decreased the necessity for hard copies of printed material. Structural intervention in workplaces and on machinery as engineering control has been exploited through the enclosure of the noise-producing parts of machinery, the installation of anti-vibration systems, the use of distance between different machinery, and the placing of roof and wall soundproofing. Proper maintenance of machines has several benefits in manufacturing, including a significant reduction of noise at the workplace. In addition, interventions on office buildings aimed at better heat insulation and creation of "tight buildings" reduces external environmental noise. Only when environmental interventions are not sufficient to reduce noise at the workplace to safe levels, workers must be equipped with appropriate personal protective equipment (PPE). PPE, such as earplugs, earmuffs and other devices for hearing protection, need to be selected based on the measured levels of exposure. When equipping workers with PPE it is necessary to take in to due account that using such devices may negatively affect safety, affecting the ability to hear alarms at the workplace. It should be kept in mind that the real-world attenuation provided by hearing protectors might vary widely between individuals and be subject to the degree of compliance in use. In addition, the need of protecting workers from the transmission of noise through anatomical structures, e.g. cranial bones, should be considered, in particular in the presence of very high exposure levels. In any noisy activity where occupational exposure may take place, regular noise monitoring at the workplace, workers' information about the monitoring results, and preventive measures when needed should always be undertaken. Exposed workers should regularly undergo hearing loss evaluation, with the periodicity based on the levels of exposure and local agreements. Since the loss of hearing due to noise is not reversible (except for temporary threshold shift), early detection and intervention is critical to improve NIHL prevention. The clinicians monitoring workers' hearing capabilities have to take into account that individuals with noise-induced hearing loss may experience significant morbidity due to hearing loss, concomitant tinnitus, and impaired speech discrimination. On the job, such hearing loss can affect worker communication and safety (e.g. for a decreased ability in monitoring the work environment and hearing warning sounds) as well as productivity. Other conditions associated with hearing loss may be depression, social isolation, anxiety, irritability, decreased self-esteem and increased risk of accidents. Workers with evidence of hearing loss will benefit from an individualized approach that takes into due consideration their need to communicate safely and effectively and to protect themselves from additional damage due to noise. Summarizing, the mainstay of prevention is to implement reduction of noise at source, whenever possible, removal from noise exposure will avoid progression above the rate that will otherwise occur due to aging. As with any personal protective equipment, hearing protection devices should be regarded as 'last resort' measures, or for sporadic or temporary use. It should be noted that the control of noise levels at the workplace might bring additional benefits as regard potential extra-auditory effects of noise exposure (see above). Finally, country- or area-specific legislations can substantially support the whole prevention process. An authoritative example might be represented by the EU Directive 2003/10/EC, which clearly defines a set of obligations for the employers, deriving from the assessment and measurement of the levels of noise to which the workers are exposed.

1.2.1 Hearing impairment caused by noise ICD Code H83.3 +Z57.0

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▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
1.2.1	Occupational exposure to noise	Z57.0	QD84.Y
1.2.1	Hearing impairment caused by noise (acute/chronic)	H83.3	AB37
1.2.1	Acute acoustic trauma	H83.3	AB37
1.2.1	Noise-induced hearing loss (NIHL)	H83.3	AB37

1.2.2 Diseases caused by vibration (disorders of muscles, tendons, bones, joints, peripheral blood vessels or peripheral nerves) ICD Code T75.2, G62.8, G56.0, M65.4, M70.0 + Z57.7	
Description of the causal agent	The term *vibration* refers to an oscillatory motion of displacement of a body from a reference point along the three orthogonal axes. Oscillatory displacements of an object involve alternately a velocity in one direction and then a velocity in the opposite direction. The relation between the displacement and the acceleration of a motion is dependent on the frequency of oscillation that corresponds to number of cycles per second and is expressed in hertz (Hz). The frequency of vibration affects the extent to which vibration is transmitted to the body (e.g. to the surface of a seat or the handle of a vibratory tool), through the body (e.g. from the seat to the head), and in the body. The magnitude of a vibration can be quantified by its displacement, its velocity or its acceleration. Often, the magnitude of vibration is expressed in terms of an average measure of the acceleration of the oscillatory motion, usually the root-mean-square (m/s^2 RMS). According to the ISO standard (ISO 5349:1986, revised), the exposure to vibration is expressed as an exposure period in combination with an exposure intensity measured in m/s^2, a frequency weighted and an 8 hour time averaged acceleration total value [A(8)]. Vibration may take place in three translational directions and three rotational directions. For seated persons, the translational axes are designated x-axis (fore-and-aft), y-axis (lateral) and z-axis (vertical). Rotations about the x-, y- and z-axes are designated r_x (roll), r_y (pitch) and r_z (yaw), respectively. Human responses to vibration depend on the total duration of vibration exposure. If the characteristics of vibration do not change with time, the root-mean-square vibration provides a convenient measure of the average vibration magnitude. If the vibration characteristics vary, the measured average vibration will depend on the period over which it is measured. Furthermore, root-mean-square acceleration is believed to underestimate the severity of motions that contain shocks, or are otherwise highly intermittent.
Occupational exposures	Many workers experience work-related vibration. For example, workers in mechanical workshops use hand tools that create vibration and forest workers drive all-terrain vehicles that create vibration. Operators of hand tools experience vibration in their hands and arms and all-terrain vehicle operators experience vibration in their whole body. Therefore, occupational exposure to vibration is subdivided into two main categories: hand-arm vibration (HAV) and whole-body vibration (WBV). Sometimes the term hand-transmitted vibration (HTV) is used instead of HAV. Exposure to HTV takes place in any non-occasional occupational activity performed with the use of tools, equipment, machines and devices able to transmit vibrations to the hand-arm system. The main sectors are construction and engineering, where exposure occurs in the use of electrically and pneumatically powered vibrating tools. The exposure is however common in industrial manufacture, forestry and agriculture, as well as in handicraft, servicing and repair jobs. Miners and forestry workers, foundry workers, metal workers and construction workers are at greatest risk too. Examples of tools with significant HTV per different activity are: • Metal workers: percussive metal-working and rotary tools, including powered hammers for riveting, caulking, grinding, spinning, fettling, hammering, clinching and flanging, pedestal grinders, hand-held portable grinders, flex-driven grinders and polishers, and rotary burring tools. • Miners and building construction workers: hammer swaging, percussive hammers, vibratory compactors, strimmers, road and concrete breakers, concrete scabblers, rock drills, impact wrenches, nibblers, needle guns, rammer, chisel, tampers, chipping hammer or other pneumatic tools. • Agricultural and forestry workers: chain saws, brush cutters, circular saws, and shears hardwood cutting machines. WBV is mechanical vibration transmitted into the human body through the surface upon which it is supported. Thus, exposure to whole-body vibration may occur in several activities, the most common of which is driving on irregular surfaces, especially in vehicles with poor vibration damping (trucks, agricultural tractors, forklifts, buses, etc.).

1.2.2 Diseases caused by vibration (disorders of muscles, tendons, bones, joints, peripheral blood vessels or peripheral nerves) ICD Code T75.2, G62.8, G56.0, M65.4, M70.0 + Z57.7

Biological mechanisms, main health effects and diagnostic criteria

Short profile of the biological mechanisms	Many occupational exposures are intermittent, vary in magnitude from moment to moment or contain occasional shocks. The severity of such complex motions can be accumulated in a manner that gives appropriate weight to, for example, short periods of high magnitude vibration and long periods of low magnitude vibration. The adverse effects from exposure to HTV may be assumed to be related to the energy dissipated in the upper limbs. Energy absorption is highly dependent on factors affecting the coupling of the finger-hand system to the vibration source. Variations in grip pressure, static force and posture modify the dynamic response of the finger, hand, and arm and, consequently, the amount of energy transmitted and absorbed. For instance, grip pressure has a considerable influence on energy absorption and, in general, the higher the hand grip the greater the force transmitted to the hand-arm system. Prolonged exposure to HTV from powered processes or hand-held tools such as pneumatic tools (e.g. concrete breakers), chainsaws, grinders, etc. – is associated with an increased occurrence of symptoms and signs of disorders in the vascular, neurological and osteoarticular systems of the upper limbs. HTV causes a range of conditions and diseases, including: white finger, also known as "dead finger", i.e., damage to the hands causing whiteness and pain in the fingers; carpal tunnel syndrome and other symptoms similar to occupational overuse syndrome; sensory nerve damage; muscle and joint damage in the hands and arms, e.g. "tennis elbow". These conditions can have serious personal and occupational consequences for people. The effects can be permanently disabling even after a few years of uncontrolled exposure. The complex of these disorders is commonly called hand-arm vibration syndrome with the terminology of "hand and arm vibration syndrome" used in the ICD-11. The effects on the body from exposure to vibration depends on: length of exposure time, frequency and magnitude or size of the vibration (acceleration, speed or distance covered). Long-term occupational exposures to intense WBV has been predominantly associated with neck, shoulder and lower back pain. The transmitted vibration, static postures, and axial rotation of the spine are likely contributory. Other conditions have been associated including cardiovascular disease, diabetes mellitus type 2, metabolic syndrome and prostate cancer. However reduced physical activity with sedentary work, long work hours, and lack of food choices are confounding issues. The longer a worker is exposed to WBV, the greater the risk of musculoskeletal disorders and possible health effects.

Name of the diseases and ICD code: **Chronic effects of hand-arm vibrations T75.2, G62.8, G56.0, M65.4, M70.0 + Z57.7**

Hand-arm vibration syndrome (HAVS) (T75.2, G62.8)

Short description of the disease

HAVS is sometimes known as dead finger, vibration white finger (VWF), traumatic vasospastic syndrome, pneumatic hammer syndrome and by a number of other colloquial terms. As a consequence of exposure to HTV, individuals may develop a secondary Raynaud's phenomenon (vascular component) and a peripheral sensory neuropathy (sensorineural component) affecting the hands.

With *secondary Raynaud's phenomenon* episodic blanching of the fingers provoked in cold conditions is the characteristic presentation. A typical attack lasts for 20-30 minutes, although it can last longer (up to an hour). On rewarming, a reactive hyperaemia occurs which is often described as a painful aching with redness of the fingers. In some patients, a cyanotic colour is present instead of the red discolouration. Gradual and mild warming of the hands can improve the recovery, although this too may be painful. True digital artery vasospasm is associated with numbness in the fingers due to the transient ischaemia of the digital nerves which is not itself considered to represent evidence of a sensory neuropathy.

1.2.2 Diseases caused by vibration (disorders of muscles, tendons, bones, joints, peripheral blood vessels or peripheral nerves) ICD Code T75.2, G62.8, G56.0, M65.4, M70.0 + Z57.7

The vascular (V) component of HAVS has been classified by the Stockholm Workshop (1986) in four clinical stages (staging to be assessed separately for each hand):

- Stage 0: no attacks.
- Stage 1V (mild): occasional attacks affecting only the tips of one or more fingers.
- Stage 2V (moderate): occasional attacks affecting distal and middle (rarely also proximal) phalanges of one or more fingers.
- Stage 3V (severe): frequent attacks affecting all phalanges of most fingers.
- Stage 4V (very severe): frequent attacks affecting all phalanges of most fingers with trophic skin changes in the fingertips.

With *peripheral sensorineural polyneuropathy*, symptoms typically include tingling and numbness in fingers and hands for more than 20 minutes after the cessation of use of vibrating tools. The symptoms may also be provoked in cold conditions but digital vasospasm should not be present. In later stages reduced sensation of touch, temperature and vibration, and an impairment of manual dexterity can be observed.

The Stockholm Workshop grading system classifies the sensorineural (SN) component of HAVS in 3 clinical stages (each hand staged separately):

- Stage 0SN: no symptoms.
- Stage 1SN (mild): intermittent numbness with or without tingling.
- Stage 2SN (moderate): intermittent or persistent numbness, reduced sensory perception.
- Stage 3SN (severe): intermittent or persistent numbness, reduced tactile discrimination and manipulative dexterity.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: the diagnosis of secondary Raynaud's phenomenon is based on the evidence of a distal to proximal sharply demarcated whiteness of the digits, as a consequence of exposure to cold, in a subject with a personal history of exposure to HTV. The other causes of Raynaud's diseases should always be considered and ruled out. Diagnosis of the sensorineural component of HAVS should be based on a good clinical history. This would normally include:
  - elicitation of intermittent or persistent symptoms of numbness and tingling in the digits;
  - establishing the presence of difficulty with grip and fine dexterity;
  - exclusion of other explanations for these symptoms, in particular other causes of peripheral neuropathy; and
  - onset of symptoms which follow the date of first exposure, rather than preceding it.
- Examinations:
  - Blood tests to rule out other causes of the disease, in particular autoimmunity.
  - Tests of vascular function: no current vascular test has been shown to accurately stage the extent of abnormality in an individual as defined by the Stockholm Workshop scale; uncontrolled cold provocation tests without any standardized criteria against which the results of the challenge can be assessed are of little value. On the other hand, the following tests under controlled conditions with reference values may be of use:
    > doppler examination of the upper and lower extremities;
    > thermometry after cold-water immersion; and
    > cold provocation digital plethysmography.

1.2.2 Diseases caused by vibration (disorders of muscles, tendons, bones, joints, peripheral blood vessels or peripheral nerves) ICD Code T75.2, G62.8, G56.0, M65.4, M70.0 + Z57.7

- Tests of neurological function: quantitative neurosensory tests may contribute to the diagnosis. The earliest symptomatic stage of the sensorineural changes associated with vibration does not show any physical sign, as defined by the Stockholm Workshop scale. Neurosensory signs and symptoms related to tingling and numbness in the hand and fingers in later stages require demonstration on physical examination. Findings of reduced sensory perception are required in stage 2 as is, in addition, reduced manipulative dexterity in stage 3; potentially revealing tests are:
  > clinical testing of sensation with the use of two point or depth perception aesthesiometry, Semmes-Weinstein monofilaments;
  > nerve conduction studies may show alterations typical of carpal tunnel syndrome (i.e., median neuropathy at the wrist – for more details refer to item 2.3.7); and
  > current perception threshold (CPT) or a combination of vibrotactile perception threshold (VPT) and temperature perception threshold (TPT) tests. There is some evidence that the neutral zone of TPT may be diagnostically more sensitive than VPT at a single frequency, but some studies suggest that a combination of both tests may be more diagnostically useful than either test alone.
- Musculoskeletal tests, such as those investigating grip and pinch strength.
- Test of fine motor hand function.
- Purdue pegboard and Moberg pick up tests may confirm reduced manual dexterity and therefore aid diagnosis.

Differential diagnosis

- Raynaud's disease secondary to other health alterations such as scleroderma or other connective tissue diseases, other vascular disease, polycythaemia, use of medication.
- Polyneuropathy and carpal tunnel syndrome of other origin.
- Thoracic outlet syndrome.

Exposure assessment

- History of occupational exposure: confirmed occupational exposure to hand-transmitted vibration prior to the onset of any symptom and, when available, information about HTV levels for specific tools.
- Minimum duration of exposure: typically several years and depending on acceleration level: e.g. 3-10 years for 3-10m/s^2 [A(8)] and 1-3 years for more than 10 m/s^2 [A(8)]. The neurological effects of a temporary threshold shift of VPT can be found after normal subjects have 30 minutes exposure to HTV, although dependent on the exposure acceleration amplitude and frequency. Similarly it is suggested that levels of HTV exposure less than 1 m/s^2 [A(8)] are not considered likely to cause vascular symptoms and this is probably also true of the neurosensory effects.
- Maximum latent period: probably months; the onset is unusual more than two years after the cessation of vibration exposure.

Other effects of hand-arm vibrations	The association between exposure to HTV and carpal tunnel syndrome has also been observed, as well as with radial styloid tenosynovitis and chronic tenosynovitis of hand and wrist. There are reports of vibration causing bone cysts or vacuoles and Dupuytren's disease, but the supporting evidence for these effects is weak. **Carpal tunnel syndrome (G56.0)** Refer to item 2.3.7. **Radial styloid tenosynovitis (M65.4)** Refer to item 2.3.1. **Chronic tenosynovitis of hand and wrist (M70.0)** Refer to item 2.3.2.

1.2.2 Diseases caused by vibration (disorders of muscles, tendons, bones, joints, peripheral blood vessels or peripheral nerves) ICD Code T75.2, G62.8, G56.0, M65.4, M70.0 + Z57.7

Name of the diseases and ICD code: **Chronic effects of whole-body vibrations M54.5, M54.4 + Z57.7**

Low back pain (M54.5), Lumbago with sciatica (M54.4)

The only health effect likely to be caused by whole-body vibrations (WBV) is low back pain (LBP), either limited to the lumbar tract of the spinal cord or associated with radiating pain along innervated areas, in particular the one corresponding to the sciatic nerve distribution (lumbago with sciatica). It is important to underline that LBP is multifactorial in aetiology, with poor correlation between structural abnormalities (as detected on X-ray, CT or MRI), and the occurrence of symptoms and the underlying disease. It can be profoundly influenced by psychological, ergonomic, and socio-economic factors. Nonetheless, back pain can cause significant personal distress for affected workers, as well as lead to high costs through work absenteeism and treatments offered.

Diagnostic criteria

Clinical manifestations (signs, symptoms and examinations)

- Focused history and physical examination are necessary to classify patients into one of five categories: (1) nonmechanical pain; (2) disc pain; (3) facet joint pain; (4) compressed nerve pain, (5) symptomatic spinal stenosis. The patient history should be assessed for psychosocial risk factors sometimes called "yellow flags" for developing chronic symptoms, and screened for "red flags" that may indicate serious causes of back pain.
- Routine use of imaging and other diagnostic testing is not recommended for patients with nonspecific pain. Diagnostic imaging and testing should be performed in patients who have low back pain with severe or progressive neurologic deficits, or when history and examination suggest that a serious underlying condition may be the cause.

Exposure assessment

- History of occupational exposure: confirmed occupational exposure to whole-body vibrations prior to the onset of any symptom and, when available, information about vibration levels and other workplace factors such as body posture, seating, seat-back inclination and postural fatigue.
- Minimum duration of exposure: typically several years.
- Maximum latent period: does not apply (it is considered that the effects of WBV are likely cumulative).

Key actions for prevention	*HAVS* can be avoided or reduced in its incidence by using tools equipped with systems addressed at avoiding or minimizing the vibration coupling between the worker and the tool itself (e.g. by means of remotely operated devices) and tools that vibrate less while maintaining a high standard of performance. Some tasks may require the use of tools with levels of vibration emission considered harmful. A risk assessment may show that use of a tool with higher vibration emission for a short time may enable a task to be completed with less HTV than more prolonged use of a lower emission tool. Job rotation can limit individual worker exposure. Training in correct tool use can limit exposure by ensuring that users do not over grip or force the tool into the work as with road breakers and drills. The proper selection of low vibration tools and their maintenance are key factors (this can be problematic if workers are required to purchase and maintain their own equipment). Personal protection equipment, such as anti-vibration gloves are not particularly effective at reducing the frequency-weighted vibration associated with risk of HAVS and some authorities state they can increase the vibration at some frequencies. There is no reliable way of assessing the vibration reduction, if any, that such gloves provide. Gloves and other warm clothing can be useful to protect vibration-exposed workers from cold and damp conditions, helping to maintain circulation. Workers' health surveillance is a useful secondary prevention measure: this allows early detection of HAVS and indicates the effectiveness of specific preventive measures.

1.2.2 Diseases caused by vibration (disorders of muscles, tendons, bones, joints, peripheral blood vessels or peripheral nerves) ICD Code T75.2, G62.8, G56.0, M65.4, M70.0 + Z57.7	
Key actions for prevention	*LBP due to WBV* can be avoided or its incidence reduced by: • introducing working methods which eliminate or reduce exposure, such as minimising the transport of goods or materials or replacing manned with unmanned machines (e.g. remotely controlled conveyors); • choosing work equipment of appropriate ergonomic design (this includes the choice of vehicles): - the difference in vibration emissions of the vehicle itself has to be considered (although this needs to be considered alongside choosing the most appropriate vehicle for the task), - visibility should be such that the machine can be operated without stretching and twisting, - getting in and out of the machine should be easy by using handholds and footholds so that the temptation to climb or jump is minimised, and - access to manually loaded areas should be unimpeded by the machinery structure and involve minimal lifting; • considering the choice of seat (including suspension seats) and the choice of tyres; • providing regular maintenance of vehicles (including their seats and suspension) and of unmade roads and ground conditions throughout sites to suit the machines that use them, as this will greatly reduce shocks and jolts; • designing the layout of workplace sites to reduce the need to transport materials, and so reduce the WBV exposure of drivers/operators; • providing suitable and sufficient information and training for workers particularly on suspension seat adjustment; • limiting the duration and magnitude of exposure; • ensuring the work schedules have adequate rest periods (a recommended precautionary measure is to take a short break between operating mobile machinery and manual handling of materials, to give tired muscles time to recover before handling heavy loads); • protecting workers from cold and damp, cold exposure may accelerate the onset or worsen the severity of back pain; it is good practice to ensure that those working in the cold are provided with warm and, if necessary, waterproof clothing; • reducing exposure below the exposure limit value; and • ensuring that workers' right to know about hazards includes WBV and how to mitigate the effects. We list here some examples of exposure limits (taken from EU directive 2002/44/EC) that, if respected, have been shown to protect the majority of workers from adverse health effects of vibrations: • For *hand-arm vibration:* (a) daily exposure limit value: 5m/s^2 A(8) (note that this value is recommended by the ACGIH as a TLV); and (b) daily exposure action value: 2.5 m/s^2 A(8). • For *whole body vibration* the EU directive 2002/44/EC recommends the following: (a) daily exposure limit value: 1.15 m/s^2 A(8); and (b) daily exposure action value: 0.5 m/s^2 A(8). • For both types of exposure, if the action values are exceeded the employer in the EU must implement an action plan to prevent exposure from exceeding limit values.

1.2.2 Diseases caused by vibration (disorders of muscles, tendons, bones, joints, peripheral blood vessels or peripheral nerves) ICD Code T75.2, G62.8, G56.0, M65.4, M70.0 + Z57.7

Further reading

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▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
1.2.2	Occupational exposure to vibration	Z57.7	QD84.3
1.2.2	Secondary Raynaud's phenomenon due to vibration (effects of vibration, includes pneumatic hammer syndrome, traumatic vasospastic syndrome)	T75.2	BD42.1, NF08.2, NF08.2Y
1.2.2	Small fibre peripheral neuropathy (other specified polyneuropathies)	G62.8	8C0Y
1.2.2	Carpal tunnel syndrome	G56.0	8C10.0
1.2.2	Radial styloid tenosynovitis	M65.4	FB40.5
1.2.2	Chronic tenosynovitis of hand and wrist	M70.0	FB40.Y
1.2.2	Low back pain	M54.5	ME84.2
1.2.2	Lumbago with sciatica	M54.4	ME84.20

1.2.3 Diseases caused by compressed or decompressed air — ICD Code T70, W94

General characteristics of the causal agent	The term *compressed or decompressed air* refers to a condition of the environment where air pressure exceeds or is significantly less than atmospheric pressure measured at sea level (one standard atmosphere). This condition may be harmful to humans; the associated diseases are directly due to the effect of pressure itself on the human body, or the consequences of inhaled gases at pressure, or to events that occur when the body is brought back to ambient pressure. The organs that are most susceptible to hyperbaric and hypobaric conditions are: middle ear, sinuses, lungs, and the bone tissue.
Occupational exposures	Occupational exposure to hyperbaric circumstances occurs in professional underwater diving (ship salvage, oil pipe construction and repair, military and emergency training and operations), in construction using pneumatic caissons and tunnels, and in hyperbaric and decompression chambers. Occupational exposure to hypobaric circumstances occurs during the return to atmospheric pressure levels following exposure to high pressures (e.g. professional underwater divers, building workers in pneumatic caissons, health workers who tend to patients in hyperbaric chambers), but can occur at high altitudes, while flying, and in hypobaric chambers during training of commercial and military crews. In modern commercial aircraft, the cabin is pressurized to a moderate low-pressure equivalent to 2,000-2,500 m above sea level.
Biological mechanisms, main health effects and diagnostic criteria	
Short profile of the biological mechanisms	Liquids are not easily compressed and are not subject to volume variation when the pressure changes, whilst Boyle's law for gases states that for any gas, at a constant temperature, the volume varies inversely with the total pressure. Contraction of the volume of gas causes damage with an implosive mechanism, whilst expansion causes damage with an explosive mechanism. In addition, at higher than normal atmospheric pressure, the partial pressure of nitrogen and oxygen is proportionally higher. While oxygen is absorbed for aerobic metabolism, inhaled nitrogen dissolves in the body fluids, tissues and cavities. In water, pressure increases by one atmosphere for every 10 meters of depth. At normal atmospheric pressure (1 atm or 1 bar or 1 kg/cm^2), the body tissues and blood are fully saturated with air. When subjected to increased pressure, more of the inhaled gases (mainly nitrogen and oxygen) are taken up by the blood and tissues. If the ambient pressure is reduced too quickly, dissolved gases nucleate as bubbles and increase in volume causing impaction and damage. The symptoms and signs of nitrogen bubbles blocking blood vessels and leading to tissue damage from complex mechanisms is called decompression sickness. Similarly, gases that were compressed within body cavities increase in volume and may cause direct barotrauma. Finally, when exposed to a lower than normal atmospheric pressure, such as that at a high altitude (approximately above 2,800 to 3,000 meters), the body receives less oxygen than physiologically required. Metabolic impairment leads to slowed physiological and psychological reactions to environmental conditions, along with changes occurring to the cardiovascular and respiratory systems.

Name of the diseases and ICD code: **Acute diseases caused by the mechanical effect of pressure: Otic barotrauma (T70.0), Sinus barotrauma (T70.1), Pulmonary barotrauma (T70.2), Arterial gas embolism (T79.0)**

Short description of the disease

The term *barotrauma* refers to mechanical damage caused to tissues by changes in ambient pressure: the injury is sustained from failure to equalize the pressure of an air-containing space with that of the surrounding environment. Barotrauma can affect several different areas of the body, including the ear, face and lungs:

- *Barotrauma of the outer, middle, and inner ear* can be related both to the volume contraction due to an increase of external pressure or volume increase due to reduction of the external pressure.
- *Barotrauma of the sinuses* occurs when the changes in gas volumes within the paranasal spaces with changing environmental pressure cannot be compensated by the communication of gas between the sinuses and the nasopharynx. There may be mucosal oedema and mucosal detachment with submucosal haematoma and blood clots. The presence of obstructions such as nasal polyps may represent a predisposing factor.

1.2.3 Diseases caused by compressed or decompressed air — ICD Code T70, W94

- In *pulmonary barotrauma*, over-distension of the lungs with a rapid reduction in environmental pressure may lead to rupture. This can occur with an ascent from diving at depths as shallow as 1 meter when using diving equipment with pressurised air. The volume of air in the lungs at depth can exceed the total lung capacity, which may lead to barotrauma if the excess air is not exhaled, or when the diver coughs, sneezes or takes a deep breath. Pulmonary barotrauma causes mediastinal emphysema, pneumothorax and may also lead to arterial gas embolism, since communication is opened for the entry of air into the circulation. An uncommon condition is a "lung squeeze" due to overcompression of the lungs during diving descent in breath-hold and surface supply diving. The effects may be chest pain, haemoptysis, pulmonary haemorrhage and death.
- *Arterial gas embolism* occurs when the lung ruptures as a result of pulmonary barotrauma, and gas is released into the pulmonary venous system, with a varying amount of gas bubbles bringing about flow obstruction. When this condition affects the brain, it takes the name of *cerebroarterial embolism*.

Diagnostic criteria

Clinical manifestations of barotrauma of the ear

- Signs and symptoms: "clogging" of the ear, ear pain, ear discharge, haemorrhage from the ear, reduced hearing, ringing of the ear (tinnitus), tympanic membrane abnormalities, dizziness and impaired balance. If the oval or, more commonly, round window tear, the perilymph may leak from the inner to the middle ear (perilymph fistula).
- Examinations: depending of the portion of the ear affected, pure tone audiometry may show sensorineural, conductive or mixed hypoacousis.

Clinical manifestations of barotrauma of the sinuses

- Signs and symptoms: nasal discharge, dental pain, facial paraesthesia.
- Examinations: radiologic abnormalities may be absent in many cases; in other cases, CT scans may show partial to complete opacification of one or more of the paranasal sinuses. Magnetic resonance imaging may show an area of hyperintensity.

Clinical manifestations of pulmonary barotrauma

- Signs and symptoms: chest pain, dyspnoea and haemoptysis following lung rupture.
- Examinations: physical examination may show subcutaneous emphysema of the thorax, decreased cardiac dullness, decreased heart sounds, hoarseness, and features of pneumothorax according to severity. Chest X-ray and CT may show pneumomediastinum or pneumothorax.

Clinical manifestations of arterial gas embolism

- Signs and symptoms: they depend on the affected body regions, and are due to severe hypoxia. In its most severe form, arterial gas embolism has a catastrophic onset, with collapse, loss of consciousness, apnoea, and cardiac arrest. In victims who do not die suddenly, the signs and symptoms of arterial gas embolism can vary substantially. Sudden loss of consciousness, hemiparesis, confusion and coordination loss follow gas embolization to the brain. If the initial signs and symptoms do not resolve spontaneously, neurological deficits of varying severity tend to persist.

Exposure assessment

- History of occupational exposure: confirmed work activities carried out in conditions where there are pressure excursions above or below atmospheric pressure level.
- Minimum duration of exposure: seconds.
- Maximum latent period: none for ear and sinus barotrauma; 36 hours for pneumothorax and mediastinal emphysema. The onset of arterial embolism is typically observed a few minutes after decompression.

1.2.3 Diseases caused by compressed or decompressed air ICD Code T70, W94

Name of the diseases and ICD code: **Decompression sickness (T70.3)**

Short description of the disease

Decompression sickness, also known as decompression illness (DCI), 'bends', diver's disease or caisson disease, is caused by gas dissolution into the tissues or blood under reduced pressure, such as when ascending from diving or flying at high altitudes. The symptoms are caused by expanding gas bubbles in blood and tissues, depending on the site of their mechanical obstruction and the inflammatory cascade that may ensue. In the case of flying, bubbles do not usually form at low altitudes unless the individual has been diving in the preceding 24 hours.

A common presentation of decompression illness is an influenza-like condition. Other frequent complaints are various sensory disorders, local pain, particularly in the limbs, and other neurologic manifestations, which may involve higher functions, special senses and motor weariness, less commonly, the skin and lymphatic systems may be involved. In some groups of hyperbaric workers, the most common presentation of decompression illness is pain. This may be a discrete pain about a specific joint or joints, back pain or referred pain, when the pain is often located in the same limb as are overt neurologic deficits; less commonly, in an acute decompression illness, vague migratory aches and pains may be noticed. Pain in the joints, muscles or limbs (called 'bends') may develop soon after working, in an hour or even later. The pain can be severe or mild. Occasionally, workers may suffer from a more serious type of compressed air illness affecting the nervous system, lungs or heart. Workers usually feel and appear ill. The onset can be during or soon after (usually within 45 minutes) decompression or up to 24 hours later. Decompression illnesses due to the formation of bubbles in tissues and in blood vessels usually become evident within minutes or hours after decompression. Indeed, it is reasonable to state that the manifestations of decompression illnesses are protean. Any illness in a hyperbaric worker that occurs up to 24-48 hours after a decompression should be assumed to be related to that decompression until proven otherwise. The symptoms include myalgia, arthralgia, loss of balance, neurological manifestations with weakness, paralysis, paraesthesiae or loss of consciousness, breathing difficulties including haemoptysis or pleuritic pain, skin rash and cutis marmorata, and collapse with shock. DCI can be fatal or result in permanent disability and should be treated as a medical emergency.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms:
  - *Musculoskeletal symptoms* result in osteoarticular pain, acute dysbaric osteo-arthralgia (ADOA) or "*bends*". DCI is generally seen in the knee as a common site for caisson workers, saturation divers and aviators. Other joints such as the shoulder, hip, elbow and ankle are also affected. An ill-defined discomfort develops over an hour or so into a dull ache followed by a pain of fluctuating intensity. Untreated, the pain will increase over the following 24 hours before diminishing over the following week.
  - *Neurological manifestations* of DCI on air diving tend to affect the brain, the spinal cord and the peripheral nerves. Repetitive air dives seem to cause more spinal DCI effects. Spinal cord DCI is characterized by ascending paraesthesia and paralysis and is frequently accompanied by bowel and bladder dysfunction. Disturbance of cerebral function is less common, although well documented, and may include behavioural change or even loss of consciousness.
  - *Skin DCI* is present in 10-15% of cases, and symptoms range from pruritus to marbling of the skin, which is a serious sign of DCI, because similar effects occur in other organs.
  - *Pulmonary DCI*, or "*chokes*", causes tachypnoea, cough and chest pain when around 10% of the pulmonary vascular bed is affected. This may progress to an adult respiratory distress syndrome with evidence of right heart failure and pulmonary oedema.
  - *DCI affecting the cochlea* presents with tinnitus and sensorineural hearing loss. Deep helium diving to >100m can cause hearing loss in isolation but more commonly it occurs together with other symptoms.
- Examinations: CT scan or MRI can usually identify gas bubbles.
- The diagnosis is confirmed when any of the above mentioned symptoms is relieved with recompression, within 24 hours of diving (or flying).

Exposure assessment

- History of occupational exposure: confirmed history of diving work especially involving rapid resurfacing. The condition may occur following a drop in pressure such as when flying.
- Minimum duration of exposure: minutes.
- Maximum latent period: few hours.

1.2.3 Diseases caused by compressed or decompressed air — ICD Code T70, W94

Name of the diseases and ICD code: **Chronic effects: dysbaric osteonecrosis (M90.3* + T70.3†)**

Short description of the disease

Dysbaric osteonecrosis (DON) is a form of avascular necrosis or aseptic bone necrosis that is linked with previous experience of DCI or inadequate decompression. The mechanism of the pathologic process is not completely understood, and the bone changes are not necessarily related to the site of the previous DCI. The most common sites are the shoulder, knee and the hip, with around 20% going on to articular collapse. Medullary lesions occur in the femur and humerus and suggest a risk of further DON. Common areas involved are the lower end of the femur and upper end of the tibia. Where the joint surfaces such as the hip or shoulder joints are involved, about 22% have been reported to become disabled. The risk factors may include high pressures, long exposure duration, rapid decompression and previous DCI treatment. The exact cause is still unknown. It can be detected by conventional radiography although MRI of the bones and joints is more sensitive.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: in most cases, if the affected bone does not involve the joints, there are no visible symptoms. The juxta-articular lesions may be asymptomatic, but the presentation is usually with pain on movement of the joint; symptoms can develop over months to years as the result of secondary osteoarthritic changes. Other causes of aseptic necrosis must be excluded.
- Examinations: diagnosis is best made by MRI appearance since X-ray changes take longer to appear and do not show the full extent of damage.

Exposure assessment

- History of occupational exposure: confirmed previous occupational experience of decompression. In well-managed military divers, estimates of 2.5% incidence of the diseases are reported, although much higher rates are seen in some studies of commercial divers.
- Minimum duration of exposure: single exposures to hyperbaric environments have been recorded.
- Maximum latent period: the onset of the disease can be after many years of working in compressed air. Diagnosis can be delayed and the disease ignored by the affected worker.

Name of the diseases and ICD code: **Acute conditions caused by the toxic effects of inhaled gases: Nitrogen narcosis, Hypoxia, High pressure neurological syndrome (W94)**

The conditions that follow do not strictly relate to the effect of compressed and decompressed air. However, since they mostly apply to professional diving activities, a brief description of their characteristics is considered to be useful in the present item.

Short description of the disease

- *Nitrogen narcosis* identifies inert gas narcosis, also known as "*rapture of the deep*", which is probably due to a mechanism similar to that of anaesthesia. The depth of the water is the main determinant of the risk.
- *Hypoxia* is inadequate oxygenation of body tissues. It might occur as a consequence of gas supplies being contaminated with carbon monoxide or having a low pO_2, or because a diver may exhaust the cylinders carried; it might also be a feature of breath-hold diving on ascent.
- *High-pressure neurological syndrome (HPNS)*, also known as high pressure nervous syndrome, is distinct from inert gas narcosis and is associated with the use of helium and oxygen mixtures for diving below 100m.

Diagnostic criteria

Clinical manifestations of nitrogen narcosis

- Signs and symptoms: cognitive impairment is the most significant effect, whilst motor coordination tends to be less affected. Mood may be affected, causing euphoria or, in some cases, anxiety and terror. Other effects include vertigo and visual or auditory disturbances. Effects are usually observed during diving on air at more than 30m.

Clinical manifestations of hypoxia

- Signs and symptoms: sudden loss of consciousness, although this may be heralded by impaired concentration and reduced performance.

1.2.3 Diseases caused by compressed or decompressed air — ICD Code T70, W94

Clinical manifestations of HPNS

- Signs and symptoms: tremors of the hands are typical symptoms along with myoclonic jerks, dizziness, sleepiness, nervousness, visual disturbance, dyspnoea, nausea, decreased mental performance, and somnolence. Tremor returns to normal following decompression; however when HPNS has been experienced, changes in long-term memory and psychomotor performance may persist.
- Examinations: electroencephalogram alterations (e.g. impairment of alpha rhythm and increase in 2-7 Hz activity, sometimes with interhemispheric differences).

Exposure assessment

- History of occupational exposure: confirmed history of diving work.
- Minimum duration of exposure: immediate to minutes.
- Maximum latent period: few minutes.

Key actions for prevention

The risk of rapid change in pressure is significantly lower in compressed air work where compression/decompression rates and working chamber pressure levels are controlled by a pressure lock operator. However, explosive decompression can occur as a result of equipment failure. Most situations where workers are exposed to hyperbaric conditions or to high altitude are unavoidable. However, the very recent use of remote-controlled or "smart" self-governing equipment can avoid the deployment of workers at the actual site to perform operations.

In most cases, technical improvements of equipment, health-based selection of workers and the surveillance of their health conditions are integrated to prevent accidents and occupational diseases. Workers involved in activities carried out in hyper-/hypo-baric conditions should undergo regular health surveillance, performed by occupational health professional specialized in compression/decompression-related disorders. Preplacement evaluation of fitness for work is important for workers in hyper-hypo-baric conditions both for their own and the safety of co-workers or other third parties. Health surveillance has the dual purpose of identifying early signs and symptoms of the abovementioned disorders, as well as of assessing the workers' continuing fitness for work.

In the natural environment of the deep sea and high altitude, the effect of extreme cold temperature needs to be taken into consideration to correctly plan prevention interventions [see item 1.2.6(1)]. For prevention of decompression sickness related to flying, at least 12 hours should be spent at ground level after diving; this time should reach 24 hours if the dive lasted more than four hours and 48 hours if the subsequent flight is to be at an altitude above 8,000 ft (about 2,500 meters). Individuals should be selected after being tested in a decompression chamber, to exclude their susceptibility to decompression sickness. Exposure to altitude should be limited by use of pressurized aircraft. Finally, denitrogenation by breathing 100% oxygen should be performed before take-off.

The safety of underwater work benefits from the wealth of physiological knowledge gained over more than one century of military and civil activities. Both free divers and surface-supplied divers undergo pre-placement and periodic checks according to agreed protocols and schedules, and their activities are tracked to highlight early signs of health impairment. For professional and leisure underwater diving, and for professional crew of leisure divers, the best prevention lies in the use of the most advanced technical equipment and means (including artificial breathing gases that use inert gases as diluents of oxygen with a water solubility lower than that of nitrogen) and in the accurate planning of operations, including the use of decompression tables suggested by several agencies to take into account individual scenarios (water depth and temperature, ambient height level, duration of the diving, extent of physical exercise necessary to perform the task). Compression and decompression standardized procedures should be always identified and stated in working activities involving hyper-/hypo-baric conditions. Professional on board ship divers are assisted by specialized crew and health professionals. The vessels are equipped with life-sustaining equipment, that include stationary decompression chambers for large groups and individual decompression chambers that can be air-deployed to specialized health care units.

Professional divers who perform industrial tasks meet this scenario in the most demanding jobs. However, there is still a great number of professional divers in the informal sectors who use improvised, if any, equipment to perform underwater jobs, such as pearl diving, aquaculture, fishing and underwater repairs. A proper training of these workers is fundamental in prevention strategies. Risk assessment and careful planning of diving operations is in any case recommended.

Some national guidelines suggest limits of exposure for working in compressed air conditions, such as 0.7 bar (70 kPa) for periods of time no longer than 8 hours. In addition, people exposed to compressed air should spend at least 12 consecutive hours at atmospheric pressure in any 24-hour period.

1.2.3 Diseases caused by compressed or decompressed air — ICD Code T70, W94

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▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
1.2.3	Otitic barotrauma (external, middle and inner ear)	T70.0	NF04.0
1.2.3	Sinus barotrauma	T70.1	NF04.1
1.2.3	Pulmonary barotrauma	T70.2	NF04.Y
1.2.3	Decompression sickness	T70.3	NF04.2
1.2.3	Arterial gas embolism	T79.0	NF0A.0
1.2.3	Dysbaric osteonecrosis	M90.3* + T70.3†	NF04.2/PH74/PB54
1.2.3	Nitrogen narcosis, Hypoxia, High pressure neurological syndrome	W94	PH74/PB54
	Occupational exposure to risk factors	Z57	WD84.Z

1.2.4 Diseases caused by ionizing radiations	ICD Code T66, W88 +Z57.1
General characteristics of the causal agent	Ionizing radiation is a type of energy released by atoms in the form of electromagnetic waves or particles. Ionizing radiation has so much energy it can cause the separation of electrons from atoms and molecules, a process known as ionization. Ionizing radiation can affect the atoms in living things, so it poses a health risk by damaging tissue and DNA in genes. Some types of radiations of relatively low energy, such as ultraviolet light, can cause ionization under certain circumstances. To distinguish these types of radiation from radiation that always causes ionization, an arbitrary lower energy limit for ionizing radiation is usually set around 10 kiloelectron volts (keV). Ionizing radiations are part of the human environment. There are natural and artificial sources of ionizing radiations. Natural sources are, for example, cosmic rays and naturally occurring radioactive materials, while artificial sources include X-ray machines, radioactive isotopes used in nuclear medicine, gamma cameras, nuclear gauges and nuclear power plants. Ionizing radiations thus include (1) energetic subatomic particulate radiation (e.g. alpha and beta particles emitted from radioactive materials and neutrons from nuclear reactors and accelerators) and (2) electromagnetic radiation (e.g. gamma rays emitted from radioactive materials and X-rays from electron accelerators and X-ray generators). Directly ionizing radiation consists of charged particles. Such particles include energetic electrons, positrons, protons, alpha particles, charged mesons, muons, and heavy ions (ionized atoms). This type of ionizing radiation interacts with matter primarily through the Coulomb force, repelling or attracting electrons from atoms and molecules by virtue of their charges. Indirectly ionizing radiation consists of uncharged particles. The most common kinds of indirectly ionizing radiation are photons above 10 keV (X-rays and gamma rays) and all neutrons. Some essential properties of ionizing radiation are summarised below. *Radioactivity*, i.e., the strength of a radioactive source, is measured in units of Becquerel (Bq): 1 Bq represents one event of radiation emission or disintegration per second. The old unit for this is the Curie (Ci): 1 Bq = 2.7 x 10^{-11} Ci (and 1 Ci = 3.7 x 10^{10} Bq). The *energy* of ionizing radiation is measured in electronvolts (eV); since 1 eV is an extremely small amount of energy, another commonly used unit of measure is the joule, corresponding to 6.24 x 10^{18} eV. When ionizing radiation interacts with the human body, energy is transmitted to the body tissues. The biological effects of ionizing radiations are normally classified into deterministic and stochastic. A *deterministic effect* (e.g. cataract) is a biological effect caused by ionizing radiation whose probability of occurrence is zero at small absorbed doses but will increase steeply to unity (100%) above some level of absorbed dose (i.e., the threshold). A *stochastic effect* (e.g. cancer) is a biological effect caused by ionizing radiation whose probability of occurrence increases with increasing absorbed dose, probably with no lower threshold, but whose severity is independent of absorbed dose. Regarding the threshold, available biological and biophysical data are in agreement with the hypothesis that the risk would continue in a linear fashion at lower doses without a threshold and that even the smallest dose has the potential to cause a small increase in risk to humans. This assumption is termed the "*linear-no-threshold*" (LNT) model. Radiation damage to tissue and organs depends on the dose of radiation received or the absorbed dose. The potential damage from an absorbed dose depends on the type of radiation and the sensitivity of different tissues and organs. The absorbed dose is the amount of energy absorbed per unit weight of the organ or tissue and is expressed in units of gray (Gy). 1 Gy is defined as 1 joule of energy deposited in 1 kilogram of mass. The old unit of measure for this is the rad: 1 Gy = 100 rad.

1.2.4 Diseases caused by ionizing radiations — ICD Code T66, W88 +Z57.1

Equal doses of all types of ionizing radiation are not equally harmful to human tissue. To account for the way in which different types of radiation cause harm in tissue or an organ, radiation dose is expressed as equivalent dose in units of sievert (Sv). The *equivalent dose* in Sv is equal to the total external and internal absorbed doses multiplied by a 'radiation weighting factor': this is a number that, for a given type and energy of radiation, is representative of values of the relative biological effectiveness of that radiation in inducing stochastic effects at low doses. The values of the radiation weighting factor are related to linear energy transfer (i.e., the energy a charged particle imparts to matter per unit length as it traverses the matter). The *effective dose* (still measured in Sv) is used to measure ionizing radiation in terms of the potential for causing harm: it takes into account the type of radiation and sensitivity of tissues and organs and is the sum of the weighted equivalent doses in all the tissues and organs of the body. Formally, it corresponds to the sum of organ doses multiplied by the 'tissue weighting factor': this represents the contribution of tissue or organ to the total detriment due to all of the stochastic effects resulting from uniform irradiation of the whole body, and it is used because the probability of stochastic effects due to an equivalent dose depends on the tissue or organ irradiated. The old unit of measure for equivalent/effective dose is the rem: 1 Sv = 100 rem.

The table below summarises units of measure (u.m.) and conversion factors for some of the abovementioned properties:

Property	Current u.m.	Former u.m.	Conversion factor
Radioactivity	Becquerel (Bq)	Curie (Ci)	1 Bq = 2.7 x 10^{-11} Ci 1 Ci = 3.7 x 10^{10} Bq
Absorbed dose	Gray (Gy)	rad	1 Gy = 100 rad
Equivalent/Effective dose	Sievert (Sv)	rem	1 Sv = 100 rem

Occupational exposures

The use of radioactive sources involves risks due to radiation exposure. Exposure to ionizing radiation occurs in many occupations.

Ionizing radiations are present in X-ray machines, used not only in health care activities but also in industry, particle accelerators, gamma radiography sources, nuclear reactors, any activity involving use of isotopes, uranium and other mines, any other activity conducted underground, and ordinary workplaces in areas that are rich in radon emission. Radon daughters are airborne radioactive isotopes produced in the uranium decay chain. Radiation dose to the lungs due to inhalation of airborne radon daughters is the main concern in underground uranium mines as well as in other underground activities, radon daughters are of concern in some indoor environments where the soil or the building materials are contaminated with radium. Aircrew members are exposed to cosmic radiation, a form of ionizing radiation coming from the outer space that include galactic cosmic radiation and solar particle events, sometimes called "solar flares".

Artificial sources of radiation are commonly used in the manufacturing, service, and defence industries, in research institutions and universities, and in the nuclear power industry. They are extensively used by physicians and health professionals, in the diagnosis and treatment of diseases.

Biological mechanisms, main health effects and diagnostic criteria

Short profile of the biological mechanisms

Ionizing radiation is capable of depositing enough localized energy to dislodge electrons from the atoms with which it interacts. Thus, as radiation collides randomly with atoms and molecules in passing through living cells, it gives rise to ions and free radicals, which break chemical bonds and cause other molecular changes that injure the affected cells.

Any molecule in the cell may be altered by radiation, but DNA is the most critical biological target because of the limited redundancy of the genetic information it contains. Damage to DNA that remains unrepaired or is misrepaired may be expressed in the form of mutations, the frequency of which appears to increase as a linear, non-threshold function of the dose (approximately 10^{-5} to 10^{-6} per locus per Gy). Radiation damage to the genetic apparatus may cause changes in chromosome number and structure, the frequency of which has been observed to increase with the dose in radiation workers, atomic bomb survivors, and others exposed to ionizing radiation.

1.2.4 Diseases caused by ionizing radiations — ICD Code T66, W88 +Z57.1

Short profile of the biological mechanisms

Among the earliest reactions to irradiation is the inhibition of cell division, which appears promptly after exposure, varying both in degree and duration with the dose. Although the inhibition of mitosis is characteristically transitory, radiation damage to genes and chromosomes may be lethal to dividing cells. Mature, non-dividing cells are relatively radioresistant, but the dividing cells in a tissue are radiosensitive and may be killed in sufficient numbers by intensive irradiation to cause the tissue to become atrophic. The rapidity of such atrophy depends on cell population dynamics within the affected tissue: in organs characterized by slow cell turnover (e.g. the liver and vascular endothelium), the process is typically much slower than in organs characterized by rapid cell turnover such as the bone marrow, epidermis and intestinal mucosa. For most effects of radiation, the sensitivity of exposed cells thus varies proportionally with their rate of proliferation and inversely with their degree of differentiation. In this context, the embryo and growing child are especially vulnerable to injury, and the lesions appear sometime after irradiation, whether this has been brief or prolonged. Radiation effects encompass a wide variety of reactions, varying markedly in their dose-response relationships, clinical manifestations, timing and prognosis. The effects are often subdivided, for convenience, into two broad categories: (1) *heritable* effects, which are expressed in the descendants of exposed individuals (whose germ cells are affected), and (2) *somatic* effects, which are expressed in exposed individuals themselves. The latter include acute effects, which occur relatively soon after irradiation, as well as late (or chronic) effects, such as cancer, which may not appear until months, years or decades later.

The acute effects of radiation result predominantly from the depletion of progenitor cells in affected tissues and can be elicited only by doses that are large enough to kill many such cells (i.e., a threshold can be identified). For this reason, such effects are viewed as *nonstochastic*, or *deterministic*, in nature, in contrast to the mutagenic and carcinogenic effects of radiation, which are viewed as *stochastic* phenomena resulting from random molecular alterations in individual cells that increase as linear, non-threshold functions of the dose. Although the existence of thresholds for these effects cannot be excluded, their frequency is assumed to increase with any level of exposure.

The nature, frequency and severity of the somatic effects thus depend on the quality of radiation as well as on the dose and conditions of exposure. In this context, it is worth mentioning that gamma rays and neutrons represent the main concern for external exposure, while alpha particles are the least penetrating and do not present a risk of radiation dose from external exposure (as the surrounding air, clothing, or outer layer of the skin will absorb them). On the contrary, they are the main concern in case of internal exposure, which might occur when the radioactive material is inhaled, swallowed, or absorbed through the skin or cuts and wounds.

Name of the diseases and ICD code: **Acute diseases caused by ionizing radiations**
(Specific disease code) **+T66, W88 +Z57.1**

Acute radiation syndrome: Aplastic anaemia (D61.2), Medullary hypoplasia (D61.9), Gastroenteritis and colitis (K52.0), Neurovascular effects (G40.5, R25.1, R27.0, T73.2)

Short description of the disease

The acute effects of ionizing radiation consist of a syndrome known as acute radiation syndrome (or sickness), radiation toxicity or radiation poisoning. It is one of the deterministic effects due to whole body irradiation. The disease appears after intense exposure to mostly external ionizing radiation and may last for several months. The symptoms depend on the levels of exposure suffered: for smaller doses, gastrointestinal and haematological effects are prominent, consisting of nausea, vomiting and symptoms related to bone marrow impairment such as infection and bleeding. In cases of exposure to relatively higher doses, neurological effects such as seizures and rapid death may appear.

The speed of the onset depends on the absorbed dose: in higher exposure, the delay is shorter, and vice versa. Although the entire body, or a significant portion of it, must have received the dose in order for acute radiation syndrome to develop, the type of effects depends on the body areas primarily exposed: hematopoietic syndrome is observed as a consequence of exposure of the areas of bone marrow actively forming blood elements (such as the pelvis and sternum in adults), the neurovascular symptoms require exposure of the brain, whilst gastrointestinal syndrome is usually not observed if the stomach and intestines are not exposed.

In summary, the main phase of the illness typically takes one of the following forms, depending on the predominant locus of radiation injury: haematological, gastrointestinal, and neurovascular.

Diagnostic criteria

In general, doses up to 100 mSv are not characterized by any clinical effect. From 100 to 500 mSv some laboratory changes can be observed, in particular a decrease in lymphocyte count.

1.2.4 Diseases caused by ionizing radiations — ICD Code T66, W88 +Z57.1

Clinical manifestations of the haematological form

In the case of bone marrow massive exposure, the main feature is aplastic anaemia with initial lymphopaenia, accompanied by neutropaenia and thrombocytopaenia. Chromosomal aberrations are usually present, and lymphocytes are the most sensitive indicators of bone marrow injury, with the consequent onset of infections, bleeding, and anaemia in heavily exposed subjects. These changes are usually observed for doses above 1 Gy, but they have been reported after a whole-body acute dose as low as 0.25 Gy. In severe cases of radiation injury, bone marrow aplasia may lead to death. Death may occur in some individuals at 1.2 Gy, the LD50/60 (the dose necessary to kill 50% of the exposed population in 60 days) is about 2.5 to 5 Gy.

Clinical manifestations of the gastrointestinal form

Nausea, vomiting, loss of appetite, diarrhoea, and abdominal pain are usually observed as a consequence of a dose of 6-30 Gy. In the gastrointestinal apparatus, the oesophagus and rectum are relatively radioresistant, whilst the stomach and small intestine are much more sensitive, the first symptoms affecting the gastrointestinal tract are usually observed for doses higher than 500 mSv. If the latency of symptoms is less than one hour (e.g. within 30 minutes), it is possible to estimate that the whole body dose has been >3 Gy, if more than three hours <1 Gy.

Clinical manifestations of the neurovascular form

Neurovascular effects are observed in the case of exposures greater than 30 Gy, though they may occur at 10 Gy. The main symptoms are dizziness, tremor, ataxia, headache, or decreased level of consciousness. The onset is, in the most severe cases, within minutes to a few hours. Neurovascular effects are usually followed by fatality.

Exposure assessment

- History of occupational exposure: evidence of external whole-body irradiation exceeding at least 1 Gy for X-ray or gamma-ray irradiation and 0.3 Gy for neutrons. Chromosomal aberrations may represent a useful marker of radiation exposure and dose.
- Minimum duration of exposure: few minutes.
- Maximum latent period: two months.

Acute pulmonary manifestations due to radiation (J70.0)

Short description of the disease

The lung is not highly radiosensitive, but rapid exposure to a dose of 6 to 10 Sv can cause acute pneumonitis to develop in the exposed area within one to three months.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: cough, dyspnoea, fever, chest pain, up to respiratory failure.
- Examinations: radiation pneumonitis can usually be observed as ground glass opacities at CT scan.

Exposure assessment

- History of occupational exposure: evidence of occupational exposure to ionizing radiations to lungs, as either external or internal beam radiation (after inhalation of radioactive materials), usually exceeding doses of about 6-7 Gy.
- Minimum duration of exposure: few weeks.
- Maximum latent period: months.

Thyroiditis (E06.9), Hypothyroidism (E03.9)

Short description of the disease

Although the thyroid gland is not particularly sensitive to ionizing radiations, acute effects (thyroiditis and hypothyroidism) can be observed for external irradiation in the neck area or in case of inhalation/ingestion of iodine isotopes (with consequent accumulation in the gland). In particular, exposure to iodine-131, which is absorbed by the thyroid gland like ordinary iodide, can cause destruction of the thyroid cells and thus provoke hypothyroidism.

1.2.4 Diseases caused by ionizing radiations ICD Code T66, W88 +Z57.1

Diagnostic criteria

Clinical manifestations

- Signs and symptoms:
  - Thyroiditis is characterised by rapid destruction of thyroid tissue, resulting in pain, tenderness, tachycardia, insomnia, weight loss.
  - Hypothyroidism becomes manifest with reduced heart rate, asthenia, anorexia, and weight gain.
- Examinations:
  - At the initial stages of thyroiditis, destruction of thyroid tissue results in the release of stored T3 and T4 and suppression of the thyroid-stimulating hormone (TSH). As the disease progresses into overt hypothyroidism, serum TSH levels elevate, free triiodothyronine (FT3), and free thyroxine (FT4) levels decrease.
  - Thyroid ultrasonography shows hypoechogenic thyroid.

Exposure assessment

- History of occupational exposure: evidence of occupational exposure to iodine isotopes via inhalation/ingestion or intense external irradiation of the neck area. Clinically significant acute thyroiditis is unlikely at radiation doses below 200 Gy; for hypothyroidism, the radiation dose is about 60 Gy in case of acute external exposure and 300 Gy in case of prolonged internal exposure.
- Minimum duration of exposure: few minutes.
- Maximum latent period: months.

Alopecia (L58.1)

Short description of the disease

Alopecia, characterized by temporary hair loss, can occur due to partial body irradiation (around the head or neck) or localized irradiation of the scalp.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: temporary hair loss.

Exposure assessment

- History of occupational exposure: evidence of external X-ray or gamma-ray irradiation exceeding 3 Gy around the head or neck or directly to the scalp.
- Minimum duration of exposure: a few minutes.
- Maximum latent period: two months.

Infertility (N46, N97.0)

Short description of the disease

The gonads are the most radiosensitive tissues of the body. A temporary reduction in sperm count, which may last several weeks, can occur for exposure to doses as little as 0.15 Gy, whilst the threshold for transient effects on the ovaries in females is five to ten times higher. A single dose above 2 Gy may cause permanent azoospermia in males. Doses of 2.5–6 Gy or more can cause permanent sterility in both sexes.

Diagnostic criteria

Clinical manifestations

- Oligospermia and azoospermia in men.
- Ovulation failure and menstrual disorders in females.

Exposure assessment

- History of occupational exposure: evidence of external X-ray or gamma-ray irradiation occurring in the occupational setting.
- Minimum duration of exposure: a few minutes.
- Maximum latent period: two months.

1.2.4 Diseases caused by ionizing radiations — ICD Code T66, W88 +Z57.1

Acute radiodermatitis (L58.0)

Short description of the disease

Cells in the germinal layer of the epidermis are highly radiosensitive. As a result, rapid exposure of the skin to a dose of 6 Sv or more causes erythema (reddening) in the exposed area, which appears within a day or so, typically lasts a few hours and is followed two to four weeks later by one or more waves of deeper and more prolonged erythema, as well as by epilation (hair loss). If the dose exceeds 10 to 20 Sv, blistering, necrosis and ulceration may ensue within two to four weeks, followed by fibrosis of the underlying dermis and vasculature, which may lead to atrophy and a second wave of ulceration months or years later.

Diagnostic criteria

Clinical manifestations

- Erythema, following acute exposures above 6-8 Gy or chronic exposures above 30 Gy, mild reddening and papule-like changes have been observed after exposure to lower doses of beta rays, i.e., 3-5 Gy.
- Epilation (hair loss), including alopecia if irradiation occurs around the head or neck or is localized at the scalp: it might be temporary, following acute exposures above 3-4 Gy, or permanent, for acute exposures above 7 Gy or chronic exposures of 50-60 Gy fractioned across several weeks.
- Dry epidermitis, exudative epidermitis, skin ulcerations, and necrosis, following acute exposures above 5 Gy, 12-20 Gy, 18 Gy, and 25 Gy, respectively.

Exposure assessment

- History of occupational exposure: evidence of occupational exposure of the skin to ionizing radiations.
- Minimum duration of exposure: few minutes.
- Maximum latent period: two months.

Name of the diseases and ICD code: **Chronic diseases caused by ionization radiations**
(Specific disease code) **+T66, W88 +Z57.1**

Chronic radiodermatitis (L58.1)

Short description of the disease

Chronic radiodermatitis is one of the delayed effects of ionizing radiations and may occur in individuals who have been repeatedly exposed to low doses of radiation over a long period. Reports from the first years of development of radiological sciences suggest that some tenths of a Sievert per week (or about 5 mGy/day) for long periods (months) are necessary for chronic radiodermatitis to develop.

Diagnostic criteria

Clinical manifestations

The skin is dry and thin and presents ulcerations, atrophy, hyperkeratosis or telangiectasia, and necrosis, together with dystrophic nail alterations. The healing of small skin wounds can be difficult.

Exposure assessment

- History of occupational exposure: evidence of occupational exposure of the skin to ionizing radiations.
- Minimum duration of exposure: six months.
- Maximum latent period: ten years.

Radiation cataract (H26.8)

Short description of the disease

Lenticular opacities and cataracts are considered among the most common delayed effects of ionizing radiation exposure. The eye may be exposed either as a consequence of local or whole-body irradiation. The threshold level for measurable microscopic posterior polar opacities is estimated to be less than 0.5 Gy. A vision-impairing cataract does not appear soon after exposure, as the latent period can be from six months to 35 years, with an average of three years.

1.2.4 Diseases caused by ionizing radiations ICD Code T66, W88 +Z57.1

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: blurred vision, glare, reduced night vision, double vision and a halo around lights. Significant reduction or even disappearance of contrast sensitivity can be observed. Veiling glare can be a problem, as light is scattered by the cataract into the eye.
- Examinations: reduced visual acuity, lens alterations at slit lamp examination and an absent red reflex while performing the ophthalmoscopic examination. Low contrast sensitivity at contrast sensitivity testing could be suggestive.

Exposure assessment

- History of occupational exposure: evidence of acute or fractionated exposures above 0.5 Gy.
- Minimum duration of exposure: it depends on the doses. For low exposures (e.g. 0.15 Sv/year), many years.
- Maximum latent period: up to 35 years (with an average of three years).

Chronic radiation syndrome (T66, W88)

Short description of the disease

Chronic radiation syndrome is observed after months or most likely years of chronic whole body high exposure to radiation at doses lower than those able to cause acute effects. The threshold for the syndrome is between 0.7 and 1.5 Gy, at dose rates above 0.1 Gy/yr. Major symptoms are inhibition of haematopoiesis and neurologic dysfunctions.

Diagnostic criteria

Clinical manifestations

- The most typical changes in peripheral blood are moderate but persistent leucopoenia, induced by the decrease in the number of neutrophils, and thrombocytopaenia. In some cases, absolute lymphopaenia has been noted.
- Impaired neurovascular regulation, autonomic dysfunction, and fatigue, with disturbances of motor and reflex movements, have been reported, the latter especially in long-term exposed subjects. After high doses (4.5 Gy), encephalomyelitis-type changes may occur in the nervous system.
- Dysfunction in other organs, most likely as a consequence of autonomic nervous system impairment has been reported, including: arterial hypotonia, altered secretory function of the gastric mucosa, mild thyroid dysfunction, and metabolic changes in the myocardium.

Exposure assessment

- History of occupational exposure: evidence of long-term occupational whole body exposure to an average ionizing radiation dose >~0.1 Gy/yr.
- Minimum duration of exposure: few months.
- Maximum latent period: few years.

Chronic bronchitis, Chronic pulmonary disease, Pulmonary fibrosis due to radiation (J70.1)

Short description of the disease

Chronic effects in the lung can appear some months or years after exposure to ionizing radiations and include bronchitis, interstitial pneumonitis, and, in the most severe cases, pulmonary fibrosis. Fibrosis can also develop in subjects without prior pneumonitis.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: cough, dyspnoea, fever, chest pain, up to respiratory failure.
- Examinations: some deterioration in pulmonary function usually occurs as fibrosis progresses; volume loss, mediastinal shift and bronchiectasis may all be seen at chest X-ray and CT scan.

Exposure assessment

- History of occupational exposure: evidence of occupational exposure of the lung through either external radiation from a beam or internal radiation after inhalation of radioactive materials (usually higher than 18 Gy for protracted exposures).
- Minimum duration of exposure: few months.
- Maximum latent period: few years.

1.2.4 Diseases caused by ionizing radiations — ICD Code T66, W88 +Z57.1

Reproduction and teratogenesis effects (T66,W88), Congenital malformation syndromes (Q86.8)

Short description of the disease

Genetic effects occurring in males and females after conception are mainly stochastic, as ionizing radiation is mutagenic to germ cells.

On the contrary, intrauterine effects are mainly deterministic: a total dose lower than 1 mSv during pregnancy has not been associated with an increased risk of adverse pregnancy outcomes. However, in certain accidental circumstances, radiation exposure of a pregnant person can cause foetal deformities. Although radiosensitivity is relatively high throughout prenatal life, the effects of a given dose vary markedly, depending on the developmental stage of the embryo or foetus at the time of exposure. During the pre-implantation period, the embryo is most susceptible to killing by irradiation, while during critical stages in organogenesis (mostly occurring in the first ten weeks of gestation) it is susceptible to the induction of malformations and other disturbances of development. In addition, prenatal high dose exposure to ionizing radiation in weeks 8-15 and, to a lesser extent, in weeks 16-25 has been associated with an increased risk of severe intellectual disability, with a threshold estimated to be around 0.4 Gy in weeks 8-15 and 0.1-0.2 Gy in weeks 16-25.

In summary, exposure to ionizing radiation can cause low birth weight, miscarriages, developmental disorders, birth defects (e.g. anencephaly, anophthalmia, general stunting), and childhood cancer (especially leukaemia). In particular, cerebral and skeletal deformities have been observed for foetal irradiation doses exceeding 0.3 Gy during the period of organogenesis, while general learning disability has been reported for foetal irradiation doses exceeding at least 300 mGy after the eighth week of intrauterine life.

Name of the diseases and ICD code: **Carcinogenic effects of ionizing radiations (T66, W88 +Z57.1)**

All different types of ionizing radiation from various sources (X-ray and gamma-ray, neutrons, and internalized alpha- and beta-particles emitting radionuclides) have been observed to cause cancer and classified as a Group 1 carcinogen by the IARC. For further details, refer to dedicated item 3.1.10.

Key actions for prevention	The use of ionizing radiation is unavoidable in most current applications, especially in human and veterinary health care and in the quality control of some manufactured items. In health care, some of the diagnostic functions that are performed by X-ray imaging (radioscopy and radiography) now require much less exposure of patients, and post-acquisition digital image processing allows improvement of the quality of radiographic images and avoidance of unnecessary repeated X-rays. Complementary or alternative techniques for diagnostic imaging, such as ultrasonography and nuclear magnetic resonance, do not entail the use of ionizing radiations. In the industrial and manufacturing sector, most use of X-ray and of other nuclear equipment is aimed at detecting undesired metal fragments in goods and in industrial packaged food, at assessing on-site the quality of metal welds, and at fast analysis of some complex materials by X-ray fluorescence imaging. For some of these applications, whenever alternatives that do not entail the use of ionizing radiation are made available, they rapidly become preferred to simplify operations and to overcome the regulatory difficulties inherent in the use of ionizing radiations and of radioactive materials. The objective of radiation safety is to eliminate or minimize the harmful effects of ionizing radiation and radioactive material on workers, the public and the environment while allowing their beneficial uses. The following principles should guide the use of ionizing radiation and the application of radiation safety standards: 1. No practice involving exposures to radiation should be adopted unless it produces sufficient benefit to the exposed individuals or to society to offset the radiation detriment it causes (the *justification of a practice*). 2. In relation to the exposure of workers and members of the public, the magnitude of individual doses, the number of people exposed, and the likelihood of exposure should all be kept as low as reasonably achievable (ALARA), economic and social factors being taken into account, with the restriction that the doses to individuals delivered by the source be subject to dose constraints (the *optimization of protection and safety*).

1.2.4 Diseases caused by ionizing radiations	ICD Code T66, W88 +Z57.1
Key actions for prevention	3. The exposure of individuals should be restricted so that neither the total effective dose nor the total equivalent dose to relevant tissues or organs caused by possible combinations of exposures due to authorized practices exceeds any relevant dose limit. The limit on effective dose represents the level above which the risk of stochastic effects due to radiation exposure is considered to be unacceptable. For localized exposure of the lens of the eye, the extremities, and the skin, this limit on effective dose is not sufficient to ensure the avoidance of deterministic effects (*individual dose and risk limits*). For occupational exposure of workers over the age of 18 years, the dose limits are: • an effective dose of 20 mSv per year averaged over five consecutive years* (100 mSv in 5 years) and of 50 mSv in any single year; • an equivalent dose to the lens of the eye of 20 mSv per year averaged over five consecutive years* (100 mSv in 5 years) and of 50 mSv in any single year; and • an equivalent dose to the extremities (hands and feet) or to the skin** of 500 mSv in a year. *The start of the averaging period shall be coincident with the first day of the relevant annual period after the date of entry into force of these Standards, with no retrospective averaging. **The equivalent dose limits for the skin apply to the average dose over 1 cm^2 of the most highly irradiated area of the skin. The dose to the skin also contributes to the effective dose, this contribution being the average dose to the entire skin multiplied by the tissue-weighting factor for the skin. The employer, who has been notified of the worker's suspected pregnancy or of personal breast-feeding must adapt the working conditions in respect of occupational exposure so as to ensure that the embryo or foetus or the breastfed infant is afforded the same broad level of protection as is required for members of the public. For occupational exposure of apprentices of 16 to 18 years of age who are being trained for employment involving radiation and for exposure of students of age 16 to 18 who use sources in the course of their studies, the dose limits are: • an effective dose of 6 mSv in a year; • an equivalent dose to the lens of the eye of 20 mSv in a year; and • an equivalent dose to the extremities (hands and feet) or to the skin** of 150 mSv in a year. Radiation doses can be reduced mainly through: • minimizing the time of exposure; • increasing the distance between the body and the radiation source: this will reduce exposure by the square of the distance; and • using absorber (shielding) materials such as Plexiglas® for beta particles and lead for X-rays and gamma rays. In general, the dose limits for occupational exposure apply equally to male and female workers. However, because of the possible relevance of the greater sensitivity of the embryo or foetus or the breastfed infant to radiation, additional controls should be considered for pregnant and breastfeeding workers. Workers who are aware or who suspect that they are pregnant or who are breastfeeding should be encouraged to notify their employer, and they should typically be excluded from tasks in an emergency unless such tasks can be carried out within the requirements for occupational exposure established by the regulatory authority, in accordance with the relevant international radiation protection and safety standards. Areas where any possibility of exposure has been identified should be restricted to people adequately trained, equipped with dosimeters and with personal protective equipment such as lead aprons, gloves and collar; protective lenses. Admittance into these areas should be forbidden to unauthorized/unequipped persons during irradiations for example, during X-ray examinations in health care facilities. Doors of X-ray facilities should be equipped with systems able to automatically inhibit any function of the X-ray device when open.

1.2.4 Diseases caused by ionizing radiations ICD Code T66, W88 +Z57.1

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▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
1.2.4	Diseases caused by ionizing radiations	T66, W88	NF00, PB53, PH73
1.2.4	Acute radiation syndrome	T66, W88	NF00
1.2.4	Aplastic anaemia	D61.2	3A70.Z, 3A70.11
1.2.4	Medullary hypoplasia	D61.9	3A70.Z
1.2.4	Gastroenteritis and colitis	K52.0	DA94.31, DB33.41
1.2.4	Neurovascular effects	G40.5, R25.1, R27.0, R53.0	8A6Z; 8A04.Y, MB45.0; MG22
1.2.4	Acute pulmonary manifestations due to radiation	J70.0	CA82.0
1.2.4	Thyroiditis	E06.9	5A03.Z
1.2.4	Hypothyroidism	E03.9	5A00.Z
1.2.4	Alopecia	L58.1	ED70.Z
1.2.4	Infertility	N46, N97.0	GB04.Z, GA31.Z
1.2.4	Acute radiodermatitis	L58.0	EL60
1.2.4	Chronic radiodermatitis	L58.1	EJ71
1.2.4	Radiation cataract	H26.8	9B10.2Y
1.2.4	Chronic radiation syndrome	T66, W88	NF00, PB53, PH73
1.2.4	Chronic bronchitis, Chronic pulmonary disease, Pulmonary fibrosis due to radiation	J70.1	CA82.1
1.2.4	Reproduction and teratogenesis effects	T66, W88	NF00, PB53, PH73
1.2.4	Congenital malformation syndromes	Q86.8	LD2F.Y
	Occupational exposure to radiation	Z57.1	QD84.Y

1.2.5 Diseases caused by optical (ultraviolet, visible light, infrared) radiations including laser ICD Code W89, W90 +Z57	
General characteristics of the causal agent	Optical radiations part of the electromagnetic spectrum with a wavelength range from 100 nm to 1 mm. This range includes *ultraviolet radiations* that are classified according to wavelength as UV-A (315-400 nm), UV-B (280-315 nm) and UV-C (100-280 nm). *Visible light* for the human eye refers to electromagnetic radiation with a wavelength between 380 nm and 760 nm. *Infrared radiations* are classified in many ways according to the intended purpose. The International Commission on Illumination (CIE) classifies wavelengths as IR-A (760 nm - 1400 nm), IR-B (1400 - 3000 nm), IR-C (3000 nm - 1 mm). *Laser* ("light amplification by stimulated emission of radiation") is a device that amplifies electromagnetic oscillations at wavelengths between the far-infrared and ultraviolet.
Occupational exposures	Occupational exposure to optical radiation occurs in most jobs, although only some specific activities raise concern for workers' health. *Natural ultraviolet radiation*. Exposure to natural UV radiation occurs in outdoor work, especially in direct sunlight, over reflecting surfaces of water, snow, and desert, in tropical countries, and at high altitudes. Occupational groups at high risk include farmers, gardeners, construction workers, roofers, bricklayers, road construction and quarry workers, sailors and fishermen, and postal workers. Workers with fair skin (skin type I-III, see below) are, particularly at risk. Recent dosimeter studies have revealed >500% additional exposure to UV radiation in outdoor workers compared to indoor workers. Outdoor occupational groups in northern Europe had about 600 Standard Erythemal Doses (SED) of exposure per year, whereas the average annual UV exposure for the general population in the region was about 130 SED. These measurements demonstrate that the UV exposures for outdoor workers (e.g. masons, roofers, quarry workers, horticulturists, postmen, bath attendants etc.) could exceed the standard exposure guideline set by the International Commission on Non-Ionizing Radiation Protection (ICNIRP) of 1 SED/day (i.e., 100 J/m^2/day) by up to 5 times. *Natural infrared radiation*. Exposure to natural infrared radiation and subsequent radiant heating occurs in any indoor and outdoor activity involving heat exposure [see item 1.2.6(2)]. *Artificial ultraviolet radiation*. Artificial UV radiation is used for several applications where workers' exposure is possible. Major sources of exposure are metal welding equipment (oxyacetylene and hydrogen torch, plasma arc and xenon welding), bactericidal lamps, industrial lasers, polymer curing, photo-lithography. *Artificial visible radiation*. When daylighting is deficient or absent in a confined environment, the electrical illuminants emit visible radiation. *Artificial infrared radiation*. All unshielded sources of artificial radiant heat entail operators' exposure to infrared radiation. For the thermal effects of flames and of hot bodies, such as furnace glare and molten glass, see item 1.2.6(2). Welding arcs emit radiation in the range of wavelengths from 200 to 1,400 nm (0.2 to 1.4 µm). *Lasers*. Lasers have increasing industrial uses for material cutting, drilling and machining, and high-accuracy measurements for alignment and levelling in the construction industry, mining, land surveying, marine surveying and similar applications. Lasers are frequently used in surgical applications and in common appliances, such as laser pointers for conference speakers, household items and for leisure activities.
Biological mechanisms, main health effects and diagnostic criteria	
Short profile of the biological mechanisms	Health effects of the different types of optical radiations depend on their capacity and mode of interaction with biological material. The International Commission on Illumination (Commission Internationale de l'Éclairage – standard CIE S 009 / E:2002 / IEC 62471:2006) specifies exposure limits, measurement techniques, and the classification for evaluation and control of photobiological effects of the different sources of optical radiation, as follows:

1.2.5 Diseases caused by optical (ultraviolet, visible light, infrared) radiations including laser ICD Code W89, W90 +Z57

Short profile of the biological mechanisms

CIE notation	Wavelength	Tissue interaction
UV-C	100 nm – 280 nm	Radiation is absorbed in uppermost cell layers of eye and skin; it is germicidal and highly effective in producing photo-keratoconjunctivitis. Wavelengths shorter than about 180 nm - 200 nm are termed "*vacuum ultraviolet*" (VUV) since radiation is heavily absorbed by the oxygen of the air. VUV usually need not be considered for hazard evaluation for natural UV radiation.
UV-B	280 nm – 315nm	Intermediate absorption depth; highly effective in producing photo-keratoconjunctivitis and sunburn.
UV-A	315 nm – 400 nm	UV penetrates deep into the eye and damages the lens.
IR-A	700 nm – 1400 nm	IR-A radiation focussed onto the retina, but not visible; penetrates deep into the skin; damage is observed in the choroid, retina, iris and lens.
IR-B	1400 nm – 3000 nm	IR-B and C are absorbed by the cornea and lens but do not reach the retina.
IR-C	3000 nm – 1 mm	

All UV radiations have the potential to directly damage DNA, leading to development of skin cancer. Solar radiation has been classified as a Group 1 carcinogen by IARC (carcinogenic to humans).

Chronic exposure to solar UV radiation is a significant risk factor for skin neoplasia. UV-C radiation is less harmful to human skin because the shorter wavelengths get absorbed by the outer layers of the epidermis (*stratum corneum*) and do not reach the deeper living tissue. Whereas the highly erythematous shortwave UV-B is absorbed in the epidermis, the longwave UV-A penetrates deeper layers of the skin (reticular dermis) and can cause skin pigment-darkening (*suntan*) or erythema in excessive exposure; which with repeated occurrence can initiate cellular damage. A table of phototypes (Fitzpatrick skin type) of ICNIRP guidelines is given below and links individual phenotypic characteristics to the risk of developing severe sunburn and initiating skin cancer.

Phototype	Skin response to sunlight	Typical appearance
I	Burns easily and severely (painful burn); tans little or none and peels	People with very fair skin, blue eyes, freckles; unexposed skin is white
II	Usually burns easily and severely (painful burn); tans minimally or lightly, also peels	People most often with fair skin, red or blond hair, blue, hazel or even brown eyes; unexposed skin is white
III	Burns moderately and tans	People with white skin when unexposed; generally dark hair
IV	Burns minimally, tans easily	People with white or light brown unexposed skin, dark hair, dark eyes
V	Rarely burns, tans easily and substantially	People with brown skin
VI	Never burns and tans profusely	People with dark brown or black skin

1.2.5 Diseases caused by optical (ultraviolet, visible light, infrared) radiations including laser
ICD Code W89, W90 +Z57

Short profile of the biological mechanisms

As regards exposure to visible light, unsuitable lighting conditions (poor or excessive light, blinking or flashing lights, light reflection, shade projection, glaring) in the work environment, such as office interiors, can aggravate pre-existing, non-occupational sight impairment of workers with performance deterioration for close work and the monitoring of visual display units (VDUs).

Exposure to infrared radiation exerts thermal effects. For those effects caused by generalized exposure to a working environment at excessively high temperature, see item 1.2.6(2)

Localized exposure to heat-inducing optical radiation, such as that of high energy industrial infrared lasers (mainly carbon dioxide lasers that emit at 10.6 μm) can cause irreversible ocular damage due to coagulative tissue damage that follows a rise in temperature of ~10°C or more in the retina. The high-intensity localized irradiation of visible-wavelength lasers (argon lasers at 457–524 nm; krypton red lasers around 650 nm and diode lasers at 790–830 nm) generate thermal effects when absorbed by biological chromophores. Very short exposures lasting between 10^{-6} and 10^{-3} seconds can result in thermal coagulation of eye tissue, particularly the choroid by krypton red and diode lasers, and the retinal pigment epithelium by argon lasers.

At high irradiation, even exposure to very short wavelength light for a very short time, nanoseconds or less, can produce mechanical disruption of the eye tissue. Shock waves or sonic transients in ocular tissues can be caused by the fast and localized absorption of energy, a sort of instantaneous boiling of the ocular fluid, usually associated with radiation originating from Q-switched or mode-locked lasers.

Name of the diseases and ICD code: **Acute diseases caused by UV radiations** *(Specific disease code)* **+W89 +Z57**

Photo-keratoconjunctivitis caused by UV (H16.2)

Short description of the disease

Keratoconjunctivitis caused by UV is a painful condition characterized by conjunctival hyperaemia, excess lacrimation, blepharospasm and photophobia. The acute inflammatory reaction of the superficial part of the cornea (and conjunctivae) to UV is termed 'photophthalmia'. There is generally a latent period of about 12 hours after UV exposure before damage to ocular tissues becomes apparent. The adverse effects of UV depend on the duration and intensity of the exposure and the degree of penetration. As mentioned above, UV-A reaches the lens, while the cornea absorbs the majority of UV-B. In the most severe forms, the cornea may undergo opacification.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: painful eye (foreign body sensation), eye redness, photophobia, excess lacrimation, myosis and blepharospasm.
- Examinations: corneal and conjunctival alterations at slit lamp examination; for possible deeper lesions, an ophthalmoscopic examination is suggested.

Exposure assessment

- History of occupational exposure: confirmed exposure to UV (B or C) or UV lasers and study of working conditions having evidence of exposure intensity.
- Minimum duration of exposure: about one second.
- Maximum latent period: 48 hours from acute exposure event.

Photokeratitis caused by UV (H16.1)

Short description of the disease

Photokeratitis or ultraviolet keratitis also known as arc eye, flash burns, welder's flash, corneal flash burns, bake eyes, snow blindness (niphablepsia), or photoelectric keratoconjunctivitis, is a condition due to UV exposure from either natural or artificial sources. The condition usually resolves in few days, but in the most severe cases, corneal thinning, neovascularization and scarring may arise.

1.2.5 Diseases caused by optical (ultraviolet, visible light, infrared) radiations including laser
ICD Code W89, W90 +Z57

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: excess lacrimation, photophobia, painful eye (foreign body sensation), blepharospasm and miosis normally observed several hours after exposure.
- Examinations: corneal alterations at slit lamp examination where fluorescent dye staining reveals punctate areas of uptake under ultraviolet light; the ophthalmoscopic examination is suggested in case of possible deeper lesions.

Exposure assessment

- History of occupational exposure: confirmed exposure to UV (e.g. during arc welding) and study of working conditions with evidence of exposure intensity.
- Minimum duration of exposure: about one second.
- Maximum latent period: 48 hours from acute exposure event.

Photoretinitis caused by UV (H31.0)

Short description of the disease

Solar retinopathy or retinal damage caused by UV is recognized as a photochemical reaction. The less severe form is "phototrauma of the retina", bringing about transient blindness. Persistent distortion of visual image and scotoma may occur in severe cases. No subjective symptoms may appear unless burns affect the foveal area.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: blurred central vision instantly or soon after the exposure. Lesions are typically bilaterally distributed.
- Examinations: reduced visual acuity and retinal alterations at the ophthalmoscopic examination. A yellow spot at the fovea is usually observed and likely changing to a reddish area in some days. Visual acuity gets markedly reduced; improvement may be noted in some months, but a tiny central red spot may remain.

Exposure assessment

- History of occupational exposure: confirmed exposure to UV-A, particularly industrial lasers and during welding, and study of working conditions providing evidence of exposure intensity.
- Minimum duration of exposure: fractions of a second.
- Maximum latent period: none.

Photodermatitis, Photoallergic contact dermatitis (L56.8, L57.8, L59.8), Phototoxic drug reaction (L56.0), Photocontact dermatitis, Phytophotodermatitis (L56.2)

Short description of the disease

Photocontact dermatitis often arises from an interaction between UV radiation and products containing photosensitising drugs or chemicals such as coal tar products, insecticides, some sunscreens (e.g. cinnamates or oxybenzone), fragrances, and also some plants having photosensitizing compounds in which case it is called phytophotodermatitis. Phototoxic and photoallergic mechanisms may mediate the reaction.

Diagnostic criteria

Clinical manifestations

- Photocontact dermatitis: clinical features depend on the photosensitising agent involved and the type of reaction it causes in the skin. A phototoxic reaction is generally similar to severe sunburn, whereas a photoallergic reaction appears as an erythema in the areas of contact with the responsible chemical and exposed to the sun.
- Phytophotodermatitis: clinical features include characteristic blisters, swelling, and brown streaks, resulting from brushing against a plant's stems or leaves when outdoors or lime juice squeezing over the photo contact area. With exposure to a photosensitizing plant and light, the reactions usually erupt about 24 hours after exposure and peak at 48-72 hours. Skin lesions may leave behind dark markings on the skin.
- Examinations: photo patch tests and the so-called "stop and resumption test" (i.e., the symptoms disappear once the exposure is interrupted and reappear when further exposure takes place) may verify the diagnosis.

1.2.5 Diseases caused by optical (ultraviolet, visible light, infrared) radiations including laser ICD Code W89, W90 +Z57

Exposure assessment

- History of occupational exposure: confirmed exposure to sunlight and phototoxic substances and study of working conditions providing evidence of exposure intensity.
- Minimum duration of exposure: few minutes.
- Maximum latent period: 48 hours from acute exposure event.

Name of the diseases and ICD code: **Chronic diseases caused by UV radiations** *(Specific disease code)* **+W89 +Z57**

Chronic blepharoconjunctivitis caused by UV (H10.5)

Short description of the disease

Persons undergoing prolonged exposure to UV radiation such as, for example, welders can suffer chronic blepharoconjunctivitis. The condition manifests as irritation and inflammation of the eyelids (blepharitis) and conjunctivitis. Blepharoconjunctivitis occurs when the bacteria that live on the eyelid areas cause irritation and inflammation of the eyelids that spread to the conjunctivae. Blepharoconjunctivitis is treated by regular, frequent washing of eyelashes and warm compress over the eyelids. The manifestation gets better and worse, but it never goes away completely.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: burning, irritated or itchy eyes, redness of eyelids, scaly, dry skin on the eyelids, excess lacrimation, reduced visual acuity, and chemosis. Chronic blepharoconjunctivitis may result in pingueculae, pterygiae and corneal erosion.
- Examinations: reduced visual acuity and exterior alterations at slit lamp examination; ophthalmoscopic examination is suggested in case of possible deeper lesions.

Exposure assessment

- History of occupational exposure: confirmed prolonged exposure to UV during arc welding and study of working conditions with evidence of exposure intensity.
- Minimum duration of exposure: there is no minimum duration; however, the condition may develop in about two weeks' time of exposure, depending on the intensity of the radiation.
- Maximum latent period: some years.

Actinic cataract caused by UV (H26.8)

Short description of the disease

Actinic cataract affects the anterior capsule of the lens and the sub-capsular epithelium and is characterized by a clouding or a loss of transparency of the lens that may range from slight to complete opacity and blindness. Other kinds of eye damage include pterygium (triangular-shaped, vascularised growth onto the cornea), skin cancer proximate to the eyes, and degeneration of the macula. A chain reaction is triggered by UV-A light that begins with amino acid derivatives called kynurenines and ends with protein glycation and cataract development in the lens.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: blurred vision, poor night vision, double vision and a halo around lights, lens opacity, reduced visual acuity, loss of contrast sensitivity and veiling glare (scattering of light into the eye).
- Examinations: reduced visual acuity, lens alterations at slit lamp examination and an absent red reflex while performing the ophthalmoscopic examination. Low contrast sensitivity at contrast sensitivity testing could be suggestive.

Exposure assessment

- History of occupational exposure: confirmed prolonged exposure to UV-A and UV-B rays.
- Minimum duration of exposure: one year.
- Maximum latent period: 15 years.

1.2.5 Diseases caused by optical (ultraviolet, visible light, infrared) radiations including laser ICD Code W89, W90 +Z57

Chronic actinic dermatitis (L59.8)

Short description of the disease

An uncommon type of persistent photosensitivity or light reaction is known as chronic actinic dermatitis. Typically elderly individuals with a long history of pre-existing allergic contact dermatitis (especially to plants, flowers, sunscreens and cosmetics), atopic dermatitis and photocontact dermatitis may develop this photosensitivity reaction.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: the rash develops in the areas of the body exposed to the sun. Lesions are usually itchy, red, inflamed, with scaling and lichenification of the skin, primarily in the areas exposed to sunlight or artificial light. The rash can be provoked even by exposures to the daylight of about a minute, even on dull days and through window glass. Some may react to artificial light sources, especially bare fluorescent lamps.
- Examinations: photo test reactions confirm the presence of hypersensitivity to light. Positive patch-test and photo patch-test reactions to one or more allergens (most often fragrance, sunscreens, colophony and sesquiterpene lactones) occur in 75% of subjects with chronic actinic dermatitis.

Exposure assessment

- History of occupational exposure: confirmed prolonged exposure to sunlight or artificial light and study of working conditions having evidence of exposure intensity, together with a long history of pre-existing allergic contact dermatitis, atopic dermatitis and photocontact dermatitis for many years before the photosensitivity develops.
- Minimum duration of exposure: one minute.
- Maximum latent period: one week.

Name of the diseases and ICD code: **Carcinogenic effects of UV radiations** *(Specific disease code)* **+W89 +Z57**

Non-melanoma skin cancer (C44) and skin malignant melanoma (C43)

Short description of the disease

Chronic cumulative exposure to UV radiation is strongly associated with non-melanoma skin cancer, i.e., invasive squamous cell carcinoma (SCC), actinic keratosis (in situ SCC), Bowen's disease (in situ SCC), and basal cell carcinoma (BCC). To date, in countries with a fair-skinned population, non-melanoma skin cancer is still the most frequent cancer. Given that the predominant age of manifestation of these tumours is beyond 55 years, with aging populations and an overall increase in life-expectancy the incidence of non-melanoma skin cancer is expected to further increase over the next decades in a large number of these countries.

The causal factor is usually represented by solar radiation. The relationship of ultraviolet radiation exposure to melanoma development is less direct, but substantial evidence supports an association. In contrast to non-melanoma skin cancer, melanoma frequently develops in the sun-protected skin, thus suggesting a role of factors other than UV exposure in the genesis of this cancer.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms of BCC: it affects skin areas of head, neck or shoulders. Despite being locally invasive, BCC does not metastasize. Crusting and bleeding in the centre of the tumour frequently develops. It is often mistaken for a sore that does not heal. This form of skin cancer only very seldom causes fatalities. Pigmented BCC characterized by the presence of melanin in the cells may be wrongly diagnosed as melanoma. The tumour may present as pearly nodules (i.e., nodular BCC) or flat, brown or flesh-coloured lesions with a pearly border (superficial BCC).
- Signs and symptoms of SCC: it is a malignant neoplasm of the keratinized epidermal cells characterized by a quick growth and metastasizing capacity. The first manifestation is usually a painless, nonhealing, bleeding skin ulceration in the middle of a verrucous papule or plaque, often manifesting on sun-damaged skin. SCC may present as firm, red nodules or flat lesions with scaly, crusted surfaces; all forms eventually evolve into ulcers, which are typically red with everted edges; skin around the ulcer is usually inflamed and hardened.
- Signs and symptoms of melanoma: it may present in a variety of ways, such as moles that change appearance, large brown spots with darker speckles, or small irregularly bordered lesions with portions that appear red, white, blue, or blue-black.
- Examinations:

  - Observation of the lesion, supported by dermoscopy, usually prompts the diagnosis.

  - Biopsy of the skin remains the most accurate way of assessing the histologic subtype of the tumour.

1.2.5 Diseases caused by optical (ultraviolet, visible light, infrared) radiations including laser ICD Code W89, W90 +Z57

Exposure assessment

- History of occupational exposure: confirmed repeated occupational exposure to solar radiation and working conditions having evidence of exposure intensity. A history of sunburn at the work place(s) should be obtained, even though sunburn is not a necessary condition for the induction of skin cancers.
- Minimum duration of exposure: five years (workers with immunosuppression: one year).
- Maximum latent period: none.

Name of the diseases and ICD code: **Acute diseases caused by visible light** *(Specific disease code)* **+W89 +Z57**

Photoretinitis caused by visible light (H31.0)

Short description of the disease

Broad spectrum light emitted at high power (xenon projectors, arc lamps, flashguns) as well as blue light emitted at 400 to 550 nm may cause the disease. Pathological effects are also caused by class 3 and 4, as well as continuous-wave lasers (see below).

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: acute retinal lesions, ocular pain, transient blindness, persistence of visual image, chromatic deficiency.
- Examinations: reduced visual acuity, exterior alterations at slit lamp examination and retinal alterations at the ophthalmoscopic examination.

Exposure assessment

- History of occupational exposure: confirmed exposure to visible light and working conditions having evidence of exposure intensity.
- Minimum duration of exposure: very short (a few seconds).
- Maximum latent period: one year from acute exposure event.

Name of the diseases and ICD code: **Acute diseases caused by infrared radiations**
(Specific disease code) **+W90 +Z57**

Blepharitis (H01.0) and photokeratitis (H16.1) caused by thermal effects of infrared radiation

Short description of the disease

Thermal effects of infrared radiation can result in blepharitis and keratitis.

Diagnostic criteria

Clinical manifestations of blepharitis

- Signs and symptoms: foreign body and burning sensation in the eyelids with redness, itchy and red eyes, blurred vision.
- Examinations: reduced visual acuity and exterior alterations at slit lamp examination; the ophthalmoscopic examination is suggested in case of possible deeper lesions.

Clinical manifestations of keratitis

Refer to the '*Photokeratitis caused by UV (H16.1)*' paragraph above.

Exposure assessment

- History of occupational exposure: confirmed exposure to broad-spectrum IR-B and IR-C emitters (sun, incandescent light sources) or to industrial lasers (specific sources of IR-B and IR-C are the erbium and carbon dioxide industrial lasers, respectively) and working conditions having evidence of exposure intensity.
- Minimum duration of exposure: about few minutes.
- Maximum latent period: 24 hours from acute exposure event.

1.2.5 Diseases caused by optical (ultraviolet, visible light, infrared) radiations including laser ICD Code W89, W90 +Z57

Heat-related retinal disorders caused by infrared radiation (H30.9)

Short description of the disease

A retinal injury due to heat-related burns can occur in the macula, the most central sensitive area of the retina. Injury to the para-macula, or peripheral retinal region, may have only a minimal effect upon vision, and may in many cases be asymptomatic. Thermal retinal damage is usually irreversible, even though limited visual recovery can be observed in some cases.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: ocular pain, acute lesions, transient or permanent visual loss or blindness.
- Examinations: reduced visual acuity and exterior alterations at slit lamp examination; retinal alterations using ophthalmoscopic examination. A thorough examination may discover the presence of a scotoma. Lesions often do not appear until 48 hours after the exposure. Fluorescein angiography can identify burnt areas not detectable on ophthalmoscopy.

Exposure assessment

- History of occupational exposure: confirmed exposure to IR-A through industrial lasers and working conditions having evidence of exposure intensity.
- Minimum duration of exposure: seconds.
- Maximum latent period: 24 hours from acute exposure event.

Name of the diseases and ICD code: **Chronic diseases caused by infrared radiations**
(Specific disease code) **+W90 +Z57**

Glass blowers' disease (heat-induced cataract) caused by infrared radiation (H26.8)

Short description of the disease

As the name implies, this disease typically occurs among those working in the occupation of glass blowing. Other occupational groups at risk are furnace, molten glass/metals workers, foundry workers or blacksmiths. Chronic exposure to infrared radiation emitted from heating of glass or molten metal is the very likely cause of the disease. Consequent to absorption of infrared radiation by the iris and lens of the eye, there is a probable increase in temperature and protein denaturation in the lens. Damage of the tissues appears as irregularly shaped opacification forms at the posterior cortex of the lens, and that leads to blurring of vision. The severity of the damage depends on the cumulative dose.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: blurred vision, glare effect, poor night vision, double vision and a halo around lights.
- Examinations: reduced visual acuity, lens alterations at slit lamp examination and an absent red reflex while performing the ophthalmoscopic examination. The examination may indicate localized areas of retinal oedema or patches of pigmentary disturbance. Clinically, the infrared cataract starts as a cobweb-like opacity that increases in size and density, developing into a saucer-shaped posterior cataract. If exposure continues, the opacity continues to grow and evolves into a complete opacity similar to senile cataract.

Exposure assessment

- History of occupational exposure: confirmed repeated exposure to IR-A radiation emitted by incandescent glass or metal (~1500°C).
- Minimum duration of exposure: one year.
- Maximum latent period: 15 years.

1.2.5 Diseases caused by optical (ultraviolet, visible light, infrared) radiations including laser ICD Code W89, W90 +Z57

Name of the diseases and ICD code: **Acute and chronic effects of exposure to laser radiations**
(Specific disease code) **W90 + Z57**

Short description of the disease

Laser exposure can cause eye injury. Despite skin representing a more significant target, injury to one's eyes drives significant concern on laser safety. In particular, laser lights in the visible and near-infrared red region affect the cornea and lens of the eye on the retina, with retinal burns, while invisible infrared radiation affects mainly the cornea and the lens and may cause cataracts. Ultraviolet radiation can result in spasm of the ciliary muscles.

The effect of laser radiation varies with the wavelength and part of the eye it interacts. A brief 0.25-second exposure to a <5 mW red laser such as found in red laser conference pointers does not seem to pose any health threat. There is a potential for injury if a person closely stares into a beam of a class 3R for a few seconds. For green laser pointers, the safe exposure time may be less, and with even higher-power lasers instant permanent damage should be expected.

The mechanisms of retinal and eye tissue damages are:

- *Electromechanical/acoustic damage:* laser pulses of extremely high-power density (10^9–10^{12} W/cm^2) of less than 10 microseconds duration can induce a shock wave in the retinal tissue that causes permanent tissue rupture. Acoustic damage affects a relatively larger surface of the retina and is more destructive than a thermal burn.
- *Photoablation:* excimer lasers with nanosecond pulses at ultraviolet wavelengths at power densities of ~108 W/cm^2 can produce photoablative effects (photodissociation of biomolecules).
- *Thermal damage:* high power density laser energy converts into heat in the target tissues. The depth of penetration on a point (ranging from a few micrometers or millimeters diameter) varies with the wavelength of the incident radiation. Heating effects on the extent of tissues are influenced by the target absorption such as free water, haemo-proteins, melanin, and nucleic acids.
- *Photochemical damage:* whereas the light <400 nm does not focus on the retina, there may be cumulative effects over days due to the laser output and UV or blue light from a target interaction.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms:
  - A headache shortly after exposure, excessive watering of the eyes, and random occurrence of floaters (swirling distortions) in normal vision. Floaters are those dead cell tissues detached from the retina and choroid and floating in the vitreous humour. Floaters appear most often after a blink or closing of eyes for a few seconds. Minor corneal burns cause a gritty feeling, like sand in the eye.
  - Exposure to a visible laser can be detected by a bright colour flash, followed by an after-image of its complementary colour. However, if injury occurs at the retinal surface, detection of blue or green colours secondary to cone damage and pigmentation may be difficult.
  - Exposure to the invisible CO_2 laser beam (10,600 nm) causes burning pain in the cornea or sclera.
  - Visual disorientation due to retinal damage may be apparent with any considerable thermal damage.
- Examinations: detailed ophthalmoscopic examination is warranted since laser-related retinal injuries are very difficult to detect.

Exposure assessment

- History of occupational exposure: confirmed exposure to laser working conditions having evidence of exposure intensity
- Minimum duration of exposure: few microseconds.
- Maximum latent period: some years.

1.2.5 Diseases caused by optical (ultraviolet, visible light, infrared) radiations including laser ICD Code W89, W90 +Z57

Key actions for prevention

Exposure to natural sources of optical radiation in workplaces and regular daily activities is unavoidable. The effect of deficient or excessive illumination in the workplace can cause discomfort and lead to diseases. This calls for strategic good lighting design for the various workplace and task requirements.

Epidemiological data from several studies are strongly affirmative that about 5 years of outdoor work (≥75% in the open) triple the risk for actinic keratosis, squamous cell carcinoma, and basal cell carcinoma. Nonetheless, exposure to natural ultraviolet radiation in tasks that are necessarily performed in the open environment, such as by farmers, construction builders, sailors and fishermen, is mostly unavoidable. The most reasonable protection for people remaining in an outdoor environment for a long duration is to adopt personal protection, such as full clothing and sun screens (physical or chemical UV filters) for the exposed areas, full eye protection with the use of eyeglasses and goggles, and an organization to aim at minimizing exposure in the situations where exposure is highest. In detail, according to the STOP principle:

- Substitution: though usually serving as the primary strategic aspect in prevention, it may not be feasible in outdoor professions.
- Technical measures: sun shields.
- Organizational measures: schedule work tasks out of the highest UV irradiation phase between 11 AM and 3 PM (85% of daily UV radiation exposure); thus also avoiding IR-induced heat stroke, spending all breaks in full shade.
- Personal protective equipment: brimmed hats, neck protection, long-sleeved shirts and long trousers, gloves, and broad-spectrum sunscreens (UVA/UVB, Sun Protection Factor ≥ 30).

Outdoor workers generally lack skin cancer awareness and have higher risk behaviour and low health literacy. For that reason, tailored health education for outdoor workers is pivotal to enable sun-smart behaviour. Secondary prevention for skin cancer surveillance should be made available to all outdoor workers.

Laser radiation, high intensity UV, and IR radiation warning signs must be displayed both inside and outside the work area. The workplace planning and work practices may be organized according to the classification of the types and sources of optical radiations, and thereby preventing eye injury or skin damage. Personal protective devices, like eye protection devices, invariably can bring substantial relief against occupational risks.

Labeling the laser equipment with an appropriate safety class number is an effective way to educate workers about the ocular risk associated with the use of different types of laser equipment.

To protect workers and other users of laser equipment from the ocular risk of their use, laser equipment is labelled with a safety class number. The International Electrotechnical Commission standard (IEC 60825-1:2014) has given a detailed specification of different classes of the laser.

Low-powered lasers (Class 1 and Class 1M) emitting visible light radiation are potentially less dangerous. In case Class 2 and 3A lasers are used, a trained laser safety officer should carry out an assessment of the potential radiation hazard and implement appropriate controls. Where Class 3B and 4 lasers are used, the operators should wear eye protection at all times. Moreover, Class 3A/3R, 3B and 4 lasers can cause eye injury not only by direct line-of-sight viewing but also by reflected or scattered beams by smooth mirror-like surfaces. This latter scenario is often difficult to forecast, and can be the source of serious or irreversible damage to the eye since reflection is mostly unexpected. Therefore, in rooms where work with lasers is carried, the walls should only be non-reflective, and non-scattering tools should be used. Even plastic covers, wristwatch glasses, jewellery can be reflective enough to cause a beam reflection sufficiently intense to blind a distant, unrelated and unaware operator.

All workers should undergo eye examinations before and during their employment to work with Class 3B and 4 laser products. In the industrial use of a laser, it is mandatory for all operators to be trained in their tasks, usage, and maintenance of the devices and aware of the incurring risks for safety and health. For any accidental exposure of the eye to a laser, a medical examination of the operator should be conducted.

1.2.5 Diseases caused by optical (ultraviolet, visible light, infrared) radiations including laser ICD Code W89, W90 +Z57

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1.2.5 Diseases caused by optical (ultraviolet, visible light, infrared) radiations including laser ICD Code W89, W90 +Z57

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▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
1.2.5	Exposure to man-made visible and ultraviolet light	W89	XE436
1.2.5	Exposure to other nonionizing radiation (infrared, laser)	W90	XE6JQ
1.2.5	Photo-keratoconjunctivitis caused by UV	H16.2	9A60.Y
1.2.5	Photokeratitis caused by UV	H16.1	9A73, 9A78.Z
1.2.5	Chronic blepharoconjunctivitis caused by UV	H10.5	9A60.4
1.2.5	Photoretinitis caused by UV and visible light	H31.0	9B62
1.2.5	Actinic cataract caused by UV	H26.8	9B10.2Y
1.2.5	Blepharitis caused by thermal effects of infrared radiation	H01.0	9A06.Y
1.2.5	Photokeratitis caused thermal effects of infrared radiation	H16.1	9A72
1.2.5	Heat-related retinal disorders caused by infrared radiation	H30-9	9B65.2
1.2.5	Cataract caused by IR (Glass blowers' disease)	H26.8	9B10.2
1.2.5	Photo dermatitis	L56.8, L57.8, L59.8	EJ6Y, EK2Z, EK01
1.2.5	Phototoxic drug reaction	L56.0	EH75
1.2.5	Photocontact dermatitis, Phytophotodermatitis	L56.2	EK2Z
1.2.5	Chronic actinic dermatitis	L59.8	EJ30.1
1.2.5	Skin malignant melanoma	C43	2C30.Z
1.2.5	Non-melanoma skin cancer	C44	2C3Z
	Occupational exposure to risk factors	Z57	QD84

1.2.6(1) Diseases caused by exposure to extreme cold temperatures ICD Code T68, T69, L50.2, T33-T35, T95 +Z57.6	
General characteristics of the causal agent	The internal temperature (core body temperature) of the human body needs to be maintained at 37°C ± 2°C. If it rises or falls beyond this, an impairment of health can arise, with a severity dependent on the difference between the ideal temperature of 37°C and the one reached by the subject. A core temperature below 35°C represents the threshold for hypothermia. The main factors affecting the effects of cold environments to workers are air temperature, wind speed, and humidity. In particular, workers feel colder if wind speed increases, and humid air conducts away heat out of the body faster than dry air. The most reliable way to obtain an estimate of core body temperature in cold conditions is rectal measurement.
Occupational exposures	The most favourable temperatures are between 15° and 22°C for work with moderate physical activity. Anyone working in a cold environment may be at risk of cold stress. Some workers may be required to work outdoors in cold environments and for extended periods, for example, snow clean-up crews, sanitation workers, construction and ground activities, reindeer herding, forestry activities, sawmills, underwater diving, farming, tourist industry working, trapping, police officers and emergency response and recovery personnel, e.g. firefighters, search and rescue teams, and emergency medical technicians. High exposures to cold temperatures may occur in activities performed in cold indoor environments such as food freezing, food processing, and storing in chilled environments. The sources of cold exposure can be the ambient air, usually outdoors, local exposure from cold plates and surfaces in fish and food industries and restaurants, cold waters in diving and in rescue operations. Exposure to extreme or moderate temperatures and high air velocity outdoors or indoors cause cold exposure. The repair and maintenance of power lines, high rise buildings and other technical facilities constitute one of the main sources. Most incidents caused by exposure to cold have been reported among occupational groups such as agricultural and fishery workers, craft and related trades workers, plant and machine operators, assemblers and technicians, and associated professionals.
Biological mechanisms, main health effects and diagnostic criteria	
Short profile of the biological mechanisms	The human body's mechanisms of heat retention are significantly less efficient than its ability to dissipate heat. The mechanisms of heat retention and production include: peripheral vasoconstriction, piloerection, and shivering. Leading to metabolic heat production from muscle activity, shivering may hinder a worker's performance, although physical activity can generate heat through a general increase in metabolic activity. If the skin temperature falls due to cold exposure then alternate vasoconstriction and vasodilatation may follow. Generalised shivering increases as core temperature falls, with supervening exhaustion then death. There are mainly two cold-related pathologies: hypothermia and frostbite. Hypothermia is defined as a decrease in the core body temperature to at least 35°C. It is usually graded as mild, moderate or severe according to the core temperature. The condition occurs when the heat dissipation is greater than the rate of metabolic production and external heat gain. Frostbite is a freezing cold injury to the skin, which does not recover within 30 minutes (frostnip). The body areas most prone to frostbite are the hands, feet, nose, ears and cheeks. Several other diseases are either caused or triggered by cold exposure: cardiovascular disorders are seen in the peripheral vessels (Raynaud's phenomenon), in coronary arteries (ischaemic heart disease, IHD), and in cardiac function (arrhythmias). Whether cold as such will generate IHD is uncertain. Epidemiological studies report high IHD rates and high mortality in populations living in the cold climate zones. The risk of cardiac mortality and risk of stroke is estimated to grow below the optimal temperature zone at the rate of 1%/1°C. The respiratory system responds by spasm, mucus secretion, swelling of the epithelial cells and breathing difficulties. Workers with asthma and chronic obstructive pulmonary disease (COPD) may find cold exposure to be a triggering factor for breathing difficulties. There has been uncertainty whether cold as such can cause asthma. The recent evidence on cold exposure in intensive physical work and particularly in winter sports such as cross country skiing shows high rates of non allergic type of asthma. Finally, it has to be noted that the combined cognitive (i.e., lowered alertness), psychomotor and musculoskeletal effects of exposure to cold temperatures affect the worker's performance and increase the risk of accidents. This is an important factor in several types of work such as high radio mast and windmill maintenance, driving of vehicles like snowmobiles in reindeer herding, and cold water diving. While not directly related to occupational diseases, cold-induced effects should be taken into account in accident investigations and in accident risk assessment.

1.2.6(1) Diseases caused by exposure to extreme cold temperatures ICD Code T68, T69, L50.2, T33-T35, T95 +Z57.6

Name of the diseases and ICD code: **Acute effects of cold (T68, T69, L50.2, T33-T35) +Z57.6**

Exposure to cold may cause systemic problems such as hypothermia with decreased core body temperature and local soft tissue injury classified as:

- Non-freezing, that includes immersion hand and foot, chilblains, and cold urticaria.
- Freezing, that includes frostnip, superficial and deep/complicated frostbite.

Hypothermia (T68)

Short description of the disease

This condition is defined as a core body temperature of below 35°C. As the core temperature falls, cognitive and neurological functioning decreases. People working in and around cold water are at risk of "cold shock" and subsequent immersion hypothermia, which can render them unable to swim leading to drowning. Inadequate clothing hastens hypothermia. The table below reports a classification of hypothermia by core body temperature, with corresponding symptoms and signs.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: numbness, stiffness or pain (especially in the neck, arms and legs), poor coordination, slurred speech, slow breathing and pulse, low blood pressure, severe shivering, confusion and collapse. As hypothermia progresses, atrial fibrillation is common at body temperatures less than 32°C, but as the core temperature drops further the risk of cardiac arrest increases.
- Examinations: core body temperature reading of below 35°C.

Exposure assessment

- History of occupational exposure: confirmed occupational exposure to cold.
- Minimum duration of exposure: in general, in cold, dry environments, hypothermia occurs over a period of hours; in cold water, core temperature can drop to dangerous levels in a matter of minutes.
- Maximum latent period: 24 hours.

Phase	Core temperature (°C)	Physiological reactions	Psychological reactions
Normal	37	Normal body temperature	Thermoneutral sensation
	36	Vasoconstriction, cold hands and feet	Discomfort
Mild hypothermia	35	Intense shivering, reduced work capacity	Impaired judgment, disorientation, apathy
	34	Fatigue	Conscious and responsive
	33	Fumbling and stumbling	
Moderate hypothermia	32	Muscle rigidity	Progressive unconsciousness, hallucinations
	31	Faint breathing	
	30	No nerve reflexes, heart rate slow and almost unnoticeable	Consciousness clouds
	29		Stuporous
Severe hypothermia	28	Heart dysrhythmias (atrial and ventricular)	
	27		
	26	Pupils not reactive to light, deep tendon and superficial reflexes absent	
	25	Death due to ventricular fibrillation or asystole	

1.2.6(1) Diseases caused by exposure to extreme cold temperatures
ICD Code T68, T69, L50.2, T33-T35, T95 +Z57.6

Non-freezing cold injuries (NFCI) (T69.0, T69.1, L50.2)

- *Frostnip* is a condition in which superficial tissues are affected by temporary loss of peripheral sensation accompanied by slight freezing. Recovery is complete after a 30-minutes rewarming period. The condition typically affects one or more finger or toe tips.
- *Immersion hand and foot (or trench foot)* is caused by prolonged exposure of the hands or feet to damp, unsanitary, and cold conditions (0-15°C). Damage to the neurovascular structures lead to pain, paraesthesia, hyperhidrosis with possibly lifelong effects. Tissue damage may result in gangrene requiring surgery. Clinical appearances have been divided into four stages: stage 1 (injury), stage 2 (rewarming), stage 3 (hyperaemia), and stage 4 (recovery).
- *Chilblains* are localised inflammatory lesions in the extremities due to cold exposure also known as perniosis. The bluish-red lesions are possibly caused by prolonged vasoconstriction due to a small vessel vasculitis triggered by cold. They present as itchy or painful red-purple macules, papules or plaques, most commonly affecting the fingers and toes, though other body extremities including the heels, nose and ears can be involved.
- *Cold urticaria* involves the formation of localised or general wheals and itching usually after contact exposure to cold. This form of urticaria is caused more by the rate of change of temperature in the skin than by the absolute temperature of the cold environment.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: evidence of manifestations as described above.

Exposure assessment

- History of occupational exposure: confirmed occupational exposure to cold.
- Minimum duration of exposure: frostnip and contact urticaria can occur in few minutes. Immersion of a hand or foot for as little as 45 minutes in water at 0°C may produce mild NFCI, but three hours are needed to result in overt injury.
- Maximum latent period: few hours for frostnip, weeks for other injuries.

Freezing cold injury - Frostbite (T33-T35)

Severe tissue injury derived from both freezing and vasoconstriction occurs in this condition. In the superficial form, it usually affects the fingers and toes, or the exposed parts of the face, such as the ears, nose, chin, and cheeks. Changes are usually observed in subjects exposed to temperatures below 0°C without sufficient protection. The disease is more frequent in skin areas where subcutaneous tissue is pliable. Patients suffer pain, paraesthesia or anaesthesia and the skin is white, cold and waxy. Rewarming causes cyanosis and erythema, oedema, and superficial blisters. The symptoms include sensory loss, pain, and changes in temperature perception. When it is accompanied by tissue necrosis of muscle, tendons, nerves, and deeper blood vessels impairment, the condition is called “deep frostbite”. The affected extremity is hard, feels woody and reduction or total impairment of function occurs. Oedema of the hands or feet, vesicles and bullae, tissue necrosis, and gangrene can be observed. The affected area appears mottled, yellow, violaceous-white, deep purple or red with blisters that are often blood-filled. The appearance of vesiculation surrounded by oedema and erythema implies a deep frostbite. This condition may result in the loss of fingers and toes.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: as described above.

Exposure assessment

- History of occupational exposure: confirmed occupational exposure to cold.
- Minimum duration of exposure: depending on temperature alone (indoor activities) or together with wind speed (for outdoor activities), minimum duration of exposure to develop frostbite can be a matter of minutes. This time reduces to seconds if touching very cold metal surfaces.
- Maximum latent period: days.

1.2.6(1) Diseases caused by exposure to extreme cold temperatures
ICD Code T68, T69, L50.2, T33-T35, T95 +Z57.6

Name of the diseases and ICD code: **Sequelae of frostbite (T95.0, T95.1, T95.2, T95.3, T95.8, T95.9) +Z57.6**

The most common sequelae of frostbite include chronic pain, residual neurological defects, hyperhidrosis, joint pain and stiffness, skin and nail abnormalities, and chilblain. In severe cases, necrosis and loss of the frozen area (e.g. finger or toe).

Note that NFCI, even when subclinical, may have sequelae, such as a prolonged vasoconstrictive response to further cold exposure (cold sensitization).

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: as described above.
- Examinations: X-ray may reveal typical appearance of 'frostbite arthritis', usually described as an erosive arthritis with subchondral osteosclerosis and cystic defects affecting proximal and distal interphalangeal joints as well as metacarpophalangeal joints.

Exposure assessment

- History of occupational exposure: confirmed occupational exposure to cold.
- Minimum duration of exposure: depending on temperature alone (indoor activities) or together with wind speed (for outdoor activities), minimum duration of exposure to develop frostbite may range from 30 to less than two minutes.
- Maximum latent period: two weeks.

Key actions for prevention	It is unlikely that occupational exposure to extreme low temperatures can be totally avoided, especially in some areas of the world and for several outdoor jobs and tasks. However, preventive measures can be instituted. Adequate protective equipment and working tools should be made available. In some cases appropriate interventions consist of sheltering workers in climate-controlled enclosures, supplying insulated clothes, boots and equipment, and managing the work schedules in order to alternate tasks and to allow for proper recovery periods. Exposed workers should be supplied with adequate food, easy digestible and able to provide the necessary caloric intake. Drinking alcoholic beverages while at work in cold conditions, although popular in some countries, can be very dangerous. There is increased risk of excessive heat dispersion through vasodilatation and of impairment of the physiologic response to stimuli, as a consequence of the slower metabolism of alcohol that occurs at low ambient temperature. The tasks should be organized to avoid lone working in significant cold. Response to emergencies should be planned. Dressing properly is extremely important to prevent cold stress. The type of fabric worn should be considered, together with a multi-layer system: i) an inner layer for micro climate control, ii) a middle layer for insulation control, and iii) an outer layer for environmental protection. The inner layer should be non-absorbent to water, if sweating cannot be sufficiently controlled. A middle layer should provide loft to allow stagnant air layers. The outer layer must be selected according to additional protection requirements, such as wind, water, oil, fire, tear or abrasion. The type of fastenings and closures should be conducive to easy handling in cold conditions. Mittens provide the best overall insulation for the hands and undergloves can be worn. Hats and hoods with a facemask may be required but the clothing ensemble may need to accommodate other protective equipment such as earmuffs. Footwear (boots) needs to provide high insulation to the ground from the sole.

1.2.6(1) Diseases caused by exposure to extreme cold temperatures
ICD Code T68, T69, L50.2, T33-T35, T95 +Z57.6

Key actions for prevention

To summarize, the key issues in cold prevention are:

- Good planning and organization of work and risk assessment.
- Ensuring safe working environments, e.g. controlling risk of slipping by choosing materials and by removing snow and ice.
- Organization of outdoors work, warm transportation to worksite, warm cabins for breaks.
- Tents or shelters for machine maintenance and repair, e.g. in arctic lumbering.
- Warmed handles of the hand tools, chainsaws, drills, powered tools.
- Warm and specially designed clothing for cold protection, permitting free moving and providing good ventilation, with the possibility of a clothing change if wet.
- Personal protective devices designed for cold work.
- Training and education of cold work good practices.
- Provision for warm meals and drinks.
- Provision of occupational health services competent in cold work issues.

It is important to keep in mind that weather conditions such as wind speed, affect how the temperature is perceived by the individual. The combined effect of cold air and wind speed is expressed as the "wind chill" temperature in degrees Celsius or Fahrenheit. It can be used as a general guideline for deciding clothing requirements and assess the possible health effects of cold.

Occupational health surveillance should be directed towards the identification of vulnerable workers (i.e., those with poor physical condition or suffering from heart or kidney diseases, hypertension, hypothyroidism, and diabetes) and early signs of health impairment. Workers previously affected by diseases due to exposure to cold should be returned to work with careful consideration.

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▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
1.2.6(1)	Acute effects of cold	T68, T69, L50.2, T33-T35	NF02, NF03, EB01.1, NE40- NE42
1.2.6(1)	Hypothermia	T68	NF02
1.2.6(1)	Trench foot	T69.0	NF03
1.2.6(1)	Chilblains	T69.1	NF03.0
1.2.6(1)	Cold urticaria	L50.2	EB01.1
1.2.6(1)	Frostbite	T33-T35	NE40-NE42
1.2.6(1)	Sequelae of frostbite	T95 (T95.0, T95.1, T95.2, T95.3, T95.8, T95.9)	NE40, NE4Z, NE41
	Occupational exposure to extreme cold temperatures	Z57.6	QD84.Y

1.2.6(2) Diseases caused by exposure to extreme hot temperatures ICD Code L74.0, +Z57.6, T67	
General characteristics of the causal agent	Heat stress affecting the body is defined as the heat generated by the body plus the heat gained from the environment, minus the heat lost from the body to the environment. The relative humidity in the environment can affect how an individual feels the temperature. For example, an air temperature of 29˚C with 0% humidity will actually be perceived as 26˚C, but the same temperature with 80% humidity will actually be perceived as 36˚C. When considering high air temperature, other factors such as work rate, humidity and clothing worn while working should be assessed, as they affect the physiological response through which the person transfers heat from the body back to the environment, in order to maintain the internal body temperature. In the range of environmental temperatures from 32˚ to 40˚C, heat cramps and exhaustion can happen. Between 40˚ and 54˚C, heat exhaustion is more likely. Environmental temperature over 54˚C often leads to heatstroke.
Occupational exposures	Occupational exposures occur for any indoor and outdoor location and activity intrinsically involving heat such as bakeries, compressed air tunnels, foundries and smelting operations, welding, firefighting, working in non air-conditioned premises during the hot summer months, as well as for work activities not necessarily associated with heat exposure such as agriculture and construction, but performed outdoor in hot climates. Performing strenuous physical activities increases the body temperature and therefore increases the health risk due to heat, in particular in warm and humid environments as in tropical regions, and in extremely hot and dry climates such as in deserts.
Biological mechanisms, main health effects and diagnostic criteria	
Short profile of the biological mechanisms	The body reacts to heat by increasing the blood flow to the skin's surface, and by sweating. This results in cooling, as heat is carried to the surface of the body from within by the increased blood flow and sweat evaporates from the body surface. Heat can also be lost by radiation and convection from the body surface. The internal temperature (core body temperature) of the human body needs to be maintained at 37°C ± 2°C. Whilst bodily responses to heat exposure are necessary, levels of exposure can be reached in which compensatory mechanisms are no longer capable of maintaining body temperature, and this generates the condition able to cause heat diseases. When the core body temperature rises beyond the range of 37°C ± 2°C, an impairment of health can arise, with a severity depending on the difference between the ideal temperature of 37°C and the one reached by the subject. Exposure to heat can bring about effects with different degrees of severity, ranging from minor illnesses, such as heat oedema, heat rash, heat cramps, heat tetany, heat syncope and heat exhaustion, up to hyperthermia, heatstroke, circulatory collapse, renal failure, and death when the core temperature exceeds 41°C. Without proper and prompt intervention, the picture can rapidly progress from minor signs and symptoms to life-threatening heatstroke. Heatstroke is the most severe heat-related illness and is defined as a core body temperature higher than 40°C (104°F), associated with neurologic dysfunction. Traditionally, rectal temperature has been used for measuring core body temperature. In recent years, intragastric temperature, measured with a temperature-sensitive radio pill, has increasingly replaced rectal measurement to assess core body temperature. However, practical and cost-related issues hamper its use as a routine monitoring method. New technologies have been introduced: for example, infrared sensors used to measure the temperature in the ear canal (sometimes incorrectly called 'tympanic' temperature) may provide a simple solution.

1.2.6(2) Diseases caused by exposure to extreme hot temperatures
ICD Code L74.0, +Z57.6, T67

Name of the diseases and ICD code: **Acute effects of heat (L74.0) +Z57.6, T67**

Acute effects of exposure to hot temperatures range in severity from rash and muscle cramps to heat exhaustion and heatstroke.

Heat rash (L74.0)

It is the most common effect observed in heat exposure and known as Miliaria. It results from an impaired ability to sweat, due to occlusion of eccrine sweat ducts. Another synonym is "prickly heat" for the intensely itchy sensation of prickling, burning or tingling skin. Removal from the heat source prevents the body from overheating with reduced ability to cool by sweating.

Heat cramps (T67.2)

They are a mild disorder consisting of very painful spasms affecting the muscles of the arms, legs, or lower abdomen consequent upon mild dehydration and loss of body sodium. They are usually observed in workers who sweat profusely during strenuous activity.

Heat oedema (T67.7)

A transient swelling of the extremities. This condition is commonly secondary to increased aldosterone secretion, leading to water retention and difficulty in salt excretion. Symptoms include flushing of the face, swollen hands, feet and ankles, and sweating. It usually resolves within hours after removal from exposure to heat, or days after the acclimatization of the worker to the warmer environment.

Heat syncope (T67.1)

It is one of the most serious effects of heat exposure. In hot situations, in particular when strenuous activities are performed, the affected person may progress from muscle cramps to syncope in a very short time. Patients typically complain of profound weakness, are very tired and then become dizzy and faint after heat exposure. This usually occurs in persons who stand for prolonged periods, are dehydrated but continue to work in hot conditions.

Heat exhaustion (T67.3)

It occurs when the body responds to an excessive loss of water and salt through profuse sweating. It commonly occurs following strenuous physical exercise, including sport activities such as a marathon race, but can theoretically affect any subject exposed to high temperatures, in particular those who undergo low-salt diets or who take diuretics. It is the result of failure of thermoregulatory sweating on exposure to heat as a result of water deprivation and inadequate replacement of the fluids lost. Early clinical features of the disease are usually hyperventilation after physical exercise, accompanied by headache, dizziness, nausea, profuse sweating, blurry vision, muscle weakness, skin flushing, irritability, agitation, confusion, vomiting and, in the most severe cases, collapse. In these cases, the core temperature is usually around 40°C. If physical activity is not interrupted, heatstroke can eventually occur.

Heatstroke (T67.0)

Heatstroke, also called sunstroke when caused by prolonged exposure to direct sunlight, occurs when there is elevation of core body temperature above 40.6°C due to environmental heat exposure and a failure of thermoregulation. Although not that common, it is the most serious among heat-related disorders. It can be fatal or cause damage to the brain and other internal organs. Heatstroke is observed in subjects working in very hot and humid environments and those with underlying chronic illness or taking certain medications. The onset of heat stroke is usually abrupt with disturbances of the central nervous system, consciousness often being depressed. Premonitory symptoms include headache, nausea, seizures, confusion, disorientation, and behavioural disturbances. Existing evidence suggests that permanent neurologic deficits with cerebellar dysfunction may develop following heatstroke in the most severe cases.

1.2.6(2) Diseases caused by exposure to extreme hot temperatures

ICD Code L74.0, +Z57.6, T67

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: severe hyperthermia with a core/deep body temperature usually exceeding 40.6°C; disturbances of the central nervous system; hot, dry skin with cessation of sweating. Additional effects: headache, nausea, weakness, dizziness, confusion, muscle cramps, seizures, convulsions, sudden shortness of breath, decreased urination, unconsciousness and, in the most severe cases, coma. If core body temperature reaches 45°C, irreversible heat denaturation of proteins causes multiple organ failure or disseminated intravascular coagulation. In this condition, acute kidney injury usually appears.

Exposure assessment

- History of occupational exposure: confirmed occupational exposure to heat, in particular when associated with strenuous activities and inadequate hydration.
- Minimum duration of exposure: from minutes to hours (depending on the levels of exposure).
- Maximum latent period: 24 hours.

Key actions for prevention

It is unlikely that exposure to heat and hot environments can be totally avoided, but preventive measures can be instituted. In particular, workers can be sheltered for most of their work time in climate-controlled enclosures, and some tasks can be performed with the assistance of remote controlled devices. Working in the hottest hours of the day (i.e., between 11 a.m. and 3 p.m.) should be avoided. Workplaces should be equipped with covered and shady zones. When the presence of human operators in extremely hot working environments is unavoidable, adequate protective equipment and working tools should be made available. Possible preventive interventions include:

- controlling temperature by cooling the heat sources;
- sheltering workers in climate-controlled enclosures;
- supplying heat-protective equipment;
- managing the work schedules in order to alternate tasks;
- making available rehydrating drinks and encourage workers to drink frequently; and
- acclimatizing workers through gradual exposure to hot work environments.

Full-body protective clothing for exposure to extreme heat, such as in firefighting, oven and foundry work should be provided and used. These garments used to be made with asbestos fibres, while now mostly man-made mineral fibres and organic polymers are used. When wearing protective clothing and performing heavy work in hot and humid conditions, additional caution should be exercised: the risk of heat stress could even increase, since both the type of clothing and the humidity of the environment may restrict sweat evaporation. A high work rate can increase endogenous heat production. If heat is not sufficiently lost, core body temperature will rise and the body will react by sweating which may lead to dehydration. It should be kept in mind that heat and heavy workload can increase heart rate, which in turn can put additional strain on the body. Urine examination is useful to detect early changes in its specific gravity and electrolyte content, thus possibly avoiding the onset of early mild symptoms.

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▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
1.2.6(2)	Effects of heat and light	T67	NF01
1.2.6(2)	Heatstroke	T67.0	NF01.0
1.2.6(2)	Heat syncope	T67.1	NF01.1
1.2.6(2)	Heat cramps	T67.2	NF01.Z
1.2.6(2)	Heat exhaustion	T67.3	NF01.2, NF01.3
1.2.6(2)	Heat oedema	T67.7	NF01.Z
1.2.6(2)	Heat rash	L74.0	EE02
	Occupational exposure to extreme hot temperatures	Z57.6	QD84.Y

1.3. Biological agents and infectious or parasitic diseases

1.3.1 Brucellosis	ICD Code A23 +Z57
General characteristics of the causal agent	Brucellosis, also known as Malta fever, Crimean fever, Gibraltar fever, Mediterranean fever, Bang's disease, rock fever or undulant fever, is a zoonotic disease, caused by aerobic coccobacilli of the Brucella genus. Several species of the microorganism infect different mammals that can act as reservoirs for the disease. Among the natural reservoirs for bacilli are sheep (*B. ovis*), goats (*B. melitensis*), pigs (*B. suis*), cattle (*B. abortus*), dogs (*B. canis*), horses, rabbits and rats (*B. neotomae*), voles and red foxes (*B. microti*), and marine mammals (*B. maris*). The *Brucellae* most relevant to human disease are *B. ovis*, *B. melitensis*, and *B. abortus*, while the others are rarely associated with a disease transmissible to humans. *Brucella* species are Gram-negative, small in size (0.5-0.7 by 0.6-1.5 µm), lack capsules, flagellae, endospores or native plasmids, and survive in extreme conditions of temperature, pH, and humidity. As such, even frozen and aborted infected materials can be reservoirs of viable, infectious microorganisms.
Occupational exposures	*Brucellae* are pathogens that pose a serious hazard to workers and may present a risk of spreading to the community. They can reach and infect humans through direct contact or ingestion of products from infected animals. This is why, in the general population, consumption of infected raw milk was the most common route of infection before the adoption of routine milk heat treatment, pre-market pasteurization or in-house pre-consumption boiling. Note that *Brucellae* may resist the technological treatments involved in cheese manufacturing. In the occupational setting, the most common routes of exposure are inhalation of spores and viable organisms, and contact of the open skin or mucosae with infectious material. The occupational groups at greater risk are agricultural, livestock, dairy, and abattoir/slaughterhouse workers, meat packers, butchers, and veterinarians. One particular, although relatively small, group at risk for brucellosis is represented by workers in clinical and veterinary laboratories and in research facilities, since the manipulation of infected biological samples can generate disease-producing aerosols even during simple operations such as the opening of test tubes and the transfer of samples by pipetting.
Biological mechanisms, main health effects and diagnostic criteria	
Short profile of the biological mechanisms	The response to Brucella infection and its outcome are influenced by the virulence, phase, and species of the infecting strain. Exposure to the pathogen produces both cell-mediated and humoral immune responses. Antibodies promote clearance of extracellular *Brucellae* but are not able to eradicate infection by themselves. The target cells of the infection are the macrophages: bacterial mechanisms to counteract intracellular killing and apoptosis result in very large intracellular populations, and consequent persistent infections within the cells. As is the case in other types of intracellular infection, initial replication of *Brucellae* most likely takes place within cells of the lymph nodes draining the entry point of the pathogen. Subsequent spread through the bloodstream may result in chronic localized infection at almost any site. The disease shows up as a flu-like symptoms characterized by pyrexia, sweating, fatigue, anorexia, myalgia, and arthralgia, after two to four weeks of symptomless incubation; less severe cases can go undiagnosed for long time, given the very slow growth of the microorganism and the intracellular defence mechanisms, which both limit the exposure to the host immune system at the initial stages. The approximate relative severity of human acute brucellosis caused by different species is: *B. melitensis* > *B. suis* > *B. abortus* ≥ *B. canis*.

1.3.1 Brucellosis — ICD Code A23 +Z57

Name of the diseases and ICD code: **Brucellosis (A23 +Z57)**

Short description of the disease

The clinical manifestations of the disease appear between two and four weeks after infection, with an acute or insidious onset. At the beginning, symptoms are nonspecific and similar to any other pyrexial condition. In some cases, a skin rash can be observed, occasionally accompanied by lymphadenopathy and liver and spleen enlargement. Systemically, the disease may often affect joints, the nervous system, and the heart.

The main complications observed in particular in the undulant and chronic forms, are arthritis, spondylitis, central nervous system impairment, peripheral neuropathy, uveitis, and severe endocarditis which can be life-threatening.

In many patients, symptoms last for 2 to 4 weeks, followed by spontaneous recovery. Others may develop intermittent fever and symptoms that typically appear at 2 to 14 day intervals. Most people with this undulant form recover completely in 3 to 12 months. In a few subjects, relapses may occur months after the initial symptoms.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms:
  - Nonspecific influenza-like symptoms such as fever (often associated with rigors), arthralgia, and myalgia are typical; if becoming chronic, the manifestations may assume an undulant nature, with periods of normal temperature between acute attacks; symptoms may persist for years, either intermittently or continuously.
  - Specific symptoms related to the target organ may arise, such as: back pain in spondylitis; seizures in chronic meningoencephalitis, with headache, fever, stiff neck, confusion, visual sensitivity to light, unsteady gait, irritability or lethargy; psychological disturbance in case of central nervous system involvement; fatigue, night sweats, shortness of breath, chest pain, and swelling of feet, legs or abdomen in endocarditis.
- Examinations:
  - Hepatosplenomegaly and lymphadenopathy are common findings at physical examination.
  - Blood exams can reveal pancytopaenia and low grade hepatitis.
  - *Brucella* can be isolated from blood cultures (usually positive in 90% of cases), urine, cerebrospinal fluid, bone marrow, or other sites. Cultures are however more likely to be negative in chronic forms.
  - Serum IgM or IgG antibodies against the pathogen may be evident.
  - Rose Bengal plate agglutination test (RBPT) is a screening test for rapid confirmation of infection due to any form of Brucella species.
  - Molecular characterization techniques using PCR are useful for rapid detection and confirmation of the *Brucella* genome.

Exposure assessment

- History of occupational exposure: confirmed contact with infected animals, parts of animals, or animal products, in particular milk, at the workplace or during a work activity. Accidental inoculation or conjunctival contamination with *Brucella* vaccine is an additional risk affecting veterinarians.
- Minimum duration of exposure: a single exposure can cause the disease.
- Maximum latent period: three months.

Key actions for prevention	Where animal husbandry is practiced industrially, under standardized and well controlled conditions, the main sources of infection are occupational exposure and ingestion of contaminated food products. Therefore, most countries have enforced policies for routine monitoring of *Brucellae* in animals of economic interest, mainly cattle and goats, for eradicating the disease in domestic herds and for preventing or limiting the spread from wildlife reservoirs, when this can occur. As for example, in sub-Saharan Africa brucellosis has established a wildlife reservoir for cattle in African buffalo (*Syncerus caffer*); in Northern America the wild American buffalo (*Bison bison*) fulfills the same ecological role. From a public health perspective, vaccination of cattle, veterinary slaughtering of infected units followed by thorough sanitization or disposal of contaminated pens, and pasteurization of milk are the main and most effective interventions. Cooking is sufficient to eliminate the microorganism from food meat. The infectious *Brucellae* in cheese can persist as long as their typical maturation time, in the order of three months.

1.3.1 Brucellosis	ICD Code A23 +Z57
Key actions for prevention	On the other hand, in countries where nomadic or migratory animal husbandry is the predominant life style, or on small traditional farms, all sections of the population may be exposed to infection by direct contact with animals or from contaminated food. Although the observance of some basic measures of elementary hygienic precautions can considerably reduce the risk of brucellosis, their practice can be difficult for some populations, especially in arid or semiarid areas. Personal protection devices, such as facemasks and gloves are available in cattle rearing in countries with industrialized agriculture, and should be used to prevent the possible transmission of the disease to workers, such as cattle farmers and veterinarians. In laboratories, *Brucellae* isolates should be manipulated under biosafety conditions. Exposed and potentially exposed laboratory workers should undergo surveillance and follow-up.

Further reading

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▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
1.3.1	Brucellosis	A23	1B95
	Occupational exposure to risk factors	Z57	QD84

1.3.2 Hepatitis viruses — ICD Code (B15-B19) + Z57, Y40-Y84

General characteristics of the causal agent

Viral hepatitis is an infectious disease of the liver which can be caused by many viruses. The major hepatotropic viruses are those identified as A, B, C, D and E. In addition, hepatitis G virus and transfusion transmitted virus are described as minor hepatotropic viruses. Other systemic viruses, such as herpesviruses (including varicella virus), Epstein-Barr virus, cytomegalovirus, and adenovirus, can also cause hepatitis.

Hepatitis B, C and A viruses are the predominant occupational hazards; whilst hepatitis E is increasing in importance, other viruses seldom cause occupational hepatitis. The onset of clinically apparent disease can be delayed by months or years from the event(s) that caused the infection, and during this time (carrier phase), the infected subject can transmit the disease to other persons. This feature of the disease increases the related occupational risk.

The table below summarizes the main characteristics of the major hepatotropic viruses.

Name	**Hepatitis A Virus (HAV)**	**Hepatitis B Virus (HBV)**	**Hepatitis C Virus (HCV)**	**Hepatitis D Virus (HDV)**	**Hepatitis E Virus (HEV)**
Family	*Picornaviridae*	*Hepadnaviridae*	*Flaviviridae*	*Deltaviridae**	*Hepeviridae*
Genome**	(+)ssRNA	dsDNA-RT	(+)ssRNA	(-)ssRNA	(+)ssRNA
Source	Faeces	Blood and blood-derived fluids	Blood and blood-derived fluids	Blood and blood-derived fluids	Faeces
Route of transmission	Orofaecal	Percutaneous and permucosal	Percutaneous and permucosal	Percutaneous and permucosal	Orofaecal
Chronic infection	No	Yes, 10% chance	Yes, > 50% chance	Yes, < 5% if coinfection, > 80% if superinfection	No
Prevention	Pre- and post-exposure immunization	Pre- and post-exposure immunization, blood donor screening	Blood donor screening	Pre- and post-exposure immunization	Ensure safe drinking water

* Genus-level classification: HDV is not classified into a viral family because it is a unique virus dependent on HBV.

** (+/-)ssRNA: positive/negative-sense single-stranded RNA; dsDNA-RT: double-stranded DNA-reverse transcriptase.

Occupational exposures

Hepatitis B, C and D are transmitted through contact with infected human blood and body fluids. Health workers, police and ambulance crews, and workers employed in rescue services may be exposed. Sharp injuries, as needle-stick accidents, are the most frequent exposure events. In the non-working environment, hepatitis B and C can be transmitted from carrier individuals mainly by personal relationships (sexual intercourse, mother-to-child transmission, sharing of personal items, such as shaving razors, scissors, toothbrushes, and needles).

Hepatitis A and E are contracted through the orofaecal route. Workers in direct contact with untreated contaminated water and sewage or with faeces of infected patients can face exposure to these hepatitis viruses.

Workers in clinical laboratories may handle biological specimens from infected individuals or directly handle the virus.

Whilst HBV and HCV are frequent concerns, especially for health workers, hepatitis E may be contracted as a zoonotic infection and is an emerging issue in pig breeding and related activities, such as slaughterhouses.

1.3.2 Hepatitis viruses — ICD Code (B15-B19) + Z57, Y40-Y84

Biological mechanisms, main health effects and diagnostic criteria

Short profile of the biological mechanisms

- *Hepatitis A:* infection is transmitted by contamination of food and water with infected faeces and has an incubation period of 2 to 6 weeks. HAV infection does not persist and does not lead to chronic hepatitis.
- *Hepatitis B:* infection is transmitted through contact with infected human blood and body fluids and can give rise to acute and chronic outcomes. In both instances, high levels of infectious HBV particles or "virions" circulate in the bloodstream. Virions are thought to pass through fenestrations of the liver sinusoidal endothelial cells and reach the surface of hepatocytes. The combination of the viral replication level and the host's immune response determines the degree of liver inflammation. The incubation period goes from 4 to 24 weeks. Approximately 95% of those acutely infected develop antibodies against hepatitis B surface antigen (HBsAg), clear HBsAg and HBV virions, and fully recover. The remaining develop chronic infection (see below).
- *Hepatitis C:* transmission route is analogous to HBV; infection with HCV has an incubation period of 2 to 26 weeks. Approximately 15-45% of subjects acutely infected with HCV lose virologic markers for HCV. Thus, about 55-85% remain viraemic and may develop chronic liver disease (see below).
- *Delta hepatitis:* hepatitis D virus can propagate only in the presence of HBV. HDV is an RNA virus, which encodes a nucleocapsid antigen but does not have an envelope. In HBV infected people, HDV can use HBV envelope with co-infection occurring either acutely with HBV or in addition to chronic HBV.
- *Hepatitis E:* the transmission route is analogous to HAV. The incubation period is 2 to 8 weeks. There is no carrier state.

Name of the diseases and ICD code: **Acute hepatitis (B15-B17) + Z57, Y40-Y84**

Acute hepatitis A (B15), Acute hepatitis B (B16), Acute hepatitis C (B17.1), Acute delta-(super)infection of hepatitis B carrier (B17.0), Acute hepatitis E (B17.2), Acute viral hepatitis, unspecified (B17.9)

Short description of the disease

All hepatitis infections can be, in some periods of their evolution, asymptomatic. Identification of possible infectious individuals can therefore be complicated. In acute viral hepatitis infection, fever, anorexia, nausea, abdominal pain, pale stools, dark urine, and jaundice may be commonly observed.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms:
  - *Hepatitis A:* malaise, anorexia, nausea, and vomiting are usually present for several weeks. In more severe cases, jaundice develops. In subjects already affected by chronic HBV or HCV, the consequences of HAV infection may be more severe, including death. The mortality is less than 0.5% in those under 40 years but up to 2% in the older persons.
  - *Hepatitis B:* only around a third of infected adult subjects show significant symptoms. Infection can commonly present without jaundice when the features may be flu-like, with arthralgia and an urticarial rash. A fulminant hepatitis is rare (0.3%).
  - *Hepatitis C:* acute infection does not usually cause symptoms. Even when it is symptomatic, acute HCV infection tends to follow a mild course. Up to 80% of those infected are unable to clear HCV spontaneously.
  - *Delta hepatitis*: it causes either acute self-limiting hepatitis or a worsening of pre-existing chronic hepatitis.
  - *Hepatitis E:* HEV infection causes fever and acute hepatitis, with anorexia, jaundice, and hepatomegaly. Mortality happen and reports have shown a higher mortality in pregnancy (less than 20%).

1.3.2 Hepatitis viruses — ICD Code (B15-B19) + Z57, Y40-Y84

- Examinations:
  - *Hepatitis A:* serological testing to detect an increase in specific antibodies (HAV-Ab IgM and IgG); aminotransferase levels are usually elevated for several weeks; cholestatic hepatitis can also be present characterised by increased alkaline phosphatase, rather than aminotransferase, levels.
  - *Hepatitis B:* the presence of HBV DNA indicates that the virus is still active in the infected person, even after the end of the acute phase. The pattern of hepatitis B markers can distinguish an acute infection, natural immunity, the carrier state, and immunity as a result of vaccination (see summary table at the end of this item).
  - *Hepatitis C:* the presence of positive/indeterminate HCV antibody with negative HCV RNA documents past/no infection. The presence of HCV RNA indicates that the virus is still active in the subject, even after the end of the acute phase.
  - *Delta hepatitis:* it is present in concomitance with HBV infection and is confirmed by serology for HDV antigen, antibodies, and RNA.
  - *Hepatitis E:* HEV RNA is detected.
  - For all types of hepatitis, liver function tests (e.g. transaminases, serum bilirubin) and liver ultrasound can indicate the severity of liver dysfunction.

Exposure assessment

- History of occupational exposure: for hepatitis B, C, and delta, evidence of a previous event in which there has been occupational exposure – typically by inoculation injury, mucous membrane or broken skin contact – with blood or blood-stained body fluids of an infected person; for hepatitis A and E, evidence of worker contact with faeces or faeces-contaminated fluids, working tools and surfaces. Very often it will not be possible to collect clear evidence of the contact and the exposure will be only hypothesized, with different levels of evidence.
- Minimum duration of exposure: a single exposure can cause the disease.
- Maximum latent period: six months for hepatitis B and C, two months for hepatitis A and E.

Name of the diseases and ICD code: **Chronic viral hepatitis (B18) + Z57, Y40-Y84**

Chronic viral hepatitis B (B18.1), Chronic viral hepatitis C (B18.2), Chronic viral hepatitis B with delta-agent (B18.0), Unspecified chronic viral hepatitis (B18.9)

Persisting viraemia with liver inflammation characterizes chronic hepatitis, whose severity is related to the degree of viral replication and the host's immune response. The continued inflammation and necrosis may cause changes in organ structure, such as cirrhosis. Liver malignancy is a recognised sequela of hepatitis B and C chronic infection (see below).

Diagnostic criteria

Clinical manifestations

- Signs and symptoms:
  - *Chronic viral hepatitis B:* there may be few symptoms apart from fatigue. The condition may change over time with any change in immune response and may lead to jaundice or raised transaminases. Occasionally extra hepatic manifestations can occur, such as polyarteritis nodosa, glomerulonephritis and cryoglobulinaemia.
  - *Chronic viral hepatitis C:* symptoms are nonspecific, with fatigue being the most common presentation. Approximately 20% of those with chronic infection may develop cirrhosis over a period of about 20 years.
  - *Chronic viral hepatitis B with delta-agent:* rate of chronic infection with HDV resemble that for chronic HBV infection which is a prerequisite for HDV infection; the symptoms of co-infection are similar but likely to be more severe. Progression to cirrhosis may be more rapid.
- Examinations:
  - *Hepatitis B:* serological testing and persistence of hepatitis B surface antigen (HBsAg) in the serum for more than six months after the exposure event, together with liver inflammation, confirm the diagnosis. However, it is possible to have an "occult" HBV infection with HBV DNA detectable in the absence of HBsAg. When necessary, evidence of HBV DNA can be used to quantify viraemia. The pattern of chronic hepatitis B serologic markers are summarised in the table at the end of the item.
  - *Hepatitis C:* presence and persistence of HCV RNA for more than six months after occupational exposure. Anti-HCV antibodies will usually be present with HCV RNA but may be absent in those who are immune suppressed.
  - *Delta hepatitis:* present with HBV infection and confirmed by serology for anti-HD antibodies; HDV RNA is present.
  - For all types of hepatitis, liver function tests (e.g. transaminases, albumin), liver ultrasound, liver biopsy can confirm the diagnosis and indicate the severity of a liver dysfunction.

1.3.2 Hepatitis viruses — ICD Code (B15-B19) + Z57, Y40-Y84

Exposure assessment

- History of occupational exposure: confirmed occupational exposure to infected blood and body fluids.
- Minimum duration of exposure: a single exposure can cause the disease; in some cases this episode cannot be recalled despite the apparent absence of other factors.
- Maximum latent period: not applicable.

Name of the diseases and ICD code: **Carcinogenic effects of hepatitis B and hepatitis C viruses**
(Specific disease code) **code + Z57, Y40-Y84**

Liver cancer (hepatocellular carcinoma) (C22.0), Non-Hodgkin lymphoma (C85.9)

There is sufficient evidence in humans for the carcinogenicity of chronic infections with HBV and HCV, as they both cause hepatocellular carcinoma. HCV also causes non-Hodgkin lymphoma. IARC classified both chronic infections with HBV and HCV as carcinogenic to humans (Group 1). Positive associations have been observed between chronic infection with HBV and cholangiocarcinoma and non-Hodgkin lymphoma and between HCV infection and cholangiocarcinoma. Refer to item 3.1.20 for further details.

Key actions for prevention	The presence of hepatitis viruses in several job environments is endemic and unavoidable, and the activities that can expose the workers to the infectious agents are mostly essential, such as patient care. The segregation of sewage effluents and tanks is an effective measure to reduce exposure to hepatitis viruses that are transmitted by the orofaecal route. Effective organization of work at places where biological specimens are handled (e.g. clinical laboratories, animal breeding farms, and slaughterhouses), is effective in reducing exposure to hepatitis viruses that are transmitted by contact with blood and tissue. Exposures to infected biological materials should be avoided by implementing the hierarchy of controls as appropriate to the work circumstances: for instance, feasible measures in a clinical/research laboratory will differ from those of a clinical treatment area. Engineering controls in the clinical area may include using sharp-free or safety engineered safer sharp systems. Sharp injuries, as needle-stick accidents, certainly represent the most frequent exposure event for blood-borne infections. As such, many countries, as well as national and supranational institutions, have developed guidelines aimed at preventing them. Some key elements are summarized below. Risk assessment should be conducted, and include an exposure determination, and cover all situations where there is injury, blood or other potentially infectious material. Risk assessments should take into account technology, organisation of work, working conditions, and the influence of factors related to the working environment. Where the results of the risk assessment reveal a risk of injuries with a sharp and infection, workers' exposure must be eliminated by specifying and implementing safe procedures for using and disposing of sharp medical instruments and contaminated waste. Unnecessary use of sharps should be eliminated, providing medical devices incorporating proven safety-engineered protection mechanisms. Finally, the practice of recapping needles should be banned. The risk of exposure must be reduced to as low a level as necessary in order to adequately protect the safety and health of the workers concerned. Effective disposal procedures and clearly marked and technically safe containers for the handling of disposable sharps and injection equipment should be placed as close as possible to the assessed areas where sharps are being used or to be found.

1.3.2 Hepatitis viruses	ICD Code (B15-B19) + Z57, Y40-Y84
Key actions for prevention	Other routine preventive measures include: • point-of-care alcohol-based hand rub (ABHR); • point-of-use sharps containers; • appropriately functioning and accessible dispensers for hand hygiene products (alcohol-based hand rub, soap, lotion, paper towels); • designated hand washing sinks for health worker use; • appropriate supply and accessibility of personal protective equipment for routine practices, such as: - gloves; - gowns; - masks (surgical or procedure masks used by health worker); and - facial protection (masks and eye protection, or face shields, or masks with visor attachment); • appropriate occupational health and safety policies, including sharps safety and prevention of exposure to bloodborne pathogens and immunization programs; • education of health workers; and • policies, procedures and resources to support the application of: - point-of-care risk assessment; and - routine practices as the standard of care for all patients in all healthcare settings. Hepatitis A, B and D are preventable through vaccines. Hepatitis B immune globulin is effective in preventing infection in non-immune individuals significantly exposed to HBV. Screening of close contacts of infected persons should be considered and followed by vaccination as appropriate. In subjects who have been infected, reducing or avoiding cofactors such as drinking alcohol can be effective in reducing the risk of complications of chronic infections.

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▶ Common serologic patterns in hepatitis B virus infection and their interpretation

HBsAg	Anti-HBs	Anti-HBc	HBeAg**	Anti-HBe	Interpretation
+	-	IgM	+	-	Acute hepatitis B
+	-	IgG*	+	-	Chronic hepatitis B with active viral replication
+	-	IgG	-	+	Chronic hepatitis B generally with low viral replication
+	+	IgG	+ or -	+ or -	Chronic hepatitis B with heterotypic anti-HBs (about 10% of cases)
-	-	IgM	+ or -	-	Acute hepatitis B
-	+	IgG	-	+ or -	Recovery from hepatitis B (immunity)
-	+	-	-	-	Vaccination (immunity)
-	-	IgG	-	-	False-positive; less commonly, infection in remote past

* IgM antibodies may also be detected at low levels. ** The presence of HBV DNA in serum generally parallels the presence of HBeAg; however, HBV DNA is more sensitive in detecting viral replication and infectivity.

▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
1.3.2	Acute hepatitis A	B15	1E50.0
1.3.2	Acute hepatitis B	B16	1E50.1
1.3.2	Acute hepatitis C	B17.1	1E50.2
1.3.2	Acute delta-(super)infection of hepatitis B carrier	B17.0	1E50.3
1.3.2	Acute hepatitis E	B17.2	1E50.4
1.3.2	Unspecified acute viral hepatitis	B17.9	1E50.Z
1.3.2	Chronic viral hepatitis B	B18.1	1E51.0
1.3.2	Chronic viral hepatitis C	B18.2	1E51.1
1.3.2	Chronic viral hepatitis B with delta-agent	B18.0	1E51.2
1.3.2	Liver cancer (hepatocellular carcinoma)	C22.0	2C12.02
1.3.2	Non-Hodgkin lymphoma	C85.9	2B33.5
	Occupational exposure to risk factors	Z57	QD84.Y
	Needle stick associated with injury or harm in therapeutic use	Y40-Y84	PK81.F

1.3.3 Human immunodeficiency virus (HIV)	ICD Code Z20.6, Z21, B20-B24 +Z57
General characteristics of the causal agent	Human immunodeficiency virus (HIV) is a virus that most likely had zoonotic origin from a virus that infected chimpanzees to one that infects humans. It began to spread beyond the African continent in the late 1970s and is now endemic worldwide. HIV is an RNA retrovirus roughly spherical in size, with a diameter of approximately 120 nm, and an outer envelope constituted of cell materials (phospholipids and glycoproteins) deriving from the host cell. It belongs to the family of human retroviruses (*Retroviridae*) and the subfamily of lentiviruses. Two types of HIV are currently known: HIV-1 is responsible for the HIV/AIDS pandemic, while HIV-2 is mainly reported in West Africa and its infection generally takes longer to progress to symptomatic HIV/AIDS and has a lower mortality rate than HIV-1 infection.
Occupational exposures	HIV can be transmitted through unprotected sexual intercourse (vaginal or anal), and oral sex with an infected person; transfusion of contaminated blood; and the sharing of contaminated needles, syringes, surgical equipment or other sharp instruments. It may be transmitted between a mother and her infant during pregnancy, childbirth and breastfeeding (through breast milk). Individuals cannot become infected through ordinary day-to-day contact such as kissing, hugging, shaking hands, or sharing personal objects, food or water. Occupational exposure can occur wherever there is the possibility of a contact with blood or body fluids in the workplace, such as through injury caused by blood smeared instruments or accidental exposure of the skin, eyes or mucous membranes. The routes of HIV exposure are percutaneous injuries (e.g. from a needle stick or a cut with a sharp object), contact through mucous membranes, or possibly through non-intact skin (e.g. dermatitis). HIV transmission by skin-penetrating human bites has been rarely reported. Mucocutaneous exposure, such as from blood contamination of eyes and mouth is an uncommon mode of transmission but nonetheless is a concern. Surgical practice on HIV-infected patients carries a risk of exposure that will relate to the disease prevalence in the population served. The main groups at risk for infection with HIV by non-sexual transmission are health workers such as nurses, physicians, and laboratory technicians. Other groups who may be considered at risk of blood or body fluid exposure and hence of HIV infection are prison workers, emergency responders, waste disposal workers, fire fighters, police officers and aid agency workers. Sex workers are at an increased risk and can become a population reservoir for this disease, with transmission modes that are common to other sexually transmitted infectious diseases. The disease can have a long asymptomatic carrier phase and, without laboratory testing, undiagnosed subjects are clinically indistinguishable from healthy subjects. However, given that they are often unaware of the disease, they can transmit infection to sexual partners through unprotected intercourse.
Biological mechanisms, main health effects and diagnostic criteria	
Short profile of the biological mechanisms	Once in the bloodstream, the gp120 protein of HIV binds to the host cell fusing its outer membrane with the cell's own. The virus then injects into the infected cells the inner capsid and the viral reverse transcriptase enzyme, which catalyses the reverse transcription of the genomic RNA into DNA, resulting in the formation of double-stranded proviral HIV-DNA. The resulting viral DNA is then imported into the nucleus of the cell and integrated into the cellular DNA by an integrase encoded by the virus itself, together with host cofactors. Once integrated, the virus may become latent or, alternatively, be transcribed, thus producing new RNA genomes and viral proteins that are subsequently released from the cell as new virus particles that perpetuate the replication cycle. The virus targets and attacks the immune system, specifically CD4 cells (T-helper or T4), macrophages, and dendritic cells. CD4 cells play a central role in immune protection. They do so through their capacity of helping B cells make antibodies, inducing macrophages to develop enhanced microbicidal activity, recruiting neutrophils, eosinophils, and basophils to sites of infection and inflammation, and orchestrating the full array of immune responses through their production of cytokines and chemokines. Only in the infected CD4 cells the HIV-DNA is able to replicate and generate new intracellular viral particles ("virions"), which in turn bud out of the infected CD4 cell and can move to infect others. As this process repeats, more CD4 cells die out, and the immune system of the infected subject is progressively depleted. The depletion of the immune system makes the person more likely to acquire other infections or infection-related cancers. These opportunistic infections or cancers take advantage of a very weakened immune system and are indicative that the person has the acquired immunodeficiency syndrome (AIDS), the last stage of HIV infection. Tuberculosis (TB) is the most common life-threatening opportunistic infection affecting people living with HIV. It is the number one cause of death among people with HIV in Africa, and a leading cause of death in this population worldwide.

1.3.3 Human immunodeficiency virus (HIV) ICD Code Z20.6, Z21, B20-B24 +Z57

Name of the diseases and ICD code: **Human immunodeficiency virus (HIV) diseases (Z20.6, Z21, B20-B24 +Z57)**

Unspecified human immunodeficiency virus (HIV) disease (includes acquired immunodeficiency syndrome [AIDS]) (B24), HIV disease resulting in malignant neoplasms (B21), HIV disease resulting in other specified diseases (B22), HIV disease resulting in other conditions (B23), Contact with and exposure to HIV (Z20.6), Asymptomatic HIV infection status (Z21)

Short description of the disease

Although rare instances of delayed HIV seroconversion (i.e., development of antibodies against the virus) have been reported, this phenomenon typically occurs four to six weeks after the exposure, and almost invariably within 12 weeks of primary infection. In this phase, fever, generalized lymphadenopathy and a skin rash are observed. There is then a period of clinical latency which lasts for a median of 10 years. The main feature of HIV infection is represented by a progressive depletion of the number and function of CD4 cells, with consequent development of multi-organ opportunistic infections, such as from *Pneumocystis jiroveci*, *Mycobacterium tuberculosis*, *Cryptococcus*, *Cytomegalovirus*, *Herpes simplex virus*, *Toxoplasma gondii*. Immunodeficiency leads to an increased risk of malignancies such as lymphoma and Kaposi's sarcoma.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: the clinical features characterizing HIV disease at its various stages are well summarized by the "WHO clinical staging of HIV disease" in adults and adolescents (defined as 15 years or older), reported below.

Clinical stage 1

Asymptomatic

Persistent generalized lymphadenopathy

Clinical stage 2

Moderate unexplained weight loss (<10% of presumed or measured body weight)
Recurrent respiratory tract infections (sinusitis, tonsillitis, pharyngitis) and otitis media

Herpes zoster

Angular cheilitis

Recurrent oral ulceration

Papular pruritic eruptions

Fungal nail infections

Seborrhoeic dermatitis

Clinical stage 3

Unexplained severe weight loss (>10% of presumed or measured body weight)

Unexplained chronic diarrhoea for longer than one month

Unexplained persistent fever (intermittent or constant for longer than one month)

Persistent oral candidiasis

Oral hairy leukoplakia

Pulmonary tuberculosis

Severe bacterial infections (such as pneumonia, empyema, pyomyositis, bone or joint infection, meningitis or bacteraemia)

Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis

Unexplained anaemia (<8 g/dL), neutropaenia (<0.5 × 10^9/L) and chronic thrombocytopaenia (<50 × 10^9/L)

1.3.3 Human immunodeficiency virus (HIV) ICD Code Z20.6, Z21, B20-B24 +Z57

Clinical stage 4*

HIV wasting syndrome

Pneumocystis (*jirovecii*) pneumonia

Recurrent severe bacterial pneumonia

Chronic herpes simplex infection (orolabial, genital or anorectal of more than one month in duration or visceral at any site)

Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs)

Extrapulmonary tuberculosis

Kaposi's sarcoma

Cytomegalovirus infection (retinitis or infection of other organs)

Central nervous system toxoplasmosis

HIV encephalopathy

Extrapulmonary cryptococcosis including meningitis

Disseminated non-tuberculous mycobacterial infection

Progressive multifocal leukoencephalopathy

Chronic cryptosporidiosis

Chronic isosporiasis

Disseminated mycosis (extrapulmonary histoplasmosis, coccidioidomycosis)

Lymphoma (cerebral or B-cell non-Hodgkin)

Symptomatic HIV-associated nephropathy or cardiomyopathy

Recurrent septicaemia (including nontyphoidal Salmonella)

Invasive cervical carcinoma

Atypical disseminated leishmaniasis

* Some additional specific conditions can be included in regional classifications, such as penicilliosis in Asia, HIV-associated rectovaginal fistula in southern Africa and reactivation of trypanosomiasis in Latin America.

- Examinations: diagnosis of HIV infection is based almost entirely on detection of antibodies against HIV, usually with enzyme immunoassay (EIA) which typically will test for HIV-1, HIV-2 and HIV p24 antigen. EIA is a highly sensitive test but may be false positive in low risk populations. A Western blot is used as a confirmatory test, or else DNA PCR or variants. The reduction of T-Helper and T Helper/T suppressor ratio (CD4+ T cell count <200/μL), in anybody with HIV infection who develops one of the HIV-associated diseases, is considered to be indicative of a severe defect in cell-mediated immunity. CD4+ T cell count expressed as a total number or percentage of the total lymphocyte number is necessary to define the presence and the extent of immunosuppression.
- Advanced HIV is diagnosed in adults with confirmed HIV infection, a presumptive or definitive diagnosis of any stage 3 or stage 4 condition and CD4 count less than 200/μL.

Exposure assessment

- History of occupational exposure: evidence of occupational injury with a blood or body fluid contaminated sharp instrument, bone fragment, etc. In case of occupational injury involving a health worker, the risk is higher if the sharp device was visibly contaminated with blood or if the performed procedure involved a hollow bore needle previously placed in a vein or artery. Occupational exposure through contact of blood or body fluids with mucous membranes, including conjunctivae, can occur but the risk is significantly lower compared with injuries. Sex workers face prolonged exposure to risk, especially if condoms and other protective barrier devices are not used. Note that, theoretically, a single exposure is able to cause the infection but the risk is lower than that of being infected by hepatitis viruses.
- Minimum duration of exposure: a single exposure can cause the disease.
- Maximum latent period: from contact to seroconversion: 12 months; from seroconversion to overt disease: generally 10 years in the absence of treatment.

1.3.3 Human immunodeficiency virus (HIV)	ICD Code Z20.6, Z21, B20-B24 +Z57
Key actions for prevention	Prevention of HIV infection in the occupational setting shows prominent differences with that in the general population, especially when considering the non-sexual routes of exposure. HIV-1 is considered to be less resistant to environmental conditions (i.e., outside of the human body) than the agents of most other infectious diseases, and in particular of hepatitis viruses. In the health care setting, blood and other body fluids from all patients must be assumed to be potentially infectious and infection control precautions must be applied at all times. Gloves, face shields or other appropriate barriers must be used when in potential contact with blood or body fluids. Personal hygiene facilities should be installed so that hands and other skin surfaces contaminated with blood or body fluids can be washed immediately. Preventing needlestick injuries will avoid 90% of occupational transmissions of HIV. Use of safer needle devices and needleless intravenous systems, eliminating recapping of needles, and placing needles and sharps into sharps containers immediately after use are the most important ways to reduce exposure to injuries. Post-exposure prophylaxis (PEP) should be initiated as soon as possible, preferably within the first few hours and no later than 72 hours after exposure to blood or body fluids potentially infected by HIV. Baseline HIV testing is strongly recommended and could be done after initiation of PEP; testing should be repeated. The recommended timing varies, with US CDC advising serology at 6 weeks and finally 4 months post exposure, whilst others suggest that a single test at 6 weeks post exposure with 4th generation HIV Ag/Ab combination immunoassays is sufficient. Any occupational exposure to HIV should lead to evaluation and when relevant, strengthening of safety and working conditions. Outside the healthcare setting, most of the same considerations would apply, and in scenarios such as emergency management, in-field treatment of victims, and riot control, the risk of exposure due to contact with open wounds exists and additional protection of workers is needed. In case of occupational exposure through these routes, guidelines for protection against occupational exposure to HIV and for immediate post-exposure prophylaxis with antiviral drugs after exposure should be made available to affected individuals. Different countries and social groups adopt different attitudes and policies with reference to sex workers. However, sex work is still a major route for the dissemination of HIV. The World Health Organization suggests adopting non-judgemental attitudes to enhance the efficacy of risk-reduction strategies. Finally, therapy options are becoming more and more effective, and the treatment of cases reduces viral loads to undetectable levels and consequently the likelihood of transmission, thereby supporting prevention.

Further reading

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▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
1.3.3	Acquired immunodeficiency syndrome (AIDS)	B24	IC62
1.3.3	HIV disease resulting in infectious and parasitic diseases	B20	1C62.Z
1.3.3	HIV disease resulting in malignant neoplasms	B21	1C62.Z
1.3.3	HIV disease resulting in other specified diseases	B22	1C62.Z
1.3.3	HIV disease resulting in other conditions	B23	1C62.Z
1.3.3	Contact with and exposure to HIV	Z20.6	QC90.6
1.3.3	Asymptomatic HIV infection status	Z21	IC62.0
	Occupational exposure to risk factors	Z57	QD84
	Needle stick associated with injury or harm in therapeutic use	Y40-Y84	PK81.F

1.3.4 Tetanus	ICD Code A35 +Z57
General characteristics of the causal agent	Tetanus is an acute, life-threatening systemic infection caused by the exotoxins of *Clostridium tetani*, a Gram-positive, anaerobic and spore-forming bacillus that is ubiquitous in the environment. A natural reservoir of the spores is the digestive tract of animals, especially ruminants (abomasum). Spores are released with animal droppings, and soil and manure are thus major sources of environmental contamination. Vaccination is very effective in preventing infection, and medical treatment is available to cure affected persons.
Occupational exposures	Most workers can be exposed to tetanus infection from open wounds that become contaminated with dust and are not promptly cleaned, disinfected and dressed. Occupational groups at risk include agricultural workers, farmers and breeders, waste workers, paper and cardboard manufacturing workers, carpenters, metalworkers, construction and machinery workers, miners, and military personnel. Microbiology laboratory workers may also be at risk.
Biological mechanisms, main health effects and diagnostic criteria	
Short profile of the biological mechanisms	*Clostridium tetani* is a ubiquitously present sporogenic microorganism. The bacillus can develop into the vegetative state only under strictly anaerobic conditions, such as in deep perforating wounds, and is heat-labile. In the vegetative state, *C. tetani* can shed its flagellae and form spores that are very resistant to heat and acid. When entering the site of a deep, penetrating wound, the spores find an anaerobic environment, germinate, and produce and secrete two extracellular toxins: tetanolysin which is able to bind to and perforate the cell membrane although its pathogenic relevance is uncertain, and tetanospasmin, which is neurotoxic and induces the characteristic signs of tetanus. Tetanospasmin is the second deadliest natural protein toxin after the *Botulinum* toxin: it acts by blocking the release of the neurotransmitters glycine and gamma-aminobutyric acid (GABA) from inhibitory neurons, with a subsequent widespread activation of excitatory motor neurons. This causes spasms and rigid paralysis of the muscles: manifestations can range from typical signs of the disease, i.e., spastic paralysis of the jaw (*trismus, rictus*) and the back (*opisthotonus*), to life-threatening conditions with paralysis of the respiratory muscles.

Name of the diseases and ICD code: **Tetanus (A35 +Z57)**

Short description of the disease

The term "Tetanus" refers to an acute disease characterized by muscle spasms and autonomic nervous system impairment. The clinical features of tetanus can be divided into local and generalized effects.

The local form affects limited areas of the body with muscle spasm and is usually less severe. Nonetheless, when this form affects the cranial nerves, e.g. with paralysis of the laryngeal or pharyngeal muscles, the prognosis may be poorer. In case of generalized infections, the first affected area is the face, the jaw in particular, and then spasms occur in other areas of the body. In severe cases, autonomic nervous system dysfunction occurs.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms:
  - Increased muscle tone and spasms of voluntary muscles: very often, the first finding is stiffness of the facial muscles (*trismus*), muscle pain and neck stiffness, back pain, difficulty in swallowing, and a sore throat. As the disease progresses, muscle spasms develop in the arms and legs. Generalized muscle spasms can be very painful and can even provoke fractures of the spine.
  - Respiratory deficiency is due to the sustained contraction of laryngeal or respiratory muscles.
  - Autonomic nervous system damage is maximal during the second week of severe tetanus and can cause cardiovascular changes: blood pressure can fluctuate and be accompanied by tachycardia but, in some cases, bradycardia and heart block can be observed.
  - Autonomic involvement can bring about gastrointestinal stasis, sweating, increased tracheal secretions, and acute renal failure in the most severe cases.
  - If the infection is not properly treated, death can affect up to 70% of cases. Recovery usually takes place between 4 and 6 weeks but, in some cases, nerve impairment and spasms can persist for longer periods.
- Examinations: the diagnosis is made clinically. *C. tetani* can sometimes be cultured from the wound, but only a minor proportion (30%) of affected subjects has positive cultures.

1.3.4 Tetanus — ICD Code A35 +Z57

Differential diagnosis

The differential diagnosis of generalized tetanus includes strychnine poisoning and dystonic reactions to antidopaminergic medications. Cephalic tetanus can be confused with other causes of trismus, such as oropharyngeal infections. Tetanus can be confused with bacterial or viral meningoencephalitis: in this case, an intact sensorium, normal cerebrospinal fluid and the presence of muscle spasms suggest tetanus.

Exposure assessment

- History of occupational exposure: confirmed contact of open wounds with materials possibly contaminated by tetanus spores at the workplace or during work activities. Persons at the highest risk are those suffering burns and surgical wounds, in particular, if in contact with soil and faeces from ruminants and other animals. However, tetanus spores may penetrate trivial or even unapparent wounds.
- Minimum duration of exposure: a single and short exposure may be sufficient to cause the disease.
- Maximum latent period: incubation period ranges from one day to several weeks (the typical latent period does not usually exceed two weeks).

Key actions for prevention	Due to the ubiquitous presence of spores in the environment, tetanus infection cannot be eradicated. However, mass vaccination of the general population and a higher degree of attention to ensure coverage for workers at a greater risk of getting wounds from activities carried in the open field can reduce the risk of this infection. The chance of getting open wounds or minute abrasions can be minimized with the widespread use of appropriate protective clothing in activities such as agriculture and industrial work in yards and shops. Safety shoes with reinforced, pierce-proof soles and robust gloves should be provided to workers at risk as part of their work outfits. Education on the correct treatment of even minor abrasions and prompt availability of ready-to-use medication for wounds can lead to a substantial reduction of the chances that unavoidable small wounds become the source of tetanus and of other infections. A full vaccination course of five doses is usually recommended, with consideration of booster doses every 10 years.

Further reading

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▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
1.3.4	Tetanus	A35	1C13
	Occupational exposure to risk factors	Z57	QD84.Y

1.3.5 Tuberculosis	ICD Code A15 - A19 +Z57
General characteristics of the causal agent	Tuberculosis (TB) is a transmissible infectious disease caused by several strains of Mycobacteria. Most cases of human tuberculosis are caused by *Mycobacterium tuberculosis* (primarily from humans) and less frequently by *Mycobacterium bovis* (primarily from cattle), and other (Mycobacteria *M. africanum, M. canettii, M. microti*), all of which are collectively referred to as the *Mycobacterium tuberculosis* complex 'MTC' or 'MTBC'. Mycobacteria are small microorganisms characterized by the presence of a thick waxy cell wall that protects the bacillus from external environmental factors and, in the host organism, from the cytotoxic response, the immune system and several chemotherapeutic agents. Their growth is usually considered slow, with replication times of approximately 15-20 hours, if compared with other bacteria such as *Escherichia coli* (20 minutes), and requires high levels of oxygen. Reservoirs are represented primarily by humans, more rarely by primates; in some areas, diseased cattle, swine, badgers, and other mammals are also infected. Transmission of the infective agent occurs most commonly via exposure to tubercle bacilli in aerosol as airborne "droplet nuclei" (1-5 µm in diameter), produced by people with pulmonary or respiratory tract tuberculosis during expiratory efforts (e.g. coughing, sneezing, or singing). The droplets may remain suspended in the air for several hours and may reach the terminal airways when inhaled. Direct invasion through mucous membranes or breaks in the skin may occur but represents a rare event.
Occupational exposures	Tuberculosis can occur in several groups of workers: health workers especially during procedures such as bronchoscopy, intubation, and autopsy, laboratory technicians and scientific staff that work with non-human primates for development of animal models, social workers in centres for homeless and refugees, at correctional institutions, and aid workers in high-incidence countries. Occupational risk for farmers and veterinarians is lower since animal to human spread is unusual, except for contact with milk derived from cows suffering heavy infections from *M. bovis*. Workers with silicosis are deemed to be at higher risk of developing tuberculosis. If also affected by silicosis, a serious complication can arise called silicotuberculosis (for a full discussion, see dedicated item 2.1.2). The increased risk of contracting TB may be the result of workers living in cramped quarters where hygienic conditions may be poor. For this reason, additional workplace settings where the risk of TB can be considered increased are oil and gas industries, agriculture, mining and extractive industries in work camps, and businesses with a large migrant workforce.
Biological mechanisms, main health effects and diagnostic criteria	
Short profile of the biological mechanisms	Due to the requirement of a high concentration of oxygen for growth, MTBC mostly settles in the lungs. When they are phagocytized by the macrophages, their waxy cell wall protects them from the antibacterial chemicals of the lysosomes, and the mycobacteria can reproduce uncontrolled within the macrophages. The macrophages loaded with mycobacteria then undergo apoptosis, and the leaked microorganisms can propagate the infection. The resulting growth of large masses of mycobacteria and cellular debris (granulomas) causes scarring of the lung tissue and give rise to typical radiographic signs (*caseous necrosis*, see below). When macrophages drain from the lung and move to other tissues, they can disseminate the disease and lead to extra-pulmonary tuberculosis.

Name of the diseases and ICD code: **Tuberculosis (A15-A19 +Z57)**

Short description of the disease

Tuberculosis is one of the world's most widespread diseases, which affects in particular developing and underdeveloped countries. A world burden of 10 million new TB cases was estimated for 2019.

Infection with *M. tuberculosis* is not sufficient to cause clinical tuberculosis, as the disease may become manifest even years after the infection or remain silent: the active disease involves only 5 to 15% of the infected population. Among risk factors for clinical TB development, age, malnutrition, poverty, HIV infection, and silicosis have a relevant role. Tuberculosis may affect different body organs, but the lungs represent its preferential target. For this reason, TB is usually classified as 'pulmonary' and 'extra-pulmonary' (note that the two conditions can coexist). TB might have acute, sub-acute or chronic progress. The chronic picture ranges from an asymptomatic state to widespread dissemination through the pulmonary tissue and to other organs (kidney, brain, bones, etc.). When mycobacteria dissemination is massive and involves multiple organs, miliary TB arises.

1.3.5 Tuberculosis ICD Code A15 - A19 +Z57

Pulmonary TB can be classified as primary or post-primary, and the onset of the disease is usually slow. It can show no symptoms or fever and be sometimes associated with pleuritic chest pain. The primary lesion is a tubercle. Such a lesion may become inactive and is usually asymptomatic. Post-primary TB, also known as adult-type TB, reactivation TB, or secondary TB, may result from endogenous reactivation of distant latent TB infection or recent infection and is commonly localized to the apical and posterior segments of the upper lobes: here, the mean oxygen tension is higher than in the lower zones and supports mycobacterial growth. The superior segments of the lower lobes are frequently involved. The extent of lung parenchymal involvement ranges from infiltrates to extensive disease. With cavity formation, liquefied necrotic contents may be discharged into the airways and undergo bronchogenic spread, resulting in satellite lesions within the lungs that may, in turn, undergo cavitation. When lesions converge, and massive involvement of pulmonary segments or lobes occurs, caseating pneumonia can arise.

Extra-pulmonary TB covers all forms of tuberculosis in which the disease process occurs outside the lungs. Many forms of extra-pulmonary tuberculosis originate from lymphatic or haematogenous spread of mycobacteria from a primary focus in the lung. Some of them (e.g. pleural and pericardial TB) may arise from direct extension of a pulmonary lesion.

The most common types of extra-pulmonary tuberculosis are:

- Tuberculous lymphadenitis or lymph node TB.
- Pleural TB and, less commonly, tuberculous empyema.
- TB of the upper airways.
- Genitourinary TB.
- Skeletal TB.
- Tuberculous meningitis.
- Pericardial TB or tuberculous pericarditis.
- Gastrointestinal TB and tuberculous peritonitis.
- Cutaneous tuberculosis.

Miliary TB is a disseminated (both pulmonary and extra-pulmonary) form of TB due to haematogenous spread of tubercle bacilli. In adults, it can be due to either recent infection or reactivation of old disseminated foci. If unrecognized, miliary TB is lethal.

Diagnostic criteria

Clinical manifestations of pulmonary TB

- Signs and symptoms:
  - At early stages, clinical manifestations may be aspecific and consist in fever, chills, loss of appetite, weight loss, malaise, fatigue, and night sweats.
  - As the disease progresses, cough (usually productive) can arise, together with pleuritic chest pain.
  - Pallor and digital clubbing may develop in the most severe cases.
- Examinations:
  - Positive tuberculin skin test (TST):
    > An induration ≥ 5 mm in diameter is considered positive in high risk subjects, such as HIV-positive or immunocompromised subjects, people with recent contacts of individuals with active tuberculosis, and persons showing fibrotic lesions on chest X-rays.
    > An induration ≥ 10 mm in diameter is considered positive in recent immigrants from countries with a high prevalence of tuberculosis, mycobacteriology laboratory personnel, residents/workers in high risk settings such as correctional institutions, long-term facilities for the elderly, hospitals and other health care facilities, , and homeless shelters.
    > An induration ≥ 15 mm in diameter should be considered positive among low risk subjects.
    > Interferon Gamma Release Assay is an alternative test to TST and the choice of testing will depend on national guidance determined by likelihood of infection and the purpose of testing, screening or diagnosis, and resource availability.
  - Presence of acid-fast bacilli (AFB) in stained smears from sputum.
  - Isolation of *M. tuberculosis* in cultures from biological specimens.
  - Chest X-ray: the most characteristic radiological feature in primary tuberculosis is thoracic lymphadenopathy. In more advanced cases, typical upper lobe pneumonia (focal opacity or partial/total lobar consolidation) with cavitation may appear. However, it must be kept in mind that virtually any radiological pattern can be seen (from a solitary nodule to diffuse infiltrates), especially in immunocompromised subjects.
  - Several tests based on the amplification of mycobacterial nucleic acid have become available and are most useful for the rapid confirmation of TB in subjects with AFB-positive specimens, as well as for the diagnosis of AFB-negative pulmonary and extra-pulmonary TB.

1.3.5 Tuberculosis ICD Code A15 - A19 +Z57

Clinical manifestations of TB

- *Tuberculous lymphadenitis (or lymph node TB)*
  - Lymph nodes appear swollen and are usually painless; lesions are most commonly located at the posterior cervical and supraclavicular sites.
  - Fine needle aspiration biopsy or surgical excision biopsy are usually necessary to confirm the diagnosis: granulomatous lesions with or without visible AFBs are typically seen, and cultures are positive in a high percent of cases.
- *Pleural TB*
  - The effusion may be small, remain unnoticed, and resolve spontaneously or may be large enough to cause symptoms such as fever and pleuritic chest pain, together with dyspnoea.
  - On physical examination, dullness to percussion and absence of breath sounds can be noticed.
  - Chest X-rays can reveal the effusion as well as parenchymal lesions when present.
  - Needle pleural biopsy is often necessary for diagnosis as it reveals granulomas and can yield a positive culture (this procedure is recommended over pleural fluid retrieved from thoracentesis, where AFB are rarely seen).
- *Tuberculous empyema*
  - Since it results from rupture of a cavity with spillage of organisms directly into the pleural space, tuberculous empyema may become manifest as a hydropneumothorax with an air-fluid level at chest radiograph.
  - Pleural fluid is purulent and thick: acid-fast smears and mycobacterial cultures are often positive.
  - Pleural fibrosis and restrictive lung disease may eventually develop in the most severe cases.
- *TB of the upper airways (larynx, pharynx, and epiglottis)*
  - Symptoms may include dysphonia, hoarseness and dysphagia, together with chronic productive cough.
  - A laryngoscopic examination may show ulcerations.
  - Acid-fast smear of the sputum is often positive, but a biopsy may be necessary for an appropriate aetiologic diagnosis.
- *Genitourinary TB*
  - Since it can affect any portion of the urinary tract, common presenting manifestations can be nonspecific and include urinary frequency, nocturia, dysuria, haematuria, and abdominal pain. Affected subjects may also remain asymptomatic until the disease produces severe destructive lesions of the kidneys.
  - Intravenous pyelogram, abdominal CT, or MRI may show obstructions and deformities, as well as calcifications and ureteral strictures.
  - Cultures of sequential morning urinary specimens usually yield a definitive diagnosis.
  - Genital involvement occurs more frequently in females, with the disease affecting the fallopian tubes and the endometrium and causing pelvic pain, menstrual abnormalities, and even infertility; diagnosis requires biopsy or culture of specimens.
- *Skeletal TB (most commonly spinal, also known as Pott's disease or tuberculous spondylitis)*
  - It often involves two or more adjacent vertebral bodies, usually among the lower thoracic and upper lumbar vertebrae. The collapse of vertebral bodies can result in gibbus deformity.
  - A paravertebral abscess may form, which, depending on its position, may penetrate the chest wall and present as a soft tissue mass or reach the inguinal ligaments and present as a psoas abscess. In both cases, CT or MRI are usually able to show the lesion. If the abscess is large enough to compress the spinal cord, paraplegia may arise.
  - Synovial biopsy and tissue culture may be necessary for confirmation of diagnosis.
- *Tuberculous meningitis*
  - Presenting manifestations can be subtle, such as headache and slight mental changes, which usually follow weeks of low-grade fever, malaise, anorexia, and irritability.
  - If unrecognized, severe headache, confusion, lethargy, altered sensorium, and neck rigidity may arise. Paresis of cranial (especially ocular) nerves is a frequent finding and the involvement of cerebral arteries may produce focal ischaemia.
  - The disease may ultimately evolve into coma, with hydrocephalus and intracranial hypertension.
  - Culture of cerebrospinal fluid is usually diagnostic.
- *Pericardial TB (or tuberculous pericarditis)*
  - Dyspnoea, fever, dull retrosternal pain, and a pericardial friction rub, may be the presenting manifestations.
  - An effusion eventually develops, which can be seen at either echocardiographic, CT, or MRI examinations.
  - A definitive diagnosis can be obtained by culture of pericardial fluid obtained by pericardiocentesis under echocardiographic guidance.

1.3.5 Tuberculosis — ICD Code A15 - A19 +Z57

- *Gastrointestinal TB and tuberculous peritonitis*
  - The disease usually becomes manifest with abdominal pain and swelling and a palpable mass in the abdomen.
  - Fever, weight loss, anorexia, and night sweats are common presenting manifestations.
  - If the intestinal wall is involved, ulcerations and fistulae may occur.
  - If peritonitis occurs, ascites can arise, with paracentesis revealing an exudative fluid. Nonetheless, a peritoneal biopsy is often necessary to confirm the diagnosis.
- *Cutaneous tuberculosis*
  - The main manifestation is erythema nodosum, an allergic-like manifestation occurring in a few weeks after primary infection and normally resolving in a further three weeks.

Clinical manifestations of miliary TB

- Signs and symptoms:
  - Fever, anorexia, weakness, weight loss, and night sweats can be frequent presenting symptoms.
  - Other symptoms, if present, depend on the predominant site of involvement (e.g. cough or abdominal pain).
  - On physical examination, hepatomegaly, splenomegaly, and lymphadenopathy may be observed.
- Examinations:
  - Eye examination may show choroidal tubercles on fundoscopy (i.e., yellowish lesions in the choroid, more commonly unilateral, which are pathognomonic of miliary TB).
  - On chest radiography, no abnormality may be evident in the early stages of the disease. When present, radiological alterations include a miliary reticulonodular pattern, large or interstitial infiltrates, and pleural effusions.
  - Bronchoalveolar lavage (BAL) and transbronchial biopsy usually confirm the aetiology of the disease.
  - Liver or bone marrow biopsy specimens usually show granulomas.

Exposure assessment

- History of occupational exposure: evidence of close contact with a TB infected source human as well as animal or work within high risk settings (see above).
- Minimum duration of exposure: a single exposure is theoretically enough to cause the disease; nonetheless, a close contact is usually necessary, lasting most likely no less than some hours.
- Maximum latent period: in the acute forms, the onset is usually observed no more than 90 days after infection. In infected subjects, the disease can become manifest typically within two years from infection. Nonetheless, cases have been reported of the disease becoming active even several years after the infection or with immune suppression.

Key actions for prevention	Human to human spread of tuberculosis that can occur in healthcare and social work can be prevented with the use of effective TB infection-control programmes. The "Fundamentals of TB infection control" chapter of the ILO Encyclopaedia of occupational health and safety, 4th edition is a useful resource and is adapted here. Although specifically developed for the healthcare setting, most of the suggested preventive criteria can easily apply to other occupational settings where exposure to TB infected individuals may occur, thus deserving a mention in the present item. An effective TB infection control programme requires early identification, isolation and effective treatment of persons who have active TB. The primary emphasis of the TB infection control plan should be on achieving these three goals. In all health care facilities, particularly those in which persons who are at high risk for TB work or receive care, policies and procedures for TB control should be developed, reviewed periodically and evaluated for effectiveness to determine the actions necessary to minimize the risk for transmission of *M. tuberculosis*. The TB infection control programme should be based on a hierarchy of controls measures. The first level of the hierarchy, and that which affects the largest number of persons, is using administrative measures intended primarily to reduce the risk for exposing uninfected persons to persons who have infectious TB. These measures include: • developing and implementing effective written policies and protocols to ensure the rapid identification, isolation, diagnostic evaluation and treatment of persons likely to have TB; • implementing effective work practices among health workers (HWs) in the health care facility (e.g. correctly wearing respiratory protection and keeping doors to isolation rooms closed); • educating, training and counselling HWs about TB; and • screening HWs for TB infection and disease.

1.3.5 Tuberculosis	ICD Code A15 - A19 +Z57
Key actions for prevention	The second level of the hierarchy is the use of engineering controls to prevent the spread and reduce the concentration of infectious droplet nuclei. These controls include: • direct source control using local exhaust ventilation; • controlling the direction of airflow to prevent contamination of air in areas adjacent to the infectious source; • diluting and removing contaminated air via general ventilation; and • air cleaning via air filtration or ultraviolet germicidal irradiation (UVGI). The first two levels of the hierarchy minimize the number of areas in the health care facility where exposure to infectious TB may occur, and they reduce but do not eliminate the risk in those few areas where exposure to *M. tuberculosis* can still occur (e.g. rooms in which patients with known or suspected infectious TB are being isolated and treatment rooms in which cough-inducing or aerosol-generating procedures are performed on such patients). Because persons entering such rooms may be exposed to *M. tuberculosis*, the third level of the hierarchy is the use of personal respiratory protective equipment in these and certain other situations in which the risk for infection with *M. tuberculosis* may be relatively higher. Specific measures to reduce the risk for transmission of *M. tuberculosis* include the following: 1. Assigning to specific persons in the health care facility the supervisory responsibility for designing, implementing, evaluating and maintaining the TB infection-control programme. 2. Conducting a risk assessment to evaluate the risk for transmission of *M. tuberculosis* in all areas of the health care facility, developing a written TB infection control programme based on the risk assessment and periodically repeating the risk assessment to evaluate the effectiveness of the TB infection control programme. TB infection control measures for each health care facility should be based on a careful assessment of the risk for transmission of *M. tuberculosis* in that particular setting. The first step in developing the TB infection control programme should be to conduct a baseline risk assessment to evaluate the risk for transmission of *M. tuberculosis* in each area and occupational group in the facility. Appropriate infection control interventions can then be developed on the basis of actual risk. Risk assessments should be performed for all inpatient and outpatient settings (e.g. medical and dental offices). Classification of risk for a facility, for a specific area and for a specific occupational group should be based on the profile of TB in the community, the number of infectious TB patients admitted to the area or ward, or the estimated number of infectious TB patients to whom HWs in an occupational group may be exposed and the results of analysis of HW tuberculin test conversions (where applicable) and possible person-to-person transmission of *M. tuberculosis*. Regardless of risk level, the management of patients with known or suspected infectious TB should not vary. However, the index of suspicion for infectious TB among patients, the frequency of HW tuberculin skin testing, the number of TB isolation rooms and other factors will depend on the level of risk for transmission of *M. tuberculosis* in the facility, area or occupational group. 3. Developing, implementing and enforcing policies and protocols to ensure early identification, diagnostic evaluation and effective treatment of patients who may have infectious TB. A diagnosis of TB may be considered for any patient who has a persistent cough (i.e., a cough lasting for longer than three weeks) or other signs or symptoms compatible with active TB (e.g. bloody sputum, night sweats, weight loss, anorexia or fever). However, the index of suspicion for TB will vary in different geographic areas and will depend on the prevalence of TB and other characteristics of the population served by the facility. The index of suspicion for TB should be very high in geographic areas or among groups of patients in which the prevalence of TB is high. Appropriate diagnostic measures should be conducted, and TB precautions implemented for patients in whom active TB is suspected. Where resources permit, isolation of organisms of the Mycobacterium tuberculosis complex (MTC or MTBC) on culture, while confirming the diagnosis, also allows drug susceptibility of the infecting organism to be determined (which is relevant in a context of developing multi-drug resistant mycobacteria).

1.3.5 Tuberculosis	ICD Code A15 - A19 +Z57
Key actions for prevention	4. Providing prompt triage for and appropriate management of patients in the outpatient setting who may have infectious TB. Triage of patients in ambulatory care settings and emergency departments should include vigorous efforts to identify promptly patients who have active TB. HWs who are the first points of contact in facilities that serve populations at risk for TB should be trained to ask questions that will facilitate the identification of patients with signs and symptoms suggestive of TB. Patients with signs or symptoms suggestive of TB should be evaluated promptly to minimize the amount of time they are in ambulatory care areas. TB precautions should be followed while the diagnostic evaluation is being conducted for these patients. TB precautions in the ambulatory care setting should include placing these patients in a separate area apart from other patients and not in open waiting areas (ideally, in a room or enclosure meeting TB isolation requirements), giving these patients surgical masks to wear and instructing them to keep their masks on and giving these patients tissues and instructing them to cover their mouths and noses with the tissues when coughing or sneezing. Surgical masks are designed to prevent the respiratory secretions of the person wearing the mask from entering the air. When not in a TB isolation room, patients suspected of having TB should wear surgical masks to reduce the expulsion of droplet nuclei into the air. Patients suspected of having or known to have TB should never wear a respirator that has a non-shrouded exhalation valve as source control because the device would provide no barrier to the expulsion of droplet nuclei into the air. 5. Promptly initiating and maintaining TB isolation for persons who may have infectious TB and who are admitted to the inpatient setting. In hospitals and other inpatient facilities, any patient suspected of having or known to have infectious TB should be placed in a TB isolation room that has currently recommended ventilation characteristics (see below). Written policies for initiating isolation should specify the indications for isolation, the person(s) authorized to initiate and discontinue isolation, the isolation practices to follow, the monitoring of isolation, the management of patients who do not adhere to isolation practices and the criteria for discontinuing isolation. 6. Effectively planning arrangements for discharge. Before a TB patient is discharged from the health care facility, the facility's staff and public health authorities should collaborate to ensure the continuation of therapy. Discharge planning in the health care facility should include, at a minimum, a confirmed outpatient appointment with the provider who will manage the patient until the patient is cured, sufficient medication to take until the outpatient appointment and placement into case management (e.g. directly observed therapy) or outreach programmes of the public health department. These plans should be initiated and in place before the patient's discharge. 7. Developing, installing, maintaining and evaluating ventilation and other engineering controls to reduce the potential for airborne exposure to *M. tuberculosis*. Local exhaust ventilation is a preferred source control technique, and it is often the most efficient way to contain airborne contaminants because it captures these contaminants near their source before they can disperse. Therefore, the technique should be used, if feasible, wherever aerosol-generating procedures are performed. Two basic types of local exhaust devices use hoods: the enclosing type, in which the hood either partially or fully encloses the infectious source, and the exterior type, in which the infectious source is near but outside the hood. Fully enclosed hoods, booths or tents are always preferable to exterior types because of their superior ability to prevent contaminants from escaping into the HW's breathing zone. General ventilation can be used for several purposes, including diluting and removing contaminated air, controlling airflow patterns within rooms and controlling the direction of airflow throughout a facility. General ventilation maintains air quality by two processes: dilution and removal of airborne contaminants. Uncontaminated supply air mixes with the contaminated room air (i.e., dilution), which is subsequently removed from the room by the exhaust system. These processes reduce the concentration of droplet nuclei in the room air. Recommended general ventilation rates for health care facilities are usually expressed in the number of air changes per hour (ACH).

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Key actions for prevention	This number is the ratio of the volume of air entering the room per hour to the room volume and is equal to the exhaust airflow (Q, in cubic meters per minute) divided by the room volume (V, in cubic meters) multiplied by 60 (i.e., ACH = Q / V x 60). For the purposes of reducing the concentration of droplet nuclei, TB isolation and treatment rooms in existing health care facilities should have an airflow of greater than 6 ACH. Where feasible, this airflow rate should be increased to at least 12 ACH by adjusting or modifying the ventilation system or by using auxiliary means (e.g. recirculation of air through fixed high-efficiency particulate air [HEPA] filtration systems or portable air cleaners). New construction or renovation of existing health care facilities should be designed so that TB isolation rooms achieve an airflow of at least 12 ACH. The general ventilation system should be designed and balanced so that air flows from less contaminated (i.e., more clean) to more contaminated (less clean) areas. For example, air should flow from corridors into TB isolation rooms to prevent the spread of contaminants to other areas. In some special treatment rooms in which operative and invasive procedures are performed, the direction of airflow is from the room to the hallway to provide cleaner air during these procedures. Cough-inducing or aerosol-generating procedures (e.g. bronchoscopy and irrigation of tuberculous abscesses) should not be performed in rooms with this type of airflow on patients who may have infectious TB. HEPA filters may be used in a number of ways to reduce or eliminate infectious droplet nuclei from room air or exhaust. These methods include placement of HEPA filters in exhaust ducts discharging air from booths or enclosures into the surrounding room, in ducts or in-ceiling or wall-mounted units, for recirculation of air within an individual room (fixed recirculation systems), in portable air cleaners, in exhaust ducts to remove droplet nuclei from air being discharged to the outside, either directly or through ventilation equipment, and in ducts discharging air from the TB isolation room into the general ventilation system. In any application, HEPA filters should be installed carefully and maintained meticulously to ensure adequate functioning. For general use areas in which the risk for transmission of *M. tuberculosis* is relatively high, ultraviolet germicidal irradiation lamps (UVGI) may be used as an adjunct to ventilation for reducing the concentration of infectious droplet nuclei, although the effectiveness of such units has not been evaluated adequately. Ultraviolet (UV) units can be installed in a room or corridor to irradiate the air in the upper portion of the room, or they can be installed in ducts to irradiate air passing through the ducts. 8. Developing, implementing, maintaining and evaluating a respiratory protection programme. Personal respiratory protection (i.e., respirators) should be used by persons entering rooms in which patients with known or suspected infectious TB are being isolated, persons present during cough-inducing or aerosol-generating procedures performed on such patients and persons in other settings where administrative and engineering controls are not likely to protect them from inhaling infectious airborne droplet nuclei. These other settings include transporting patients who may have infectious TB in emergency transport vehicles and providing urgent surgical or dental care to patients who may have infectious TB before a determination has been made that the patient is non-infectious. 9. Educating and training HWs about TB, effective methods for preventing transmission of *M. tuberculosis* and the benefits of medical screening programmes. All HWs, including physicians, should receive education regarding TB that is relevant to persons in their particular occupational group. Ideally, training should be conducted before initial assignment, and the need for additional training should be re-evaluated periodically (e.g. once a year). The level and detail of this education will vary according to the HW's work responsibilities and the level of risk in the facility (or area of the facility) in which the HW works. However, the programme may include the following elements: • the basic concepts of *M. tuberculosis* transmission, pathogenesis and diagnosis, including information concerning the difference between latent TB infection and active TB disease, the signs and symptoms of TB and the possibility of reinfection; • the potential for occupational exposure to persons who have infectious TB in the health care facility, including information concerning the prevalence of TB in the community and facility, the ability of the facility to properly isolate patients who have active TB, and situations with increased risk for exposure to *M. tuberculosis*; • the principles and practices of infection control that reduce the risk for transmission of *M. tuberculosis*, including information concerning the hierarchy of TB infection control measures and the written policies and procedures of the facility. Site-specific control measures should be provided to HWs working in areas that require control measures in addition to those of the basic TB infection control programme; • the importance of proper maintenance for engineering controls (e.g. cleaning UVGI lamps and ensuring negative pressure in TB isolation rooms);

1.3.5 Tuberculosis	ICD Code A15 - A19 +Z57
Key actions for prevention	• the purpose of tuberculin skin testing, the significance of a positive tuberculin test result and the importance of participating in the skin test programme; • the principles of preventive therapy for latent TB infection; these principles include the indications, use, effectiveness and the potential adverse effects of the drugs; • the HW's responsibility to seek prompt medical evaluation if a tuberculin test conversion occurs or if symptoms develop that could be caused by TB. A medical evaluation will enable HWs who have TB to receive the appropriate therapy and will help to prevent transmission of *M. tuberculosis* to patients and other HWs; • the principles of drug therapy for active TB; • the importance of notifying the facility if the HW is diagnosed with active TB so that contact investigation procedures can be initiated; • the responsibilities of the facility to maintain the confidentiality of the HW while ensuring that the HW who has TB receives appropriate therapy and is non-infectious before returning to duty; • the higher risks associated with TB infection in persons who have HIV infection or other causes of severely impaired cell-mediated immunity, including (a) the more frequent and rapid development of clinical TB after infection with *M. tuberculosis*, (b) the differences in the clinical presentation of disease and (c) the high mortality rate associated with multiple drug resistant TB in such persons; • the potential development of cutaneous anergy as immune function (as measured by CD4+ T-lymphocyte counts) declines; • information regarding the efficacy and safety of BCG vaccination and the principles of tuberculin screening among BCG recipients; and • the facility's policy on voluntary work reassignment options for immunocompromised HWs. 10. Developing and implementing a programme for routine periodic counselling and screening of HWs for active TB and latent TB infection. A TB counselling, screening and prevention programme for HWs should be established to protect both HWs and patients. HWs who have positive tuberculin test results, tuberculin test conversions or symptoms suggestive of TB should be identified, evaluated to rule out a diagnosis of active TB and started on therapy or preventive therapy if indicated. In addition, the results of the HW tuberculin screening programme will contribute to the evaluation of the effectiveness of current infection control practices. Because of the increased risk for rapid progression from latent TB infection to active TB in human immunodeficiency virus, HIV-infected or otherwise severely immunocompromised persons, all HWs should know if they have a medical condition or are receiving a medical treatment that may lead to severely impaired cell-mediated immunity. HWs who may be at risk for HIV infection should know their HIV status (i.e., they should be encouraged to voluntarily seek counselling and testing for HIV antibody status). Existing guidelines for counselling and testing should be followed routinely. Knowledge of these conditions allows the HW to seek the appropriate preventive measures and to consider voluntary work reassignments. 11. All HWs should be informed about the need to follow existing recommendations for infection control to minimize the risk for exposure to infectious agents; implementation of these recommendations will greatly reduce the risk for occupational infections among HWs. All HWs should be informed about the potential risks to severely immunocompromised persons associated with caring for patients who have some infectious diseases, including TB. It should be emphasized that limiting exposure to TB patients is the most protective measure that severely immunosuppressed HWs can take to avoid becoming infected with *M. tuberculosis*. HWs who have severely impaired cell-mediated immunity and who may be exposed to *M. tuberculosis* may consider a change in job setting to avoid such exposure. HWs should be advised of the legal option in many jurisdictions that severely immunocompromised HWs can choose to transfer voluntarily to areas and work activities in which there is the lowest possible risk for exposure to *M. tuberculosis*. This choice should be a personal decision for HWs after they have been informed of the risks to their health.

1.3.5 Tuberculosis	ICD Code A15 - A19 +Z57
Key actions for prevention	12. Employers should make reasonable accommodations (e.g. alternative job assignments) for workers who have a health condition that compromises cell-mediated immunity and who work in settings where they may be exposed to *M. tuberculosis*. HWs who are known to be immunocompromised should be referred to occupational health professionals who can individually counsel the workers regarding their risk for TB. Upon the request of the immunocompromised HW, employers should offer, but not compel, a work setting in which the HW would have the lowest possible risk for occupational exposure to *M. tuberculosis*. 13. All HWs should be informed that immunosuppressed HWs should have appropriate follow-up and screening for infectious diseases, including TB, provided by their medical practitioner. HWs who are known to be HIV-infected or otherwise severely immunosuppressed should be tested for cutaneous anergy at the time of tuberculin testing. Consideration should be given to retesting, at least every six months, those immunocompromised HWs who are potentially exposed to *M. tuberculosis* because of the high risk for rapid progression to active TB if they become infected. 14. Information provided by HWs regarding their immune status should be treated confidentially. If the HW requests voluntary job reassignment, the privacy of the HW should be maintained. Facilities should have written procedures on confidential handling of such information. 15. Promptly evaluating possible episodes of *M. tuberculosis* transmission in health care facilities, including tuberculin skin test conversions among HWs, epidemiologically associated cases among HWs or patients and contacts of patients or HWs who have TB and who were not promptly identified and isolated. Epidemiological investigations may be indicated for several situations. These include, but are not limited to, the occurrence of tuberculin test conversions or active TB in HWs, the occurrence of possible person-to-person transmission of *M. tuberculosis* and situations in which patients or HWs with active TB are not promptly identified and isolated, thus exposing other persons in the facility to *M. tuberculosis*. The general objectives of the epidemiological investigations in these situations are as follows: • to determine the likelihood that transmission of and infection with *M. tuberculosis* has occurred in the facility; • to determine the extent to which *M. tuberculosis* has been transmitted; • to identify those persons who have been exposed and infected, enabling them to receive appropriate clinical management; • to identify factors that could have contributed to transmission and infection and to implement appropriate interventions; and • to evaluate the effectiveness of any interventions that are implemented and to ensure that exposure to and transmission of *M. tuberculosis* have been terminated. 16. Coordinating activities with the local public health department, emphasizing reporting and ensuring adequate discharge follow-up and the continuation and completion of therapy. As soon as a patient or HW is known or suspected to have active TB, the patient or HW should be reported to the public health department so that appropriate follow-up can be arranged and a community contact investigation can be performed. The health department should be notified well before patient discharge to facilitate follow-up and continuation of therapy. A discharge plan coordinated with the patient or HW, the health department and the inpatient facility should be implemented. For what concerns preventive actions that can be implemented at a community level, international institutions have highlighted that employers and workers have much to contribute to TB control: the workplace represents an opportunity for TB control activities, since workers attend on a regular basis, communication systems are in place, and existing structures, services, and facilities can be used for prevention, care, and support. Specific guidelines have been developed on this topic in a joint document by the WHO and the ILO ("*The contribution of workplace TB control activities to TB control in the community*"), which should be referred to for further discussion. Finally, for what concerns bovine tuberculosis, preventive measures mainly consist in dairy cattle of tuberculin testing and slaughtering of TB reactor animals, together with pasteurization or boiling of milk.

1.3.5 Tuberculosis — ICD Code A15 - A19 +Z57

Further reading

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▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
1.3.5	Tuberculosis	A15-A19	1B10 - 1B1Z
	Occupational exposure to risk factors	Z57	QD84.Y

1.3.6 Toxic or inflammatory syndromes associated with bacterial or fungal contaminants ICD Code J66.8, J67.7 +Z57	
General characteristics of the causal agent	Inhalation of organic dusts (0.1 to 50 µm in size) such as fragments of grain kernels, insects' bodies, bacteria, fungal spores, and moulds can cause an inflammatory reaction, mainly localized in the respiratory tract. The involved causative agents are bacterial endotoxins, mycotoxins, and other agents present in organic dusts. Common biologically important constituents of organic dusts which can be involved in the causation of toxic or inflammatory syndromes are: • Among *microbial agents*: endotoxins, protease enzymes, some mycotoxins; endotoxins are lipopolysaccharides (lipid glycosides) that are attached to the outer cell surface of Gram-negative bacteria. (1,3)-β-D-glucan is a polyglucose component of the cell wall of moulds and of some bacteria that enhances the inflammatory response caused by endotoxins and alters the function of inflammatory cells (particularly of macrophages and T-cells); • Among *plant agents*: tannins (complex polyphenols with protein-binding activity), histamine (itself a mediator of the allergic response), plicatic acid (the allergenic active component of the wood resin of cypress and thuja trees), some alkaloids (e.g. nicotine, and cytochalasins, fungal metabolites with actin-binding activity); • Among *animal agents*: allergenic proteins and enzymes. Workers who suffer from a disease caused by exposure to organic dusts can often present a mixture of different disease entities. This item addresses only toxic and non-allergic inflammatory syndromes, whilst allergic conditions and those that may involve an allergic reaction are addressed in detail elsewhere (see items 2.1.6, 2.1.7, and 2.1.8).
Occupational exposures	Several work environments, processes, activities, and agents might entail exposure to organic dusts, a non exhaustive list: • *Agriculture:* handling of grain, hay or other crops, especially in silage; sugar-cane processing; work in greenhouses. • *Animals:* work in swine and dairy shelter buildings, in poultry houses and processing plants; handling of laboratory or farm animals and pets. • *Waste processing:* work in sewage water plants; handling of silt, household garbage, or compost. • *Industry:* plant fibre processing (cotton, flax, hemp, jute, sisal); timber and wood processing (wood dusts); fermentation processes in food (brewery, industrial bakery) and biotechnological industries. Exposure to organic dusts, or aerosols, can occur with inhalation of microorganisms such as *Legionella pneumophila*, which can be found in processed ambient air when contaminated from water in badly maintained humidifiers; microbial growth can occur on structures or in ventilation ducts (e.g. *Stachybothris chartarum* or black mould in shower cabins).
Biological mechanisms, main health effects and diagnostic criteria	
Short profile of the biological mechanisms	Organic dust toxic syndrome (ODTS) is caused by an immunological non-allergic reaction. Endotoxins enhance the inflammatory response and alter the function of inflammatory cells, particularly macrophages and T cells, which release inflammatory cytokines, such as interleukins and IFNγ. As such, the mechanism is immunological but not due to sensitization. Symptoms occur as an acute, non-infectious, non-allergic, febrile illness associated with chills, malaise, myalgia, a dry cough, dyspnoea, headache, fatigue, and nausea. Other manifestations may include joint pains, neurosensory effects, skin problems, and intestinal disorders. Respiratory function may worsen to the point where hypoxia occurs, and damage to the airways may lead to non-cardiogenic pulmonary oedema between one and three days following exposure. A condition similar to ODTS can be caused by contaminated aerosols or mists and is known as *humidifier fever*.

1.3.6 Toxic or inflammatory syndromes associated with bacterial or fungal contaminants ICD Code J66.8, J67.7 +Z57

Name of the diseases and ICD code: **Organic dust toxic syndrome (J66.8 +Z57)**

Short description of the disease

Inhalation of dust generated in the handling of material contaminated by gram-negative bacteria and fungi results in a disease commonly referred to as "Organic dust toxic syndrome" (ODTS), characterized by fever, headache, malaise, myalgia, nausea, vomiting, dry cough and dyspnoea. Rhinitis, keratitis and conjunctivitis can be present, and skin irritation may occur in grain handling. The latency between exposure and onset of the disease is usually 4-12 hours; the symptoms persist from one to five days. Recovery is usually complete if the affected subject is withdrawn from exposure; clinical manifestations only recur following further significant exposure to organic dusts.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: may last for one to five days, may necessitate bed rest, and usually include:
  - Fever, headache, malaise, and myalgia.
  - Nausea and vomiting.
  - Dry cough, dyspnoea, and rhinitis.
  - Keratitis, conjunctivitis, and skin irritation.
- Examinations:
  - Pulmonary function tests and chest X-ray findings are usually normal, although carbon monoxide transfer factor may be reduced.
  - Leucocytosis may be found on the blood count.
  - Bronchoalveolar lavage may show increased neutrophil count.
  - Precipitin tests to identify antigens are typically negative.

Differential diagnosis

- ODTS has many clinical features in common with acute farmer's lung and other forms of hypersensitivity pneumonitis, including the presence of raised neutrophil count in bronchoalveolar lavage (BAL). Distinct from hypersensitivity pneumonitis, chest X-rays do not show infiltrates, severe hypoxaemia rarely occurs, and prior sensitization to antigens of the organic dust is not required. In addition, ODTS does not usually leave sequelae of symptoms such as recurrent attacks or pulmonary fibrosis, which are commonly seen in chronic hypersensitivity pneumonitis.

Exposure assessment

- History of occupational exposure: confirmed occupational exposure to organic dust.
- Minimum duration of exposure: few hours.
- Maximum latent period: 48 hours.

Name of the diseases and ICD code: **Humidifier fever (J67.7 +Z57)**

Short description of the disease

Inhalation of a bioaerosol generated by bacterial growth in the water of humidifiers may cause the so-called "*humidifier fever*". The disease is characterized by symptoms resembling extrinsic allergic alveolitis (EAA), but the underlying pathogenetic mechanism is different, as this is a non-allergic acute toxic alveolitis due to inhalation of bacterial endotoxins into the lungs.

Symptoms include mild fever, malaise, nausea, myalgia, sweating, chest tightness and breathlessness on exertion, few hours after exposure. The onset usually occurs within 4-12 hours from starting work, with symptoms typically settling within 24 hours. Continuous exposure can lead to tolerance, so that the intensity of symptoms decreases near the end of the working week and worsens on the first working day. The clinical picture quickly improves after cessation of exposure.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: symptoms may be mild and "flu-like" or presenting as an acute illness with cough, breathing difficulty, malaise, headache, fever, myalgia and nausea. The symptoms usually resolve within 24 hours, are worst on the first working day, and improve over the working week. Symptoms recur on further exposure after an absence from work.

1.3.6 Toxic or inflammatory syndromes associated with bacterial or fungal contaminants ICD Code J66.8, J67.7 +Z57

- Examinations:
  - On physical examination, the presence of fine respiratory crackles on chest auscultation.
  - Chest X-ray is often normal.
  - Although lung fibrosis is absent, pulmonary function tests show mild restrictive features that improve over the working week or when away from work. Diffusing capacity may also be reduced.
  - Specific IgG antibodies against the involved microorganisms can be detected in the affected subjects; precipitin tests can identify antigens.
  - A useful and simple diagnostic tool is self-recording of body temperature by the worker: it should be performed twice a day, before and after the occupational exposure, and on days off, and may indicate work-related pyrexia.

Exposure assessment

- History of occupational exposure: confirmed occupational exposure to humidified air contaminated with microorganisms; this can occur in workplaces where careful control of indoor air quality, humidity in particular, is not regularly performed.
- Minimum duration of exposure: few hours.
- Maximum latent period: 24 hours.

Key actions for prevention	Employers and workers should minimize the risk of exposure to organic dusts by taking appropriate precautions, such as: • Be aware of the health effects of breathing organic dust. • Carefully harvest and store agricultural products to minimize decomposition. • Use automated equipment to move putrefied materials. • Use local exhaust ventilation as well as wet methods of dust suppression to minimize dust dispersion, although overuse of water must be avoided. • Use engineering controls to reduce the dust exposure of silo unloaders, such as: - Design the silo to ensure product turnover thus creating hostile conditions for microbial growth. - Design the conveyor to avoid material spillage and to sufficiently ventilate dust. - Use ventilated loading spouts when filling railroad cars and trucks with silage. • Use appropriate respirators e.g. those equipped with high-efficiency particulate air (HEPA) filters when exposure to organic dust cannot be avoided. • Prevent the spread of dusts by removing contaminated clothes at the end of the work activity.

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▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
1.3.6	Organic dust toxic syndrome (ODTS)	J66.8	CA80.Y
1.3.6	Humidifier fever	J67.7	CA70.7
	Occupational exposure to risk factors	Z57	QD84.Y

1.3.7 Anthrax	ICD Code A22 +Z57
General characteristics of the causal agent	Anthrax is an infection caused by the bacterium *Bacillus anthracis*, a non motile, Gram-positive, endospore-forming, rod-shaped bacillus. The bacterium usually rests in spore form in the soil and can survive in this state even for decades. It is pathogenic, mainly for herbivores, such as goats, cattle, and sheep, which are often infected while grazing and represent the main host of the bacterium. This is why the disease in humans is generally consequent to contact with anthrax-infected animals or anthrax-contaminated animal products. The name "anthrax" derives from the Greek word for coal and has been given to the bacterium because of the coal-black, necrotic eschars that develop following skin infection.
Occupational exposures	The main routes of occupational exposure are inhalation of spores and dermal contact with contaminated soil, infected animals, infected meat, and animal horns and hides. Workers susceptible to exposure include animal breeders, agricultural workers and hunters, veterinarians and veterinary care workers, butchers and slaughterhouse workers, wool, hair and hide processors, tanners and textile workers, staff in veterinary and inspection laboratories. The inhalation form of anthrax was previously known as "wool-sorters' disease", due to the association with this work activity. Gastrointestinal exposure to anthrax, although unlikely in occupational settings, may be possible through the consumption of contaminated meat from infected animals. Anthrax spores have been used as biological weapons in a few cases of bioterrorism acts. Emergency response crew, police, firefighters, health services workers, who are responsible for intervention in such episodes, may face exposure to anthrax spores as fine powders or mists.
Biological mechanisms, main health effects and diagnostic criteria	
Short profile of the biological mechanisms	Spores of *Bacillus anthracis* are the infectious form of the organism. They germinate into vegetative bacteria that multiply locally after dermal contact or ingestion but may also disseminate to cause systemic infection. Inhaled spores are ingested by lung macrophages and carried via the lymphatic system to regional lymph nodes, where they can germinate, multiply and eventually, invade the bloodstream. Once in the bloodstream, the bacilli release three proteins named lethal factor, oedema factor, and protective antigen. This last combines with the first two factors allowing cellular entry of these agents producing the lethal and oedema toxins, respectively, which are the primary agents of tissue destruction of the host. Invasion of the bloodstream by the bacilli can lead to sepsis. Clinical manifestations of anthrax depend on the route of exposure, in detail: • *Cutaneous anthrax*, following skin contact, characterized by a painless and often itchy skin lesion that evolves into black eschar, accompanied by extensive local oedema, lymphadenopathy, and fever. • *Pulmonary anthrax*, following inhalation, characterized by fever, malaise, non-productive cough, and dyspnoea. • *Gastrointestinal anthrax*, following ingestion, characterized by nausea, loss of appetite, vomiting and fever, followed by abdominal pain, haematemesis, and diarrhoea. Oropharyngeal involvement may result in oral ulceration. The most frequent form of the disease is caused by skin infection (95% of reported cases), whilst forms caused by inhalation or ingestion are less common. In all forms of anthrax, if toxins are released into the bloodstream, manifestations can become systemic.
Name of the diseases and ICD code: **Cutaneous anthrax (A22.0 +Z57)**	
Short description of the disease Cutaneous anthrax consists typically of a pruritic papule evolving over 2-6 days to a painless and vescicular stage, followed by the development of a charred looking skin lesion, in some cases with surrounding oedema. The skin infection is usually consequent to spore penetration in a skin lesion by direct contact with infected animals or contaminated animal products. Systemic manifestations of the disease (i.e., sepsis or meningitis) are observed when toxins reach the bloodstream.	

1.3.7 Anthrax — ICD Code A22 +Z57

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: the typical lesion is represented by an erythematous papule, which vesiculates, ulcerates and undergoes necrosis, ultimately progressing to a purple to black eschar. The eschar is characteristically painless; pain might indicate secondary bacterial superinfection (e.g. from staphylococcus or streptococcus). Regional adenopathy, fever, malaise, headache, nausea, and vomiting may be present.
- Examinations: staining of cutaneous ulcer exudate with methylene blue or Giemsa stain, Gram stain of the blood and blood culture for *Bacillus anthracis* and use of a PCR-based test can confirm the aetiology of the lesion.

Differential diagnosis

Herpes virus and rickettsial infections, tularaemia, pseudomonal bacteraemia (*ecthyma gangrenosum*), spider bites and, in general, other bacterial skin infections.

Exposure assessment

- History of occupational exposure: confirmed occupational exposure to *Bacillus anthracis* spores via skin contact (abrasions or minor cuts might be essential to allow for the bacterium to penetrate the skin).
- Minimum duration of exposure: a single contact may cause the infection.
- Maximum latent period: usual incubation period is 5-7 days but a time window of up to 19 days has been reported.

Name of the diseases and ICD code: **Pulmonary anthrax (A22.1 +Z57)**

Short description of the disease

Pulmonary anthrax, also known as wool-sorter's disease or rag-pickers' disease, is usually attributable to the inhalation of spores from bones, hairs or hides of herbivores, but in some cases can also be related to the processing of infected meat. Inhaled spores reach alveolar spaces, are phagocytised by macrophages, and are transported to the mediastinal and peribronchial lymph nodes. They then proliferate with the production of oedema and lethal toxins, which are the primary agents of tissue destruction. Subsequent haematogenous spread of bacteria is accompanied by general sepsis with cardiovascular collapse and death. The rapid onset of sepsis may evolve with haemorrhagic meningitis, which is frequent and represents a poor prognostic sign. The earliest viral-like symptoms of pulmonary anthrax are typically fever, malaise, cough, and shortness of breath, but they can rapidly progress to a terminal condition.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: fever, malaise, cough, dyspnoea. The onset of symptoms is usually within 4-6 days after exposure. In the fatal cases, death is observed a few days later, the overall mortality rate is 55%. Pulmonary anthrax differential diagnosis includes any severe chest infection.
- Examinations:
  - Gram stains of the blood for *Bacillus anthracis*, PCR-based tests as well as blood cultures can confirm the aetiology of the disease. Total white blood cell counts usually show values around ~10,000 cells/μL; transaminases tend to be elevated.
  - Radiological findings: characteristic mediastinal widening and haemorrhagic pleural effusions on chest X-ray and CT have been observed; the parenchyma may appear normal.

Exposure assessment

- History of occupational exposure: confirmed occupational exposure to *Bacillus anthracis* spores via inhalation.
- Minimum duration of exposure: a single contact may cause the infection.
- Maximum latent period: onsets up to eight weeks after exposure have been observed.

Name of the diseases and ICD code: **Gastrointestinal anthrax (A22.2 +Z57)**

Short description of the disease

The gastrointestinal form of anthrax usually occurs 2-5 days after consumption of meat contaminated with anthrax spores. The disease is characterized by acute inflammation of the pharynx and the intestinal tract. Initial signs are nausea, loss of appetite, vomiting and fever, followed by abdominal pain, haematemesis, and severe diarrhoea. Oropharyngeal involvement will result in oral ulceration. Ascites may be a prominent feature.

1.3.7 Anthrax ICD Code A22 +Z57

Clinical manifestations

- Signs and symptoms: nausea, vomiting, loss of appetite, fever, abdominal pain, diarrhoea, haematemesis, ascites and oral ulceration, with oedema and membrane formation in the case of oropharyngeal involvement.
- Examinations: Gram stains of the blood, blood culture for *Bacillus anthracis* and PCR-based tests can confirm the aetiology of the disease.

Exposure assessment

- History of occupational exposure: confirmed occupational exposure to *Bacillus anthracis* spores through ingestion of contaminated meat.
- Minimum duration of exposure: a single contact may cause the infection.
- Maximum latent period: seven days.

Name of the diseases and ICD code: **Anthrax sepsis (A22.7 +Z57)**

Short description of the disease

In all forms of anthrax, as soon as toxins are released into the bloodstream, manifestations can become systemic and produce features of general sepsis and anthrax meningitis. Anthrax sepsis is an indicator of late stage, fulminant disease and represents a poor prognostic sign.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: in the case of meningeal involvement, the presentation may resemble that of other forms of bacterial meningitis, with headache, nuchal rigidity, and photophobia (these symptoms may also be initially absent).
- Examinations: Gram stains of cerebrospinal fluid and PCR-based tests can confirm the aetiology of the disease. Haemorrhage often manifests as bloody cerebrospinal fluid on spinal tap or as subarachnoid or intraparenchymal haemorrhages on CT.

Exposure assessment

- History of occupational exposure: confirmed occupational exposure to *Bacillus anthracis* spores, either through inhalation, dermal contact or ingestion.
- Minimum duration of exposure: a single contact may cause the infection.
- Maximum latent period: as anthrax meningitis may arise from haematogenous spread of any of the clinical forms of anthrax, the maximum latent period resembles that of the initial disorder.

Key actions for prevention	Impervious nitrile, vinyl or latex gloves may protect workers from cutaneous anthrax exposure. Health workers in hospitals, clinics, and medical laboratories, who are engaged in patient care with suspected exposure to anthrax, should take precautions against the potential for re-aerosolizing any anthrax spores which may have remained on the exposed individual or clothing. The precautions can include but are not limited to the appropriate use of gloves, respiratory protection, protective clothing, work practices, and housekeeping. Person-to-person spread of the disease has not been documented. Anthrax vaccination may be used as post exposure prophylaxis in certain circumstances such as bioterrorism exposure. As the disease is generally consequent upon contact with anthrax-infected animals or anthrax-contaminated animal products, control of anthrax in livestock herds is essential for the prevention of its spread to humans. Hands should always be thoroughly washed after handling livestock. Attention should be taken of the presence of stock tanks or stagnant ponds in pastures where death losses have occurred. Animals dying from anthrax usually die suddenly, with only a brief illness preceding death: if anthrax is suspected, farms/pastures should be isolated and herds vaccinated, and the dead animals disposed of appropriately so that contamination of the soil is minimised. Spores can persist in the soil for decades and can survive boiling, freezing, or even suspension in alcohol. Their elimination needs special measures, such as steam under pressure or chemical sporicides. Hunters should wear protective gloves when field dressing (gralloching) a game animal to prevent potential exposure to bacteria, viruses or parasites. Collection of antlers, skulls or horns from animals should be avoided, as anthrax can survive even after bone bleaching. Anthrax vaccines do exist for use in livestock and have been used in humans, especially for the protection of military personnel considered to be at risk of exposure to biological weapons, laboratory workers who work with anthrax and veterinarians who handle infected animals.

1.3.7 Anthrax ICD Code A22 +Z57

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▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
1.3.7	Anthrax	A22	1B97
1.3.7	Cutaneous anthrax	A22.0	1B97
1.3.7	Pulmonary anthrax	A22.1	1B97
1.3.7	Gastrointestinal anthrax	A22.2	1B97
1.3.7	Anthrax sepsis	A22.7	1G40
	Occupational exposure to risk factors	Z57	QD84.Y

1.3.8 Leptospirosis	ICD Code A27, A27.0 +Z57
General characteristics of the causal agent	Leptospirosis is a direct zoonotic disease caused by spirochaetes belonging to pathogenic species of the genus *leptospira* (about 0.1µm in diameter, 10-20µm in length). *Leptospira* is a spiral shaped bacterium characterized by a surface architecture that resembles both Gram-negative and Gram-positive bacteria. The double membrane constitution supports Gram-negative bacteria, whereas attachment of peptidoglycan to the inner membrane resembles a Gram-positive nature. More than 260 serotypes of *leptospira* have been identified throughout the world. Very small width leptospires are hardly detectable by optical microscopes, unless a contrast-enhancing technique is used such as dark-field microscope. Live specimens are highly mobile (~15µm/sec); under visible light their rapid rotation appears as a chain of dots instead of a continual structure. Typically, leptospires spin rapidly on their axis, with one or both ends hooked, and as they move forward the front end is often straightened.
Occupational exposures	*Leptospira* species infect a wide range of animals, in which the pathogens spread haematogenously, colonize the proximal renal tubules, and are shed via urine into the environment. The primary source of leptospires is thus represented by the urines of animals, particularly mice and rats, field rabbits, foxes, but also other animals, such as horses and pigs. The infection is transmitted to humans via exposure of mucous membranes or wounded skin to the body fluid of an acutely infected animal or to water or soil contaminated by the urine of a chronic carrier. Veterinarians, fish handlers, sewer and agricultural workers, dairy and pig farmers, butchers, meat packers, abattoir workers, rice and sugarcane fieldworkers, and banana farmers are at risk due to their potential exposure to infected animals or contaminated environments. Other categories to be considered occupationally at risk are hunters and trappers, rodent control workers, forestry workers, and miners, health workers and laboratory technicians. For completeness, it is worth recalling that the disease represents a recreational hazard for bathers, campers and sportsmen in infected areas, and can occur in urban settings especially during heavy rains when floods occur.
Biological mechanisms, main health effects and diagnostic criteria	
Short profile of the biological mechanisms	The most important source of leptospires is the urinary shedding of organisms from infected animals. As such, contact with infected urine or urine-contaminated media results in human infection. Media can include contaminated food and water, animal bedding, aborted tissue, as well as soil and mud. Under favourable conditions, leptospires can survive in fresh water for about two weeks and in the soil for about three weeks. Leptospires are believed to enter the host through animal and rodent bites, sodden and waterlogged skin, abrasions in healthy skin, mucous membranes or conjunctivae, the placenta during pregnancy, the lungs after inhalation, as well as through ingestion of food and drink contaminated by the urine of an infected animal. Once inside the human or animal, the pathogens can reach the bloodstream mainly through the lymphatics, eventually producing leptospiraemia and spread to all organs, although the kidneys and the liver are the most frequently affected. Incubation usually lasts for 1-2 weeks but has been described from as short as one day to as long as one month. Leptospirosis produces a capillary vasculitis, with endothelial oedema, necrosis, and lymphocytic infiltration, which is found in every affected organ system. The resulting loss of fluid and red blood cells through enlarged junctions and fenestrae with secondary tissue injury most likely accounts for many of the clinical findings. The clinical picture of leptospirosis ranges from asymptomatic infections to severe multiorgan disease. In the most severe cases, hepatorenal failure may be observed in the form of leptospirosis icterohaemorrhagica or Weil's disease. Leptospirosis occurs worldwide, but it is particularly frequent in tropical countries. It has a seasonal pattern, with a peak in incidence in the rainy season in the tropics, and in summer or autumn in countries with temperate climates. Leptospirosis is only zoonotic in origin, and human-to-human transmission has not been documented. Leptospirosis is also known as canicola fever, haemorrhagic or infectious jaundice, mud fever, spirochaetal jaundice, swamp fever, swineherd's disease or sewerman's flu, cane cutter's fever, cane field fever, nanukayami fever (an indigenous form observed in Japan due to *Leptospira hebdomadis*), rice field fever, 7-day fever, rat catcher's yellows, pretibial fever and Fort Bragg fever. Other local names in India are Andaman haemorrhagic fever and rat fever.

1.3.8 Leptospirosis — ICD Code A27, A27.0 +Z57

Name of the diseases and ICD code: **Leptospirosis (A27), Leptospirosis icterohaemorrhagica (Weil's disease) (A27.0 +Z57)**

Short description of the disease

Most leptospiral infections are either subclinical or result in mild illness, and recover without any complications. In many cases, the infection does not bring about a clinical picture but only an asymptomatic seroconversion. In a small proportion of cases, multiple organ systems complications may develop. The incubation time is usually 7 to 14 days, but may range from 1 to 30 days. It generally does not show illness in less than a day, unless the concentration of pathogens in the bloodstream is particularly elevated. The disease is often biphasic, with a first "septicaemic" (or "leptospiraemic") phase lasting for about 10 days and characterized by fever, rigors, myalgia, and headache. Conjunctival suffusion may be present. During this phase, leptospires can be isolated from blood, cerebrospinal fluid, and tissues. After 1-3 days of symptoms improvement and absence of fever, the second or "immune" phase begins. During the immune phase, resolution of symptoms may coincide with the appearance of antibodies, and leptospires can be cultured from the urine. The most severe form of the disease that may develop (Weil's syndrome) is characterized by impaired kidney and liver function, abnormal mental status, haemorrhagic pneumonia, hypotension, and a mortality rate as high as 50%. In this form of the disease, the phases may appear indistinct.

Subjects with mild infection recover quickly; more severe infections take several weeks to recover. Subjects who recover from severe illness do not manifest usually any significant residual organ damage, the only known long-term sequelae being uveitis. Leptospirosis is one of the common causes of concomitant renal and hepatic dysfunction in febrile patients and when these occur together with deep conjunctival suffusion, subconjunctival haemorrhage, and prominent calf muscle tenderness, a diagnosis of leptospirosis is quite likely if a concomitant history of exposure is confirmed.

Leptospirosis is a dangerous condition in pregnancy for both the mother and foetus, as well as during breastfeeding since infection can be acquired through maternal milk.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms of mild forms of leptospirosis:
  - The onset of the disease is abrupt with fever (39°C or above lasting 3–10 days), eye redness, muscle pains and fatigue; persistent frontal headache may be the first symptom in some patients; a severe headache can be incapacitating.
  - Severe muscle pain especially in lower limbs, calves and thighs is common.
  - Nausea, vomiting, diarrhoea, and cough can be present.
  - Transient macular, erythematous or urticarial rash on the trunk, upper limbs or shins, may develop in 1-2 days.
  - Deep congestion of the conjunctivae is very common and can be observed even in afebrile subjects; subconjunctival haemorrhage occurs in a significant proportion of cases and can be a distinguishing factor.
  - The acute phase of leptospirosis is followed by a 1-3 day period of improvement in which the pyrexia falls, and symptoms may disappear. Subsequently, the disease either regresses to a relatively asymptomatic illness or progresses to a more severe disorder.
- Signs and symptoms of severe forms of leptospirosis (Weil's syndrome):
  - Spirochaetes disappear from blood and most tissues, after the production of specific antibodies, but the bacteria persist in different organs, including brain in particular the meninges, liver, lung, heart, and kidney. In this phase, uveitis, rashes, meningitis, encephalitis and myelitis may occur. Fever may relapse and be associated with symptoms and signs of renal, hepatic, pulmonary or cardiac dysfunction or meningitis.
  - Acute and chronic kidney inflammation is associated with acute tubular necrosis and interstitial nephritis and can be non-oliguric or oliguric.
  - Liver abnormalities can manifest with jaundice.
  - Symptoms of meningitis are seen with neck stiffness and vomiting.
  - Haemorrhages and refractory shock are common including bleeding from the mouth, eyes and other mucous membranes, and significant internal bleeding.
  - Pulmonary involvement may set in early in the course of the disease and is characterized by cough, haemoptysis, breathlessness, and lung crackles. The pulmonary syndrome may vary substantially, from mild respiratory symptoms and signs (usually without purulent sputum) to severe pulmonary haemorrhage and acute respiratory distress syndrome. Severe alveolar haemorrhage has been recognized as a separate clinical entity, called leptospira-associated pulmonary haemorrhage (LAPH), which is a severe complication with very high mortality rates.
  - Psychological changes, such as restlessness, hallucinations and psychotic behaviour may feature in some patients but are not very common.
  - Less common physical findings include lymphadenopathy and hepatosplenomegaly.
  - A cardiac syndrome may be observed, with myocarditis and, in the most severe cases, cardiac failure.

1.3.8 Leptospirosis ICD Code A27, A27.0 +Z57

- Examinations:
  - In the haematological examination, leucocytosis with neutrophilia, leucopaenia, haemolytic anaemia, mild to moderate anaemia, and thrombocytopaenia can be observed in both mild and severe leptospirosis; plasma fibrinogen levels are typically elevated.
  - Normal or mild elevation in transaminases levels and gamma-glutamyl transferase can be observed following liver impairment.
  - Blood urea nitrogen (BUN), serum creatinine, and serum electrolyte abnormalities (e.g. hypokalaemia and hypomagnesaemia) can be found due to proximal renal tubular dysfunction. Additionally, proteinuria, white cells, casts and occasional microscopic haematuria can be observed.
  - Laboratory diagnosis is classified into (a) direct (isolation of organism, microscopic demonstration of leptospires, or amplification of specific fragment of leptospiral DNA), and (b) indirect evidence (detection of antibodies to leptospires). Isolation of the organism is central to confirmatory diagnosis. Dark-field microscopy of clinical specimens as a sole diagnostic test is not recommended because of the large proportions of false positive and false negative results even in the hands of experienced technicians. The gold standard test for diagnosis is the microscopic agglutination test (MAT); it has to be performed on paired samples obtained over 2-3 weeks. For a confirmatory diagnosis, the test should demonstrate a rise in titre or seroconversion. MAT may have marginal sensitivity during the 1st week, which dramatically rises to over 80% by the 2nd to 4th week and over 95% beyond the 4th week of illness. Simple and rapid diagnostic tools are available: IgM ELISA, LEPTO Dipstick, Macroscopic slide agglutination test (Macroscopic SAT), LEPTO Lateral flow, Indirect haemagglutination assay, and LEPTO Dri Dot. Diagnosis of leptospirosis is confirmed with ELISA and PCR tests.
  - Elevation of the non-cardiac isoform of creatine kinase may indicate skeletal muscle damage. Troponin increased levels are indicative of myocarditis.
  - A chest X-ray may show nonspecific shadowing. Other findings include diffuse interstitial infiltrate patterns corresponding to hyaline membrane disease (acute respiratory distress syndrome) and small nodular infiltrates and pleural-based densities representing haemorrhage.
  - Cardiac involvement is commonly reflected on the electrocardiogram as nonspecific ST and T wave changes but also as a right bundle branch block and right and left sided ventricular dilation indicating myocarditis.
  - The bacteria can be cultured from blood and cerebrospinal fluid during the first septicaemic stages of the disease, and in urine when antibodies develop and leptospires start being eliminated.

Differential diagnosis

Disorders with similar clinical presentations, especially in the aspecific febrile phase, are influenza, typhoid fever, malaria, rickettsial infection, arboviral infections (including chikungunya and dengue fever), hantavirus infection (haemorrhagic fever with renal syndrome or hantavirus cardiopulmonary syndrome), and viral hepatitis.

Exposure assessment

- History of occupational exposure: confirmed occupational exposure to infected animals or potentially contaminated environments.
- Minimum duration of exposure: a single and short exposure may be sufficient to cause the disease.
- Maximum latent period: 30 days.

Key actions for prevention	It may be possible to eliminate leptospirosis through vaccination of animals, rodent control management, and disinfection of living accommodations, together with continuous monitoring and testing of livestock; however, these interventions most likely apply to situations where introduction of new animals is avoided (so called “closed herds”) and all pests are theoretically controlled. In more common circumstances, elimination is difficult to achieve and minimisation is the best option for managing risk, through appropriate controls on the pathogen hosts, and interventions to be taken towards subjects dealing with potentially infected animals or working in contaminated environments. All workers exposed to the risk of contracting leptospirosis should be aware of the cause and symptoms of the disease, and ways of reducing risk. Poster checklists hanging on the walls of sheds or similar places can help reminding the workers about risks, protection and first aid procedures. Risk awareness might be particularly relevant for subjects involved in seasonal work, such as lambing, drenching, shearing, tailing and dagging. Personal hygiene represents an additional irreplaceable protection. Hands should regularly be washed, using water, soap, and disinfectants. Only disposable towels should be used. When washing hands, scrubbing should be avoided as it may cause breaks in the skin. Skin cuts, scratches, blisters and breaks should be covered with waterproof, sterile coverings, which should, in turn, be changed regularly. Workers with deep wounds should wait until full healing before performing work activities close to animal urethral orifices such as shearing or crutching sheep. Smoking, drinking, and eating should be avoided when handling livestock, as those activities could introduce bacteria into the mouth.

1.3.8 Leptospirosis	ICD Code A27, A27.0 +Z57
Key actions for prevention	The aim of personal protective equipment in occupations at risk for leptospirosis is to prevent urine, contaminated water, and fluids from getting through cuts in the skin or the mucous membranes of the eyes, nose or mouth. Appropriate personal protective equipment includes goggles and face shields to protect the eyes, nose and mouth, particularly to avoid the risk of urine splash on the face; milking sleeves and clean aprons and gumboots in the milking shed; plastic aprons and gloves when assisting with animal birth, handling afterbirth and aborted foetuses, and kidneys or bladder gloves, are particularly important when scanning animals for pregnancy using rectal probes, as this requires holding the animal's tail which is often contaminated with urine; solid and sealed footwear to prevent water entry from the top (wet boots and gloves should be changed before water softens the skin and allows bacteria in). Equipment should be waterproof and clean. If working in wet conditions or assisting with lambing, extra precautions might be needed, e.g. overalls; sturdy, closed-toe, waterproof foot-wear; gloves for urine-soaked wool.

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▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
1.3.8	Leptospirosis	A27	1B91
1.3.8	Leptospirosis icterohaemorrhagica (Weil's disease)	A27.0	1B91
	Occupational exposure to risk factors	Z57	QD84.Y

2. Occupational diseases by target organ systems

2.1. Respiratory diseases

2.1.1 Pneumoconioses caused by fibrogenic mineral dust (silicosis, anthraco-silicosis, asbestosis) ICD Code J60-J62, J63.8 +Z57.2

Short profile of the aetio-pathogenesis

Pneumoconiosis has been defined as the accumulation of dust in the lungs and the tissue reaction to its presence. The term "fibrogenic" refers to the capacity of any chemical agent, and especially of particulate solids (i.e., dust), defined as an aerosol composed of solid inanimate particles, to elicit biochemical reactions in living tissue that ultimately produce a fibrous protein material (collagen) in the place where living cells have been destroyed (scar). This phenomenon leads to impairment of tissue and organ functions.

Primary fibrogenic minerals of occupational relevance are silicon dioxide, coal (often contaminated with silica) and asbestos. There are many minerals, silicates in particular such as talc, kaolin, and mica, which are intermediate in their ability to produce fibrotic lesions in the lungs. Exposure to aluminium dust has been associated with lung fibrosis, but the evidence is not consistent in determining whether fibrogenesis is caused by pure aluminium or by other contaminants (a thorough discussion on lung diseases caused by aluminium can be found in item 2.1.10).

Silicon dioxide (SiO_2), commonly known as silica or free silica, is an important component of the earth's crust and exists in three main forms: crystalline, micro-crystalline and non-crystalline (amorphous).

1. *Crystalline silica*. The three main types of crystalline silica are quartz (alpha and beta), tridymite and cristobalite. Tridymite and cristobalite are well known as more fibrogenic than the others. These forms are also called "free silica" to distinguish them from the silicates. The silica content in sandstone, granite and slate, varies from 20 to nearly 100%. Other less common forms of crystalline silica are keatite, coesite, stishovite, and moganite.
2. *Micro-crystalline silica.* This form includes other minerals such as flint, chalcedony and chert, which are formed by thermal sintering (diagenesis) of crystalline silica.
3. *Amorphous silica.* The most important form of amorphous silica is diatomite. The main components of diatomite are the skeletons of microscopic marine animals. This form of silica is not fibrogenic by itself; however, if heated, it gives rise to the strongly fibrogenic cristobalite or trydimite.

Coal is a natural black-brown solid carbonaceous material derived from the slow transformation (coalification) of buried plant materials during millions of years. Coals are classified into four general categories or ranks, according to age, completeness of conversion of organic carbon into the mineral elemental form, and crystallinity of the solid. Coal ranks range from lignite "brown coal", through sub-bituminous and bituminous coal to anthracite "glossy black coal", "black diamond", reflecting the progressive response of former plant material to heat and pressure. Lignite is the softest and anthracite is the hardest with about 85 to 95% carbon content. Higher-rank coals are associated with a greater risk of anthraco-silicosis. Man-made carbonaceous material generated by controlled combustion of vegetation based materials within days is referred to as "charcoal" and is not considered in this item.

Asbestos is a fibrous silicate existing in nature in different forms. Its fibres are long and thin with a length-to-diameter ratio > 3 and either curved (serpentine) or straight (amphiboles). The main natural forms are chrysotile among serpentine asbestos and crocidolite, amosite, actinolite, tremolite, anthophyllite among amphiboles. The species most commonly used in industry are chrysotile or white asbestos, amosite or brown asbestos, and anthophyllite. The use of crocidolite or blue asbestos has been drastically reduced nowadays due to its ban in many countries of the world.

Talc or talcum, is a clay mineral composed of hydrated magnesium silicate; it is often found contaminated with silica or asbestos.

Kaolin or china clay, is the name given to rocks of kaolinite, a layered silicate mineral whose main component is aluminium.

Mica occurs in nature in several forms (e.g. muscovite, phlogopite) and is composed of potassium-aluminium silicate.

Inorganic mineral and coal dust enters the human body mainly through inhalation. Only the coarsest fraction is intercepted in the mouth and swallowed and, for this fraction, the toxicological hazard depends on the presence of chemical agents that can be leached from the dust in the gastrointestinal system. The inhalable fraction of mineral dust is that with aerodynamic diameter below 10 micrometres and the depth at which it penetrates in the respiratory system essentially depends on the size of the particles, the finer ones penetrating into the lung alveoli. Asbestos fibres follow a similar destiny, as their thinness allows them to easily reach the farthest pulmonary airways.

2.1.1 Pneumoconioses caused by fibrogenic mineral dust (silicosis, anthraco-silicosis, asbestosis)	ICD Code J60-J62, J63.8 +Z57.2
Short profile of the aetio-pathogenesis	Once deposited into the lung alveoli, particles and fibres interact with the fluid lining and with the cells and exert their activity, bringing about the activation of macrophages, the production of immune mediators, the migration of cells in the affected area and the activation of fibroblastic activity. Silica and coal particles, asbestos fibres, as well as dust of silicates, although to a lesser extent, produce oxidative stress, which in turn causes local inflammation of the tissue, cell death and the replacement of dead cells with collagen (fibrosis).
Occupational exposures	*Silica***.** In most countries throughout the world, occupational exposure to silica with possible major health risks occurs in mining of almost any material, and other underground activities such as tunnelling, sand quarrying, etc. The risk is strongly related to the quartz content in the rock, which significantly varies on a geographical basis. A significant risk is reported in masonry and sculpture, foundry activities, restoration or demolition of furnaces, sand crushing and blasting, sandstone milling and grinding as well as in the manufacture and use of abrasives, glassmaking, ceramic industry, vitreous enamelling (covering of materials with a thin anti-corrosive protective layer of silica glass) and in the use of silica as a filler in the formulation of paints, elastomers, plastics and in woodworking industries. *Coal***.** Exposure to coal dust may occur in underground hard coal mines and in coal-fuelled power plants; when silica dust is present, anthraco-silicosis may develop in workers. Certain specific activities entail a higher probability of exposure to dust. In particular, most dust is found at the coal face and thus the cutting machine operators who cut coal directly at the face are usually the most exposed workers. Other workers potentially exposed to high levels of dust are roof bolters who drill through rock and loading machine operators. Also, train operators who drop sand on the track for traction may be at risk. Other professional roles, such as mechanics, electricians, and maintenance personnel, although usually present in the mine, have a minor risk of exposure. *Asbestos*. Bans on asbestos use are in place in more than 50 countries of the world, including Australia, South Africa, Japan, and the European Union. But not in Brazil, Canada, China, India, Russia, or the USA. Canada and the USA have laws regarding asbestos use restriction. Brazil accounted for about 10% of asbestos production and consumption, globally, in 2017; however, in the autumn of that same year the Brazilian Supreme Federal Court enacted a ban on extraction, commercialization, and use of asbestos throughout the entire country. Hence, the only remaining commercial producers are China, Kazakhstan, potentially Zimbabwe, and Russia, with the last being the leading producer. Estimated global consumption of asbestos minerals decreased from about 2 million tons in 2010 to nearly 1.3 million tons in 2016. Occupational exposure to asbestos is possible in countries where the mineral is still used, in the extraction and production of the different asbestos products, as well as in insulation and residual materials. Products containing asbestos cement commonly seen include pipes, clapboards, and shingles, vinyl-asbestos floor tiles, asbestos paper in insulating and filtering products, material in clutch facings and brake linings, spray products used for thermal, fireproofing, and acoustic purposes, and textile products such as yarns, tape, cord, rope, and felt. Occupations potentially associated with asbestos exposure are: insulation workers, boiler makers, plumbers, pipe fitters, welders, steamfitters, and janitors. Notwithstanding the asbestos ban currently either existing or being evaluated in many countries of the world, it is important to remember that exposure may take place even in those countries where its extraction, production and use is forbidden, when workers handle objects or plants in which asbestos is present, such as building maintenance and renovation, scrapping, decommissioning, refurbishing of ships, and asbestos removal from any manufactured goods. *Talc* has several industrial and consumer end uses: as a high temperature lubricant and parting medium in casting and moulding such as that of tyres, as a filler in heat resistant ceramics, refractories and insulators, and as an adsorbing medium in applications ranging from the food industry to personal hygiene and toiletry. Occupational exposure by inhalation to talc may occur in mining and milling and in the formulation of industrial commodities and end products. In its natural form, some talc contains asbestos; currently used talcum products should be virtually asbestos-free, in particular in industrialized countries.

2.1.1 Pneumoconioses caused by fibrogenic mineral dust (silicosis, anthraco-silicosis, asbestosis)	ICD Code J60-J62, J63.8 +Z57.2
Occupational exposures	*Kaolin* has wide industrial applications: as filler for magazine paper, in the crockery industry, as a thickener in paints, in pottery manufacturing, and as an adsorbing medium in a wide range of non-food, food and pharmaceutical applications. Occupational exposure by inhalation may occur in several steps of its extraction, purification, drying, processing, bagging, loading and compounding. *Mica* has restricted but important industrial uses. The main natural reservoirs of industrial relevance for extraction are Turkey, India, China, the USA, South Korea, Canada, France, and Madagascar. Among the still important uses are manufacturing of heat-resistant windows of furnaces from large homogeneous and transparent sheets, of electrical insulators, and incorporation of flakes into paints to obtain iridescent metalized finishing as in car paints. Occupational exposure by inhalation to mica may occur during mining and in milling lower quality material to obtain flakes.

Main health effects and diagnostic criteria

Name of the diseases and ICD code: **Silicosis (J62) +Z57.2**

Short description of the disease

Silicosis is a fibrotic pneumoconiosis attributable to the inhalation of silicon dioxide commonly known as silica, in crystalline forms, usually as quartz but also as cristobalite and tridymite. These forms are called "free silica" to distinguish them from the silicates. Silica dust exposure brings about an increased risk of lung cancer and IARC classified crystalline silica in the form of quartz or cristobalite dust as carcinogenic to humans (Group 1). Silicosis, also known as "*grinder's disease*" or "*potter's rot*", can be acute, subacute or chronic.

Acute silicosis (or silicoproteinosis) is a rare, extremely severe form of hyperacute exudative alveolitis, due to short-term exposure to particularly high concentrations of silica dust. The onset is observed within a few months from the beginning of exposure and is characterized by breathlessness and dry cough. The functional picture is restrictive, with impairment in the blood-alveoli gas exchange. The disease is very often fatal. Work activities such as sandblasting and dry rock drilling have been historically associated with this disease, which is characterized by histologic features resembling alveolar proteinosis, with surfactant proteins filling up the alveoli.

Subacute (or accelerated) silicosis has an onset usually observed within one year after the beginning of very high exposure, even in subjects already affected by the chronic form. Signs and symptoms resemble those of the chronic form (see below) but with a more rapid pace of clinical and radiological worsening. In particular, cough and dyspnoea occur early and are rapidly disabling. As a general rule, the severity of the disease and its tendency to progression are proportional to the rapidity of the onset after the beginning of the exposure.

Chronic silicosis is the most frequently observed form, still common in developing and emerging countries. It is characterized by the presence of lung opacities, which at the beginning are typical of the ILO profusion category 1/1 (the first centrally placed subcategory after the one indicating the absence of small opacities, i.e., 0/0), with an increasing size if the causal exposure is not interrupted. In simple silicosis (i.e., characterized by nodular fibrosis in overall intact lung parenchyma), symptoms may be absent, in the beginning, but cough and breathlessness usually appear as the disease progresses. The onset is usually observed after 15-20 years of exposure, with a minimum duration of exposure of about 10 years, although exposure windows as short as five years have been documented. In 20% of the cases, calcification of the hilar nodes is observed. The disease can progress in the absence of further exposure: in these cases, the picture evolves to conglomerates of irregular masses, with a diameter of at least 1 cm or, in the most severe cases, significantly larger. Symptoms of this complicated form also known as "progressive massive fibrosis" are more severe, with productive cough and disabling dyspnoea. Superinfections (e.g. tuberculosis) and complications such as chronic bronchitis and chronic obstructive pulmonary disease (COPD) are commonly associated with the complicated form. Complications follow both the direct irritant action of the inhaled dust and the mechanical obstruction of distal airways, caused by traction, compression, and torsion exerted by the mass conglomerates. Pulmonary hypertension and *cor pulmonale* can arise. The functional evaluation shows a mixed picture (i.e., restrictive and obstructive). The affected subjects are particularly susceptible to tuberculosis infection (silicotuberculosis).

In subjects with a history of sporadic exposure to silica dust, or of exposure to dust containing a small proportion of quartz, the disease usually shows no tendency to evolve into most severe forms, and is sometimes referred to as "inactive silicosis". The main picture is of simple pneumoconiosis with 'p'- and 'q'-sized rounded opacities (i.e., with diameters up to 1.5 mm and between 1.5 and 3 mm, respectively). The opacities may tend to coalesce to form irregular masses, but may remain static and calcify. A few workers may show 'r' shadows (i.e., with diameters between 3 and 10 mm) in the upper zone and hilar gland enlargement. Calcification of the nodules is the only reliable indicator that the silicotic lesion is no longer active, thus confirming the end of disease progression. In any case, a good prognosis can be considered after observing a period not shorter than 10 years without any significant tendency to progression.

2.1.1 Pneumoconioses caused by fibrogenic mineral dust (silicosis, anthraco-silicosis, asbestosis) ICD Code J60-J62, J63.8 +Z57.2

Diagnostic criteria

Clinical manifestations of acute silicosis (or silicoproteinosis)

- Signs and symptoms: rapidly developing cough, breathlessness, loss of weight, cyanosis, and weakness.
- Examinations: chest X-ray shows a bilateral alveolar filling pattern with miliary infiltration; lung function tests show a mainly restrictive picture, with reduced gas transfer measurements.

Clinical manifestations of subacute (or accelerated) silicosis

- Signs and symptoms: cough and breathlessness, with an onset not as dramatically escalating as in the acute form, but more rapid than in the chronic form.
- Examinations: chest X-ray shows a bilateral alveolar filling pattern and pulmonary nodules; lung function tests show a mainly restrictive picture, with reduced gas transfer measurements.

Clinical manifestations of chronic silicosis

- Signs and symptoms: development of cough and breathlessness; in the simple form, cough is usually non-productive and dry, while it might become productive in the complicated form. In the latter, COPD frequently arises and *cor pulmonale* can occur in the most severe cases. The disease may be 'simple' or 'complicated', depending on its radiographic appearance and extent. The disease is usually observed during exposure but in some cases, especially in the less severe, asymptomatic and scarcely progressive forms, diagnosis can be made on occasional examinations perfomed even years after the end of exposure.
- Examinations:
  - Chest X-ray in the simple form: evidence of rounded small opacities with diameters up to about 1.5 mm, between 1.5 and 3 mm, or between 3 and 10 mm (ILO Classification p, q, and r, respectively) affecting both lungs, in particular, the upper zones; at this level, reticulation is usually observed.
  - Chest X-ray in progressive massive fibrosis: large opacities can be seen, which are classified as follows, according to the ILO:
    A. One large opacity having the longest dimension up to about 50 mm, or several large opacities with the sum of their longest dimensions not exceeding about 50 mm.
    B. One large opacity having the longest dimension exceeding 50 mm but not exceeding the equivalent area of the right upper zone, or several large opacities with the sum of their longest dimensions exceeding 50 mm but not exceeding the equivalent area of the right upper zone.
    C. One large opacity which exceeds the equivalent area of the right upper zone, or several large opacities which, when combined, exceed the equivalent area of the right upper zone.
  - High resolution CT (HRCT) scanning:
    > Small well-defined nodules of 2 to 5 mm in diameter in both lungs.
    > Upper lobe predominance.
    > Nodules may be calcified.
    > Centrilobular and subpleural distribution.
    > Sometimes random distribution.
    > Irregular conglomerate masses, known as progressive massive fibrosis.
    > Masses may cavitate due to ischaemic necrosis.
    > Often hilar and mediastinal lymph nodes.
    > Lung function: picture of mixed i.e., restrictive and obstructive alterations.

As a general rule, for high levels of exposure or poor working conditions, chest X-ray alongside the typical ILO classification is still acceptable for the diagnosis of silicosis. However, for lower levels of exposure, HRCT should be recommended because of its higher sensitivity.

Differential diagnosis

- Sarcoidosis: can be difficult to distinguish, although the distribution of nodules affects the upper pulmonary zones in silicosis while being typically perilymphatic in sarcoidosis.
- Infections: miliary tuberculosis, fungal.
- Haematogenous metastases: silicotic nodules in subpleural and peribronchiolar location up to the level of the secondary pulmonary lobule may have a seemingly random distribution and simulate metastases and miliary infections.
- Langerhans cell histiocytosis (LCH): can be distinguished with difficulty from silicosis in the early stage, when LCH is characterized solely by the presence of small nodules. Nodules with cavitation, reflecting airspace dilatation in the centre of granulomas, follow the destruction of the bronchiole wall by infiltrated Langerhans cells.

2.1.1 Pneumoconioses caused by fibrogenic mineral dust (silicosis, anthraco-silicosis, asbestosis) ICD Code J60-J62, J63.8 +Z57.2

Exposure assessment for acute silicosis

- History of occupational exposure: evidence of exposure to very high levels of crystalline free silica.
- Minimum duration of exposure: a few months.
- Maximum latent period: five years.

Exposure assessment for accelerated silicosis

- History of occupational exposure: evidence of exposure to very high levels of crystalline free silica.
- Minimum duration of exposure: one year.
- Maximum latent period: 10 years.

Exposure assessment for chronic silicosis

- History of occupational exposure: confirmed prolonged occupational inhalation exposure to crystalline free silica.
- Minimum duration of exposure: five years.
- Maximum latent period: not applicable.

Name of the diseases and ICD code: **Coal workers' pneumoconiosis (J60) + Z57.2**

Coal workers' pneumoconiosis (CWP), miners' silicosis (miner's lung), anthraco-silicosis (anthracosis) or black lung is a chronic disease caused by inhalation of pulverized coal mineral dust consisting of carbon and accompanying rocks containing variable amounts of silica. Coal miner's pneumoconiosis can occur as a simple or complicated disease, depending on its extent. When coal dust is entrapped in macrophages after being inhaled and entering the bronchioles, a fibrous reaction occurs with the formation of macules. These macules extend and coalesce forming areas of interstitial fibrosis. This causes distention in the bronchioles that could lead to focal emphysema. The macules may continue to coalesce leading to progressive massive fibrosis. Acute inhalation of excessive amounts of coal dust can cause coughing, wheezing and shortness of breath.

Simple coal workers' pneumoconiosis

This is usually observed after no less than 20 years of high exposure to coal mining dust with absence, or very low presence, of silica contamination. Features are of dust accumulation in the lung with a very mild tissue reaction. Removal from exposure usually inhibits any further evolution of the disease. Features of this disease can be observed in about 10% of all coal miners with a history of at least 20 years of exposure. In anthracite workers, the proportion can rise as high as 50%.

The clinical picture resembles that of chronic obstructive bronchitis or emphysema. The opacities on the chest radiograph tend to become more irregular in shape, an obstructive pattern of lung function occurs and the lungs pathologically show increasing emphysema and fibrosis around the centrilobular collections of dust-laden cells. Evidence suggests a dose-response relationship between pathological emphysema and dust exposure. An important loss of lung function very similar to the one from tobacco smoke can be observed in non-smoking coal workers. As such, smoking habits should be carefully considered in the differential diagnosis.

Progressive massive fibrosis

This condition follows very heavy dust exposure. Radiographically, it is characterized by convex, circumscribed, flattened or slightly concave masses in the inner surface, smooth in outline, which may be uniformly black or dark grey, and with diameters normally ranging from 3 to over 10 cm. These features are usually observed in the upper or middle zone of the lungs, accompanied by respiratory obstruction. Loss of lung volume due to the space occupied by large progressive massive fibrosis (PMF) may be present. The disease can be complicated by tubercular infection, especially in countries where tuberculosis is endemic. The development of the disease is unlikely in subjects with pneumoconiosis with a severity less than ILO category 2/2. Progressive massive fibrosi may develop even a long time after dust exposure has been discontinued.

Silicosis in coal workers:

In coal workers exposed to coal dust containing silica, features of sub-acute or chronic silicosis may be reported. They can typically be observed when coal has an exceptionally high quartz content, more than 10-15%. In these cases, the disease can be characterized by larger rounded opacities ('r') in the lung fields, then result in confluent irregular massive shadows in the upper zones with pleural thickening, hilar enlargement, calcification of the parenchymal shadows and eggshell calcification of the hilar nodes. Therefore, in these cases the disease may have the features of coal-workers' pneumoconiosis, with or without typical progressive massive fibrosis lesions, mixed with some features of silicosis, or characterized by a few typical silicotic nodules found in the lung or hilar nodes only at autopsy, without any overt functional impairment.

2.1.1 Pneumoconioses caused by fibrogenic mineral dust (silicosis, anthraco-silicosis, asbestosis) ICD Code J60-J62, J63.8 +Z57.2

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: cough, shortness of breath, partially black pigmented sputum, dyspnoea, hypoxaemia, signs of right heart failure in the later stages.
- Examinations:
  - Lung function: in simple CWP a reduction of lung function is not usually found, while in complicated cases restriction as well as obstruction and increased residual volume, changes in diffusion and reduction in oxygen absorption and oxygen partial pressure can be observed.
  - Chest X-ray: the radiographic pattern of simple CWP is rather nonspecific. In some cases, it is possible to observe bilateral, small (3 mm or less), usually rounded radiological opacities, more frequently in the upper and middle lung lobes, without pulmonary impairment. In some cases, and after prolonged exposures (15-20 years) to silica contaminated dust, the picture becomes similar to the one of silicosis.
  - ILO classification (see above for details): small opacities p, q, r or larger opacities A, B, C in complicated progressive massive fibrosi.
  - HRCT may allow visualization of abnormalities not clearly evident on routine chest X-rays, and may additionally distinguish other pathological processes. Nonetheless, CT is not necessary for routine clinical diagnosis of anthraco-silicosis.

Exposure assessment

- History of occupational exposure: confirmed high exposure to respirable and inhalable dust in work activities entailing exposure to coal, possibly with evidence of silica contaminations.
- Minimum duration of exposure: five years.
- Maximum latent period: not applicable.

Name of the diseases and ICD code: **Asbestosis (J61) + Z57.2**

Short description of the disease

Asbestosis is a chronic pneumoconiosis characterized by a bilateral, diffuse, interstitial pulmonary fibrosis, consequent to asbestos exposure. Once the asbestos fibres have reached the lung parenchyma, asbestos activated macrophages produce growth factors, which interact to produce fibroblast proliferation. Macrophages release oxygen free radicals that sustain the inflammatory process. When lung specimens can be obtained, pathological findings can range in severity from subtle alterations that are not visible macroscopically to small, fibrotic lungs with honeycombing; microscopically, a paucicellular collagenous fibrosis is found together with asbestos bodies (i.e., asbestos fibres that develop a ferritin-protein coat and appear typically long-beaded when stained). Progressive asbestosis may result in severe respiratory disability and, in the most severe cases, in death due to respiratory failure. Pleural plaques, which are a reliable indicator of asbestos exposure, may coexist with asbestosis. Sufficient evidence exists in humans for the carcinogenicity of asbestos, as exposure to this mineral has been shown to cause mesothelioma, and cancer of the lung, larynx, and ovary; IARC has thus classified all forms of asbestos as carcinogenic to humans (Group 1).

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: breathlessness without wheeze has an insidious onset and is an early symptom of the disease. Non-productive, dry cough is common. In patients with asbestosis, the most consistent physical finding is represented by inspiratory crackles that affect the lower lung zones, in particular at the early stages of the disease. As the disease progresses, crackles expand to the whole lung. Weight loss and cyanosis can occur. Digital clubbing can be associated with asbestosis and, when present, it indicates an advanced stage of the disease.
- Examinations:
  - Chest radiographs document diffuse irregular small opacities, usually reticular or reticulonodular, mainly in the lower lung fields. They are designated by codes 's' (up to 1.5 mm), 't' (1.5-3 mm), and 'u' (3-10 mm) of the ILO classification. In the advanced phases of the disease, these abnormalities affect the whole lung, the linear opacities become thicker and may ultimately obliterate the vascular markings; honeycombing can be seen, especially in the sub-pleural areas of the lower lobes.

2.1.1 Pneumoconioses caused by fibrogenic mineral dust (silicosis, anthraco-silicosis, asbestosis) ICD Code J60-J62, J63.8 +Z57.2

- In many countries, any asbestos-related finding at the chest X-ray leads routinely to HRCT scanning, as it can reveal abnormalities that are not detectable by plain radiography. In addition, it is useful in detecting and characterizing infiltrative lung disorders in asymptomatic individuals. CT scanning is helpful to distinguish pleural plaques from parenchymal lesions. Diffuse pleural thickening, when present, is often asymmetric and affects the lower and middle third of the chest, usually accompanied by costophrenic angle obliteration. Rounded atelectasis is a radiographic finding highly characteristic of asbestosis and represents a folded area of pleura which traps the adjacent lung tissue. In addition, the use of CT imaging may be useful when: i) a borderline finding of lung fibrosis is detected; ii) there is a discrepancy between radiographs interpreted as normal and lung function findings of restriction; and iii) widespread pleural alterations hinder the radiographic visibility of the pulmonary parenchyma.
- Lung function tests are characterized by restricted or mixed impairment of the respiratory function, with reduced diffusion capacity.
- Presence of high concentrations of ferruginous asbestos bodies or fibres in the sputum or in fluid from bronchoalveolar lavage (BAL) or lung parenchyma is not an absolute prerequisite for diagnosis but represents complementary information.

Exposure assessment for asbestosis

- History of occupational exposure: confirmed prolonged exposure to asbestos and, if available, fibre counts of workplace air. Exposure might be confirmed by the presence of asbestos bodies or fibres in biological samples (sputum, fluid from BAL or lung biopsy).
- Minimum duration of exposure: one year.
- Maximum latent period: not applicable.

Name of the diseases and ICD code: **Pneumoconiosis due to talc dust (J62.0) + Z57.2**

Short description of the disease

Chronic inhalation of talc dust produces talc pneumoconiosis. Symptomatic subjects typically present with nonspecific complaints, such as progressive exertional dyspnoea, and cough. Late complications can include emphysema, chronic respiratory failure, pulmonary arterial hypertension, and *cor pulmonale*. As talc dusts are obtained from different sources, the amount and nature of mineral contaminants can be different. As such, clinical manifestations and radiological findings due to different mineral dusts can overlap. When exposure to crystalline silica or asbestos is also documented, talc pneumoconiosis can also be referred to as talcosilicosis or talcoasbestosis, respectively.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: productive cough, dyspnoea, crackles, diminished breath sounds, limited chest expansion. As the disease progresses, cyanosis and digital clubbing may arise.
- Examinations: pneumoconiosis due to heavy talc dust exposure contaminated by asbestos has chest radiological changes consistent with fine nodular opacities that are either rounded ('p' and 'q') or irregular ('s' and 't'). Histological findings include fibrosis and foreign body granulomas containing talc fibres.

Exposure assessment

- History of occupational exposure: confirmed long-term exposure to elevated air concentrations of talc at the workplace.
- Minimum duration of exposure: two years.
- Maximum latent period: not applicable.

Name of the diseases and ICD code: **Kaolin pneumoconiosis (J63.8) + Z57.2**

Short description of the disease

Long-term exposure to kaolin can cause the development of pneumoconiosis in an exposure-related fashion. Histological evidence of fibrosis has been reported. The disease is usually associated with reduced respiratory function and relatively mild symptoms, but the deterioration of lung function has been observed in cases with prominent radiological alterations. Kaolin contains quartz, clinical manifestations and radiological findings can thus overlap with silicosis at different stages. Kaolin pneumoconiosis can sometimes resemble coal miner's lung disease.

2.1.1 Pneumoconioses caused by fibrogenic mineral dust (silicosis, anthraco-silicosis, asbestosis) ICD Code J60-J62, J63.8 +Z57.2

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: dyspnoea and cough; dark coloured sputum has been reported.
- Examinations: evidence of simple pneumoconiosis at chest X-ray, characterized by small rounded opacities, although confluent masses have been documented in some extremely severe cases; alterations in respiratory capacity, mostly restrictive, can be observed on pulmonary function tests.

Exposure assessment

- History of occupational exposure: confirmed occupational exposure to high concentrations of kaolin.
- Minimum duration of exposure: two years.
- Maximum latent period: not applicable.

Name of the diseases and ICD code: **Pneumoconiosis due to mica dust (J63.8) + Z57.2**

Short description of the disease

Chronic exposure to mica powder can cause nodular fibrotic pneumoconiosis. Although once considered to be a form of silicosis, it is now believed not to be since pure mica dust contains no free silica. The radiological appearance is often close to that of asbestosis. Contamination of mica with other minerals, such as quartz and asbestos, is not uncommon.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: progressive shortness of breath and cough.
- Examinations: chest radiological changes of diffuse infiltration predominantly seen in the lower lung fields. The characteristic histologic features of pulmonary fibrosis accompanied by prominent histiocytic granulomas containing giant cells can be observed, but also diffuse granulomatous lesions with interstitial fibrosis associated with abundant crystalline material. Chest high-resolution CT shows subpleural and peribronchovascular interstitial thickening.

Exposure assessment

- History of occupational exposure: confirmed long-term exposure to mica at the workplace, in particular to asbestos contaminated materials.
- Minimum duration of exposure: two years.
- Maximum latent period: unlimited.

Key actions for prevention	ILO, WHO and several global Non-Governmental Organisations have set the elimination of silicosis and asbestos-related diseases as a global objective. Asbestos and sandblasting have been banned in many countries. The production of dusts, however, is unavoidable in some industrial activities where materials such as rocks are mechanically crushed, cut or processed. Apart from substitution of silica-based industrial abrasives with other inorganic materials is unlikely that primary prevention interventions can be implemented in all industries. Sandblasting has been totally banned in some countries with the elimination of silicosis as a result. Many industries, including the textile industries sandblasting of jeans, have voluntarily joined the global sandblasting ban movement. The long-term action for elimination of asbestos-related diseases is the global ban of asbestos in all its uses. In many countries asbestos has not yet been banned, and even in countries where it has been, workers are exposed in the renovation and repair of the asbestos containing facilities, buildings, and machines as well as in asbestos demolition works. Some alternative materials have been developed or identified as substitutes for asbestos, such as: polyurethane foams; flour fillers (e.g. pecan shell flour, wheat flour, rice flour, rice hull ash); cellulose fibres; thermoset plastic flour (i.e., wood flour) and other fillers used to fill thermoset plastics; and amorphous silica fabrics. Prevention interventions aim at physically separating workers from the areas where dust is produced are possible in large facilities, such as the advancement fronts of tunnel works and the extractive work of large mines, where equipment of a very large size is remotely controlled by workers that operate from driving seats and console controllers placed in closed cockpits and supplied with filtered air.

2.1.1 Pneumoconioses caused by fibrogenic mineral dust (silicosis, anthraco-silicosis, asbestosis)	ICD Code J60-J62, J63.8 +Z57.2
Key actions for prevention	The protection of workers that need to be performed close to the site of dust production, such as stone cutting and carving, localized sandblasting, and asbestos removing activities, is accomplished by prevention strategies essentially based on the use of wet techniques and respiratory protection devices appropriate to the task. The use of respiratory protection for workers needs to be carefully considered and it is not a substitute for controlling the airborne levels of asbestos. Some controversial solutions have been proposed as therapies for pneumoconiosis. Inhalation of aluminium, either with prophylactic purposes or for the treatment of silicosis, was performed mostly in the first half of the 20th century: although firmly criticized in the mid-1950s, this practice remained in use up to the late '80s among Canadian miners in particular as McIntyre powder. More recently, whole-lung lavage has been proposed to treat pneumoconiosis especially in China. However, its efficacy has remained unproven and data are insufficient to determine whether this procedure can actually alter the natural history of the disease. Follow-up of asbestos exposed workers is performed in many countries through dedicated surveillance programs, whose follow-up routine may vary substantially. Nonetheless, exposure and disease history, pulmonary function testing and chest radiographs have traditionally been the primary methods, together with the more recent introduction of CT scanning. Radiographic surveillance programs are mainly aimed at the timely detection of non-malignant asbestos-related diseases, which might in turn entail interventions for a reduction in current asbestos exposure, incentives to cease smoking, encouragement of immunization against influenza and early treatment of respiratory infections, and increased health knowledge obtained by the participants of the follow-up programs. These potential benefits of surveillance programs must be weighed against the harm incurred as a result of the radiation dose received as part of radiographic surveillance. This precautionary criterion also applies to screening programs for miners or silica dust exposed workers, where the severity of respiratory symptoms, results from lung function testing, and presence/absence/progression of radiological abnormalities contribute in determining the frequency of the screening practices. The group of experts considered that the following limits of exposure of workplace atmospheric concentrations (as 8hr TLV-TWA) have been observed to provide a reasonable level of protection for workers' health and have been used in a number of countries: • Silica: 0.025 mg/m^3 (respirable fraction). • Asbestos: 0.1 fibres/cm^3. • Talc (containing no asbestos fibres): 2 mg/m^3. • Kaolin: 2 mg/m^3 (respirable fraction). For coal and mica, no entry can be found in the International Chemical Safety Cards (ICSC) database hosted on the ILO website. As a valuable example of occupational exposure limits, the American Conference of Governmental Industrial Hygienists (ACGIH) proposed the following (as 8hr TLV-TWA): • Coal (as anthracite): 0.4 mg/m^3 (respirable fraction). • Coal (bituminous or as lignite): 0.9 mg/m^3 (respirable fraction). • Mica: 3 mg/m^3 (respirable fraction).

2.1.1 Pneumoconioses caused by fibrogenic mineral dust (silicosis, anthraco-silicosis, asbestosis) ICD Code J60-J62, J63.8 +Z57.2

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▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
2.1.1	Silicosis (acute, subacute, chronic)	J62	CA60.0
2.1.1	Coal workers' pneumoconiosis	J60	CA60.1
2.1.1	Asbestosis	J61	CA60.2
2.1.1	Pneumoconiosis due to talc dust	J62.0	CA60.00
2.1.1	Kaolin pneumoconiosis	J63.8	CA60.Y
2.1.1	Pneumoconiosis due to mica dust	J63.8	CA60.Y
	Occupational exposure to dust	Z57.2	QD84.0

2.1.2 Silicotuberculosis	ICD Code J65 +Z57.2
Short profile of the aetio-pathogenesis	Individuals affected by silicosis have a much higher risk of developing pulmonary and extra-pulmonary tuberculosis (TB) compared to healthy subjects. Even in the absence of silicosis, chronic exposure to silica dust has been shown to increase the risk of TB infection and pre-existing pulmonary TB exacerbation. Silica particles seem to alter the immunological profile of the exposed workers by various mechanisms. They can destroy or alter the metabolism of the pulmonary macrophages, thereby reducing their capacity for antibacterial defence and alter lung cell-mediated immunity. It has been hypothesized that TB bacilli may be able to remain encapsulated within silicotic nodules, this mechanism might be responsible for TB reactivation. For further details on the aetiopathogenetic mechanisms of silicosis and tuberculosis considered as single entities, refer to items 2.1.1 and 1.3.5, respectively.
Occupational exposures	In most countries throughout the world, occupational exposure to silica with possible major health risks occurs in mining of almost any material, and other underground activities such as tunnelling, sand quarrying, etc. The risk is strongly related with the quartz content of the rock, which varies significantly on a geographical basis. From the beginning of the 21st century, mining employment has grown substantially, especially in the informal sector, in countries classified as having a high burden of tuberculosis by the World Health Organization. Hence, mining communities and other working activities with elevated exposure to silica dust in these countries often have the highest reported incidence of tuberculosis. A significant risk of silica dust exposure is reported in masonry and sculpture, foundry activities, restoration or demolition of furnaces, sand crushing and blasting, sandstone milling and grinding as well as in the manufacture and use of abrasives, glassmaking, ceramic industry, vitreous enamelling (covering of materials with a thin anti-corrosive protective layer of silica glass) and in the use of silica as a filler in the formulation of paints, elastomers, plastics and in woodworking industries. From a public health perspective, it is important to consider that many workers migrate to job sites and return home with tuberculosis thus representing a dissemination threat. In addition, the increased risk of contracting TB may be the result of workers living in cramped quarters where hygienic conditions may be poor. For this reason, additional workplace settings where risk of TB can be considered increased are oil and gas industries, agriculture and plantations, mining industries (other than for the risk of direct silica exposure), and businesses with large migrant workforces.

Main health effects and diagnostic criteria

Name of the diseases and ICD code: **Silicosis (J62) +Z57.2**

Short description of the disease

Silicotuberculosis refers to a tuberculosis infection of silicosis-affected subjects. The prognosis of these combined diseases is very poor. For individuals with confirmed silicosis, the risk of active tuberculosis increases by more than three-fold; while for individuals with HIV, the risk is five times higher. In a synergistic way, the risk increases more than 15-fold among workers with both HIV and silicosis. The association between silicosis and TB has been known for a long time. The increased risk of both pulmonary and extra-pulmonary TB persists although exposure to silica dust ceases. As regards extra-pulmonary TB, the pleural form is most common, accounting for about 60% of the cases, followed by the pericardial and the lymph node disease. Tuberculosis may complicate all forms of silicosis, but people with accelerated and acute disease appear to be at considerably higher risk. Active tuberculosis in silicotic workers may exceed 20% when the community prevalence of tuberculosis is high. While *M. tuberculosis* is the most common organism, atypical mycobacteria are becoming increasingly common (e.g. *M. kansasii, M. avium*). The risk of acquiring this disease is related to the severity of the silicosis and is higher with increasing silica dust exposure.

2.1.2 Silicotuberculosis — ICD Code J65 +Z57.2

Diagnostic criteria

Clinical manifestations

Clinical manifestations of silicosis and tuberculosis considered as single entities have been thoroughly discussed in items 2.1.1 and 1.3.5, respectively. In the present item, it is worth highlighting the following:

- Symptoms that are common to both diseases include cough mostly productive, wheezing, dyspnoea and vague chest pain.
- Diagnosis of active tuberculosis superimposed on silicosis can be difficult to make, especially in the early stages of the disease when radiological findings are indistinguishable from those caused by silicosis.
- *M. tuberculosis* bacilli may not be recovered from the sputum of silicotuberculosis patients because silicotic fibrosis prevents the discharge of tubercle bacilli into the sputum.

Exposure assessment

- History of occupational exposure: evidence of occupational exposure to silica dust and to jobs tasks and community settings that might predispose to mycobacterium infection.
- Minimum duration of exposure:
  - Silicosis: few months in the acute form; one year in the accelerated form; five years in the chronic form.
  - Tuberculosis: a single exposure event is theoretically enough to cause the disease; nonetheless, a close contact is usually necessary, lasting most likely no less than some hours.
- Maximum latent period:
  - Silicosis: five years in the acute form; 10 years in the accelerated form; not applicable in the chronic form.
  - Tuberculosis: in the acute forms, the onset is usually observed no more than 90 days after infection. In infected subjects, the disease can become manifest mainly within two years from infection. Nonetheless, cases have been reported of the disease becoming active even several years after the primary infection.

Key actions for prevention	Prevention of silicotuberculosis is based on both control of dust exposure and infection control: a discussion on both topics has been already provided in items 2.1.1 and 1.3.5, respectively, which should be referred to for further details. In light of the evidence linking the prevalence of silicosis and TB to silica exposure in occupational settings, investments in dust controls in the workplace are among the first actions to be put in place, in order to prevent the disease. In addition, specific interventions aimed at minimizing the combined risk of both diseases should be implemented, in details: - Current and former workers in workplaces with silica exposure should be systematically screened for active TB (this would allow detection of TB as well as other pulmonary diseases). - Subjects affected by silicosis should be tested and if positive, treated for latent TB infection, regardless of the background TB epidemiology, as they have an increased risk of progression to active TB disease. - When present, national control programmes for silicosis and for tuberculosis should be integrated, for example by establishing a collaboration between public health and labour department. - To the extent possible, documentation of workplaces and workers at risk from silica exposure should be ensured, especially in the informal sector. - A careful recording of the occupational history should always be performed to differentiate silicosis from pulmonary TB and hence avoid the risk of unnecessary anti-tubercular therapy for the former. - In areas with industries where the risk of silicosis is high, the sputum of suspected TB cases should be cultured, with antibiotic susceptibility testing of positive specimens. - Where TB infection is common, improvements to housing and living conditions around silicosis risk industries (e.g. mines should be considered). - Specific screening programmes including tuberculin skin test and X-ray should be considered for workers employed in silicosis-risk industries.

2.1.2 Silicotuberculosis ICD Code J65 +Z57.2

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▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
2.1.2	Silicotuberculosis	J65	CA60.3
	Occupational exposure to dust	Z57.2	QD84.0

2.1.3 Pneumoconioses caused by non-fibrogenic mineral dust	ICD Code J63.5, J63.8 +Z57.2
Short profile of the aetio-pathogenesis	Inhalation of non-fibrogenic mineral dusts does not elicit the production of collagen in the lung but can, in some cases, cause functional lung impairment. Pneumoconioses deriving from inhalation of these dusts are therefore often referred to as "benign" since the reaction to dust is potentially reversible and does not destroy the alveolar structure of the lung, which generally remains intact. The stromal reaction is minimal, and the deposited proteins mainly consist of reticulin fibres. Once inhaled into the lung alveoli, particles of non-fibrogenic dusts remain embedded in the tissue or are internalized by the cells but are not chemically able to elicit any further damage due to the relative chemical inertia of their constituents. The low acidity of the lung fluid and the proteinaceous layer usually covering the solid particles hamper the leaching of elements and further lower their bioavailability, thus effectively preventing their systemic toxicity. Non-fibrogenic mineral dusts of industrial relevance include tin (stannic) oxide, barium sulphate, iron (ferric) oxide, titanium dioxide, and antimony. A detailed description of ferric oxide and the pulmonary disorders following its exposure can be found in item 2.1.4 on "Siderosis". The present item will thus address pneumoconioses caused by tin oxide, barium sulphate, titanium dioxide and antimony although the evidence on disorders related to the last two metals is less consistent.
Occupational exposures	Occupational exposure by inhalation of *tin oxide* (SnO_2) can occur during the mining, smelting, refining, and production processes of tin, primarily produced from the ore cassiterite, and when working with tin alloys and solders since vapours of tin that are released from the alloys quickly oxidize in the air to tin oxide. Tin metal is mostly used to line cans for storing and transporting food, beverages, and aerosols, and in the production of alloys (e.g. bronze and pewter). In chemical production and use of organotin compounds such as antifouling agents and biocides, hydrolysis of tin tetrachloride can occur as an unwanted process, which leads to the production of tin oxide mist. Stannic oxide has been used by itself as a white colourant in ceramic glazes and as an opacifier and can be used as a polishing powder to polish glass, marble, jewellery, and silver. Occupational exposure by inhalation of *barium sulphate* ($BaSO_4$) can occur in the mining, grinding and bagging of barite, the mineral form of barium sulphate, which is primarily used in the manufacture of some specialist industrial products that exploit the high specific gravity of barium compounds, its strong X-ray absorption properties or its fluorescence enhancing properties. Crude barite is used as a thixotropic mud in oil well drilling and as filler in textiles, rubber, soaps, cement and plasters. Barite is incorporated in concrete to make X-ray shielding walls in hospital radio diagnostic facilities and in industrial X-ray inspection installations. Lithopone is a white pigment that contains 20% barium sulphate, 30% zinc sulphide, less than 8% zinc oxide and is still employed as a pigment in white paints for the interior of yards and ships. Chemically precipitated barium sulphate (*blanc fixe*) is used in high quality oil paints and as a contrast medium in X-ray imaging of the digestive tract. Barium oxide is incorporated into glass to fine-tune its refractive index. Occupational exposure by inhalation to *titanium dioxide* (TiO_2) may occur in the production and packaging of raw material (rutile) and in the manufacture of paints and paper that contain it as a white pigment. Special brands of titanium dioxide (photosensitized anatase) are incorporated into paints and even employed into textiles and to degrade airborne chemical substances such as in odour abatement applications. The use of titanium as a lightweight structural metal in alloys has greatly increased in recent decades due to a switch of the production plants from military to civil use. Industrial titanium dioxide is most commonly chemically manufactured rather than simply purified from the naturally mined mineral. In this case, due to technical constraints of the process, it is in the postproduction phases of product recovery, packaging and formulation that most exposure can occur. Production of metallurgical-grade titanium entails the chemical transformation of purified titanium oxide into the hazardous, corrosive and volatile liquid tetrachloride, whose hydrolysis generates a mist of nanoparticles of titanium oxide and hydrogen chloride. Hydrolysis of titanium tetrachloride is also used to produce smoke screens for military and civil activities.

2.1.3 Pneumoconioses caused by non-fibrogenic mineral dust ICD Code J63.5, J63.8 +Z57.2

Occupational exposures	High-purity *antimony* (Sb) is employed in the manufacture of semiconductors. Normal-purity antimony is used widely in the production of alloys, to which it imparts increased hardness, mechanical strength, corrosion resistance and a low coefficient of friction; alloys combining tin, lead and antimony are used in the electrical industry. Antimony alloys are used for bearing shells, storage battery plates, cable sheathing, solder, ornamental castings and ammunition. During processing, the antimony ore, which is extremely brittle, is converted into fine dust more rapidly than the accompanying rock, leading to high atmospheric concentrations of fine dust during such operations as reduction and screening. Dust produced during crushing is relatively coarse, and the remaining operations: classification, flotation, filtration and so on, are usually wet processes and, consequently, dust-free. Furnace workers who refine metallic antimony and produce antimony alloy and workers setting type in the printing industry are all exposed to antimony metal dust and fumes.

Main health effects and diagnostic criteria

Name of the diseases and ICD code: **Stannosis (J63.5) +Z57.2**

Short description of the disease

Stannosis occurs following chronic inhalation of respirable particles of tin oxide (cassiterite). The typical picture is of benign pneumoconiosis with radiological changes but without any pulmonary impairment. Tin is an inert dust and does not initiate an inflammatory reaction when inhaled. However, since it is not X-ray lucent, it produces a typical picture of dissemination of small, high density nodules in the chest radiogram.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: affected subjects are usually asymptomatic.
- Examinations: the chest X-ray is characteristic, showing widespread mottling (non-fibrous); alterations of lung function are usually absent. High resolution CT can show small (1-4 mm) opacities usually denser than silicotic nodules, spread initially in the upper zones of the lungs and, subsequently, in the middle and lower zones. Note that radiological manifestations may improve if the exposure ends.

Exposure assessment

- History of occupational exposure: confirmed repeated or prolonged exposure to dusts of tin oxide at the workplace.
- Minimum duration of exposure: five years.
- Maximum latent period: not applicable.

Name of the diseases and ICD code: **Baritosis (J63.8) +Z57.2**

Short description of the disease

Baritosis is a benign pneumoconiosis that occurs following inhalation of particles made up of barium sulfate and is well described in workers who crush and grind compounds containing barium, a mineral found in paints, paper, ceramics, glass, rubber, electronic components, and in drilling muds in oil and gas exploration.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: affected subjects are usually asymptomatic. However, barium sulphate is known to cause redness and itching of the eyes and nose, and irritation of the throat, following acute exposure.
- Examinations: the chest X-ray shows a radio-dense nodular pattern evenly distributed throughout both lung fields; alterations of lung function are usually absent.

Exposure assessment

- History of occupational exposure: confirmed exposure to barium sulphate at the workplace.
- Minimum duration of exposure: five years.
- Maximum latent period: not applicable.

2.1.3 Pneumoconioses caused by non-fibrogenic mineral dust ICD Code J63.5, J63.8 +Z57.2

Name of the diseases and ICD code: **Other benign pneumoconioses caused by non-fibrogenic mineral dusts**

Pneumoconiosis due to titanium dioxide (J63.8) +Z57.2

Although titanium dioxide (TiO_2) dusts are characterized by low toxicity and low solubility, evidence on pulmonary effects of TiO_2 exposure are not concordant. Some authors reported mild, if any, effects in workers occupationally exposed to TiO_2, with some evidence of airways obstruction at spirometry and very few cases with X-ray pneumoconiotic changes. On the other hand, other studies reported that workers exposed to TiO_2 for long periods showed slight fibrosis, associated with collections of carbon-like particles, these particles were found to contain titanium on energy dispersive X-ray analysis. Some authors assert that some findings might be due to exposure to titanium tetrachloride rather than TiO_2. Finally, other reports suggest that concomitant exposure to other chemicals involved in the process could not be completely ruled out in the pathogenesis of the respiratory disorder. In any case, titanium dioxide is described as having little biological effect in the majority of studies.

Antimoniosis (J63.8) +Z57.2

Several authors have obtained pneumoconiosis-like X-ray pictures from workers with long-term occupational exposure to antimony. In some of these instances, concomitant exposure to silica was likely. A study conducted on antimony process workers found a correlation between estimated lung antimony and period of employment. Some authors refer to antimoniosis, also known as antimony pneumoconiosis or, more rarely, stibiosis, as a benign disorder with no detrimental effect on health. X-ray changes indicating antimoniosis diffuse, densely distributed 1 mm punctate opacities, were found among workers in an antimony smelter, exposed for several years to dusts of antimony trioxide and antimony pentoxide, and to small amounts of free silica. Some workers showed alterations of pulmonary function tests and complained of chronic coughing. Although antimoniosis mostly appears as a relatively benign condition, chronic respiratory effects have been reported in many studies, and relevant exposure to antimony or its compounds cannot be considered harmless.

Key actions for prevention	The extraction, production and use of non-fibrogenic minerals often produce dusts. In this context, dust prevention measures are similar to those for metal mining in general. During crushing, the ore should be sprayed or the process completely enclosed and fitted with local exhaust ventilation combined with adequate general ventilation. As a general preventive measure, workers should be physically separated from the areas where dust is produced. This is usually feasible only in the exploitation of the larger mines (e.g. cassiterite), where equipment of a very large size is remotely controlled by workers that operate from driving seats and console controllers placed in closed cockpits and supplied with filtered air. The mining of the other minerals often occurs at a much lower scale, and often manual exploitation is the only way to extract the minerals. In these more common cases, it is the other rock components fibrogenic minerals, rather than the non-fibrogenic ones, that pose the greatest health hazard (for further details, refer to item 2.1.1). Where complete elimination of exposure is not possible, the hands, arms, and faces of workers should be protected by gloves, dustproof clothing and goggles. Where atmospheric exposure is high, appropriate respirators should be provided. Personal hygiene measures should be strictly observed; no food or beverages should be consumed in the worksplace, and suitable sanitary facilities should be provided so that workers can wash before meals and before leaving work. The group of experts considered that the following limits of exposure of workplace atmospheric concentrations have been observed to provide a reasonable level of protection for workers' health and to be used in a number of countries: • Tin oxide: 2 mg/m³ as 8hr TWA. • Barium sulphate: 4 ppm as 8hr TWA. • Titanium dioxide: 10 mg/m³ as 8hr TWA. • Antimony: 0.5 mg/m³ as 8hr TWA.

2.1.3 Pneumoconioses caused by non-fibrogenic mineral dust ICD Code J63.5, J63.8 +Z57.2

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▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
2.1.3	Stannosis	J63.5	CA60.9
2.1.3	Baritosis	J63.8	CA60.Y
2.1.3	Pneumoconiosis due to titanium dioxide	J63.8	CA60.Y
2.1.3	Antimoniosis	J63.8	CA60.Y
	Occupational exposure to dust	Z57.2	QD84.0

2.1.4 Siderosis	ICD Code J63.4 + Z57.2
Short profile of the aetio-pathogenesis	Siderosis is a mild form of pneumoconiosis, caused by inhalation of iron fumes or deposition and accumulation of iron-containing dusts within macrophages in the lung, following high level prolonged exposures. Ferric oxide is the main constituent of iron dusts. Little or no clinical changes have been reported in workers diagnosed with pulmonary siderosis. Following dust inhalation, the alveolar structure remains generally intact and the stromal reaction is minimal, consisting mainly of thin collagen (reticulin) fibres. As such, there is no evidence that iron oxide alone can cause fibrotic changes. Nonetheless, some experimental studies have shown that inhalation of iron oxide can cause a mild nonspecific inflammatory response and some case reports have been published of siderosis with significant fibrosis in welders. Siderosis is reported as occurring in around 7% of arc welders due to metal fume exposure during welding and it is thus known as "*welder's siderosis*" or "*arc welder's pneumoconiosis*".
Occupational exposures	Occupational exposure to iron occurs during iron (hematite) mining and related operations, during iron refining and at various stages in steelmaking, such as electric arc and oxyacetylene welding, cutting and abrading of iron-containing materials, as well as during the manufacture or use of iron-containing abrasives such as emery. Iron and steel working in building, shipbuilding, and vehicle production especially during mechanical derusting, dry cutting or polishing before welding entails occupational exposure to iron oxide. Given its use as an industrial abrasive, exposure can occur in the use of polishing discs on any kind of materials. Iron is used in metal production in various industries including construction, engineering, and vehicle and shipping production. Other uses include: iron and steel rolling or grinding, fettling, metal, glass or stone polishing with iron oxide powder, boiler scaling, mining or crushing of iron ores, mining or milling of emery, manufacture of magnetic tapes, manufacture of pigments. More than 90% of the total world production of metallic materials is in the form of steels and cast irons, and occupational exposure to iron and its compounds is, therefore, extremely widespread.

Main health effects and diagnostic criteria

Name of the diseases and ICD code: **Siderosis (J63.4) + Z57.2**

Short description of the disease

Siderosis can be observed after long term exposure to iron dust usually no less than 10-15 years, with a prevalence increasing over time. It is not generally associated with pulmonary fibrosis or functional impairment and is usually asymptomatic. Notwithstanding its mild aggressiveness, siderosis is still characterized by specific radiological features, with numerous small, high density nodules. Nodules can be similar in appearance to miliary tuberculosis or miliary metastatic deposits, and their density should be considered in differential diagnosis. The radiographic pattern in pure siderosis consists of diffuse fine reticulonodular opacities, although small, nodules can sometimes be most prominent in the middle third of the lungs, and in the perihilar regions. Nodules indicate radiopaque accumulations of iron particles in macrophages aggregated along perivascular and peribronchial lymphatic vessels, rather than reactive fibrosis.

When inhaled iron is mixed with a substantial quantity of silica, silicosiderosis can occur, which may be associated with pulmonary fibrosis and present with respiratory symptoms such as cough and dyspnoea (for further details, refer to item 2.1.1). Nodular opacities on radiographs differ from silicosis with lower density and profusion. These radiographic abnormalities can partially or completely disappear with removal from dust exposure.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: siderosis is usually asymptomatic, but silicosiderosis may present respiratory symptoms such as cough and dyspnoea.
- Examinations:
  - Radiological changes on X-ray or CT scan, are consistent with small radiodense opacities with a uniform distribution throughout the lung, without coalescence; in particular, chest X-rays may reveal a net-like (reticular) pattern or, in more severe cases, the presence of small opaque areas (micronodules). Small nodules can sometimes be most prominent in the middle third of the lungs, in the perihilar regions.
  - HR CT findings include widespread, poorly defined centrilobular micronodules and branching linear structures, or extensive ground glass attenuation without zonal predominance and fibrosis. Hilar glands are usually not enlarged but may appear radiodense.
  - No pleural changes or functional respiratory impairment usually occur.
  - Analysis of a sputum sample may reveal the presence of alveolar macrophages containing non-haemoglobin iron (siderocytes).

2.1.4 Siderosis — ICD Code J63.4 + Z57.2

Exposure assessment

- History of occupational exposure: confirmed repeated or prolonged occupational exposure to dusts or fumes of iron or its compounds (especially iron oxide) and, if available, measurements of their air concentration at the workplace.
- Minimum duration of exposure: three years.
- Maxim latent period: not applicable.

Key actions for prevention

Occupational exposure to iron dusts occurs mainly through inhalation. As a general preventive measure, workers should be physically separated from the areas where dust is produced. Precautions thus include the fencing off and remote control of machinery, the design of plant which, in modern steel-making, includes computerized control and the safety training of workers. The danger arising from exposure to dusts and fumes is countered by local exhaust and general ventilation coupled with the various forms of remote control. Where complete elimination of exposure is not possible, the hands, arms and faces of workers should be protected by appropriate gloves, dustproof clothing and goggles; where atmospheric exposure is high, appropriate respiratory protection should be provided.

It is especially important that the ducting at grinding and polishing machines and at finishing belts be cleaned and maintained at regular intervals so that the efficiency of exhaust ventilation remains at the designed standards.

When manual exploitation is the only way to extract the mineral, concurrent exposure to fibrogenic minerals is likely and poses the greatest health hazard (for further details, refer to item 2.1.1). Personal hygiene measures should be strictly observed; no food or beverages should be consumed in the workshops, and suitable sanitary facilities should be provided so that workers can wash before meals and before leaving work.

The group of experts considered that an exposure limit of 5 mg/m^3 of workplace atmospheric concentrations for iron oxide (as 8hr TWA) has been observed to provide a reasonable level of protection for workers' health and to be used in a number of countries.

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▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
2.1.4	Siderosis	J63.4	CA60.8
	Occupational exposure to dust	Z57.2	QD84.0

2.1.5 Bronchopulmonary diseases caused by hard-metal dusts	ICD Code J68 +T56.9 +Z57.2
Short profile of the aetio-pathogenesis	Bronchopulmonary diseases caused by hard-metal dusts include a group of disorders of the breathing apparatus (ranging from asthma to pulmonary fibrosis) caused by the inhalation of hard metal particles, dusts, or fumes. Hard metals, also known as sintered or cemented carbides, are manufactured by blending powdered tungsten carbide (WC, ≈ 80%) with cobalt (Co, 3-25%) and other alloying metals (e.g. chromium, titanium, tantalum, vanadium, niobium): the composition is heated under extreme pressure at a temperature close to the melting point of the metal alloy ('*sintering*'), so that the infusible tungsten carbide crystals are embedded into the metal matrix, yielding a polycrystalline material with an almost diamond-like hardness. The main components of the dust released from hard-metal tools are thus the very small (sub-micron sized) crystals of tungsten carbide and the cobalt based metal alloy used for cementing. Each component has its own toxicological characteristics, and some degree of interaction or synergism is expected to be involved in the causative mechanism of bronchopulmonary diseases due to the inhalation of hard metal dusts. Cobalt salts are known as an occupational allergenic agent and to act on the immune system: cobalt ions, slowly detached from the metal matrix of the hard particle in the oxidizing environment of the macrophage lysosome, can cause continuous recruitment of immune response cells and the enhancement of the matrix destructive activity of the immunologic reaction. Cobalt can generate cellular oxidative stress and free radicals through the decomposition of hydrogen peroxide: these free radicals have been proposed to account for several toxic properties of cobalt compounds, which may partly account for the IARC classification of '*cobalt with tungsten carbide*' as probably carcinogenic to humans (Group 2A) and of '*cobalt and cobalt compounds*' as possibly carcinogenic to humans (Group 2B). The solid micro particles of tungsten carbide, ranging in size from 20 to 500 nm (depending on the technological use of the hard-metal tool), are chemically quite inert under biological conditions but can exert foreign body reaction and potentially contribute to generate lung fibrosis. Exposure to hard metal dusts may cause various levels of respiratory impairments, ranging from asthma to pulmonary fibrosis. Many of the respiratory tract effects are believed to result from the generation of oxidants and free radicals by the cobalt ion. However, some of the respiratory effects, such as asthma, are likely to result from immunosensitization to cobalt itself. Individual susceptibility seems also to play a relevant role.
Occupational exposures	Occupational exposure to hard metal dusts is possible in the production of the material, in the manufacturing of mechanical hard metal tools and in their use for drilling, sawing, cutting, polishing or grinding operations. This material can be made into sharp slices or plaques, which in turn can be bound by surface fusion to the carbon steel shaft or screw tip of tools, such as wheel blades, cutting drill points, sharpening wheels, and percussion shaft tips. Both during manufacturing and upon use, the material flakes off generating very inert dust of inhalable particle size. Hard metal is formed by particles of tungsten carbide and other metallic carbides incorporated in a matrix formed by cobalt, which melts during sintering (i.e., pressurization plus heating at 1,500°C) and thus constitutes the structure gluing material. When sintering is done with inadequate methods, improper techniques and poor industrial hygiene, the powders can pollute the atmosphere of the work environment: workers are therefore exposed to the risk of inhalation of metallic carbide powders and cobalt powders. Exposure to hard metal dusts can take place at all stages of the production process, but the highest exposure levels have been reported during phases such as weighing, grinding, and finishing. Other activities can expose the workers to the risk of aerosol inhalation of hard metal. Sharpening of fixed inserts welded to tools is normally carried out by dry diamond grinding or, more frequently, cooled with liquids of different kinds, producing powders or mists formed by very small drops containing metallic particles. Particles of hard metal are also used in the production of a high resistance layer on steel surfaces subjected to wear, applied through methods (plasma coating process and others) based on the combination of a powder spray with an electric arc or a controlled explosion of a gas mixture at high temperature; the electric arc or the gas explosive flow determine the fusion of the metallic particles and their impact on the surface being plated. The use of hard-metal cutting tools entails the production of extreme (usually rotational) friction between the tool itself and the piece worked upon (it being metal, concrete, or even rock such as granite and basalt), not only in stone cutting but also and primarily in tunnel and oil well drilling; friction causes the hard carbide to flare away, so that especially workers who operate at a close distance from the tools are at risk of inhaling the very fine dust.

2.1.5 Bronchopulmonary diseases caused by hard-metal dusts ICD Code J68 +T56.9 +Z57.2

Main health effects and diagnostic criteria

Name of the diseases and ICD code: **Sensitizer-induced occupational asthma (J45.0 +T56.9) +Z57.2**

Short description of the disease

Occupational exposure to hard metal dusts has been associated with bronchial irritation and asthma. Asthmagenic properties of cobalt have been proved but the pathophysiological mechanisms still remain unclear. A type I allergic reaction may be involved since cobalt-related asthma is associated, in some cases, with circulating cobalt-specific IgE and generalized bronchial hyperresponsiveness; delayed type allergy may play a role too.

Symptoms of irritation are typically present during or immediately after exposure to cobalt (with a relatively short latent period following first exposure) even at very low concentrations and improve or totally disappear when the exposure ceases. Symptoms tend to appear at the end of the work shift or during the night.

Asthma symptoms due to cobalt generally tend to disappear when the subject is removed from exposure but can become chronic and irreversible if the exposure continues for some years. Some subjects might exhibit both asthmatic reactions and parenchymal involvement (see below).

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: wheezing, dry cough, shortness of breath, and chest tightness.
- Examinations:
  - A specific bronchial challenge test (in a specialist facility under carefully controlled conditions) confirms the diagnosis of occupational allergic bronchial asthma due to cobalt (suspected on the basis of case history criteria) and determines the appearance of an immediate, delayed or dual bronchospastic response.
  - Respiratory capacity tests carried out at the beginning and at the end of the work shift can help confirm the diagnosis, usually showing evidence of airway obstruction.
  - Specific IgE reaction towards a human Co-seroalbumin compound (HSA) has been found in the serum of affected subjects.
  - Radiological findings are frequently normal and may only occur in rare cases of mixed forms of asthma plus alveolitis, where alveolitis-specific radiological alterations can be found (e.g. reticular or nodular opacities and honeycombing).

Exposure assessment

- History of occupational exposures: evidence of occupational exposure to hard metal dusts and, if available, biological and workplace air monitoring data.
- Minimum duration of exposure: immediately after exposure for symptoms of irritation; in the order of one month for asthma.
- Maximum latent period: usually between 3 to 24 months but may be shorter in atopic subjects, and in exceptional cases, it may be as short as a few days. In sensitized subjects, the latency between exposure and onset of symptoms is usually no longer than 48 hours.

Name of the diseases and ICD code: **Hard metal lung disease (J68.4 +T56.9) +Z57.2**

Short description of the disease

The term "hard metal lung disease" (HMLD) identifies the interstitial lung disease due to inhalation of hard metal dusts. Other names (some of which 'historical') are: hard metal pneumoconiosis, tungsten carbide pneumoconiosis, hard metal lung, cobalt lung. The clinical manifestations of this disease range from fibrosing alveolitis to interstitial lung fibrosis, although its most typical clinical presentation consists of giant cell interstitial pneumonia (GIP). The alveolitis usually improves spontaneously with exposure discontinuance but, if exposure continues, irreversible pulmonary fibrosis may develop.

Subacute fibrosing alveolitis is characterized by the desquamation of epithelial cells and the accumulation of macrophages and multinuclear giant cells in the alveolar spaces (as in giant cell interstitial pneumonia) within a few years of initial exposure, whereas chronic diffuse mural fibrosis with honeycombing occurs several years or more after initial exposure. Although the histopathologic pattern of giant cell interstitial pneumonia is pathognomonic of hard-metal lung disease, diffuse mural fibrosis with honeycombing may predominate, accompanied by a small area of subacute fibrosing alveolitis, especially at an advanced stage of the disease.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms:
  - Shortness of breath, cough, and dyspnoea on exertion over a prolonged period; tightening of the chest, digital clubbing, fatigue, production of sputum and weight loss may be present.
  - The development of diffuse interstitial fibrosis aggravates the clinical symptoms with a worsening of the dyspnoea, which appears even after the minimal strain and then even at rest.

2.1.5 Bronchopulmonary diseases caused by hard-metal dusts ICD Code J68 +T56.9 +Z57.2

- Examinations:
  - Crackles are present in the lower lung.
  - Pulmonary function test can reveal alteration of a restrictive kind (decreased forced vital capacity) and reduced diffusing capacity. If diffuse interstitial fibrosis develops, an increase of the restrictive ventilatory impairment occurs, together with more reduced capillary-alveolar diffusion.
  - Radiographic findings include diffuse small nodular and reticular patterns and small cystic spaces, especially in advanced disease.
  - Thin-section CT findings consist of bilateral ground glass opacities or consolidation on a panlobular or multilobular scale, extensive reticular opacities, and traction bronchiectasis. In advanced stages, parenchymal distortion and honeycombing may be observed.
  - Broncho alveolar lavage (BAL) fluid is characterized by a large increase of the total cell number, mainly formed by macrophages, with numerous multinuclear giant cells, with 'cell-in-cell' or 'cannibalistic' features (pathognomonic for hard-metal lung disease). A similar pattern can be found on lung biopsy tissue samples, together with evidence of centrilobular fibrosis. The finding of the constituents of hard metal (usually only tungsten) may be a useful indicator of past exposure.
  - Histopathological features can vary, with different patterns showing:
    > Desquamative interstitial pneumonia (accumulation of numerous pigmented macrophages within most of the distal airspace of the lung and, sometimes, the presence of giant cells).
    > Obliterative bronchiolitis (fibrosis of terminal and distal bronchioles).
    > Usual interstitial pneumonia (UIP, combination of patchy interstitial fibrosis, scattered fibroblastic foci in the background of dense acellular collagen, architectural alterations due to chronic scarring or honeycomb change) pattern; while the lesions of classical GIP are usually centred on the centrilobular areas, UIP is predominantly distributed at the periphery of the acinus or lobule (in advanced cases of the disease, the UIP pattern may be the prominent feature).

Exposure assessment

- History of occupational exposure: evidence of occupational exposure to hard metal fumes/dusts and, if available, biological and workplace air monitoring data.
- Minimum duration of exposure: six months.
- Maximum latent period: 20 years.

Key actions for prevention	Prevention of hard metal disease consists of reduction and, whenever possible, elimination of inhalation of hard metal dusts with dust control measures similar to those for metal mining and processing in general. During crushing, the ore should be sprayed or the process completely enclosed and fitted with local exhaust ventilation combined with adequate general ventilation. For more detailed guidance on workplace dust control, refer to item 2.1.1. The number of people at risk is normally underestimated because many sharpening activities are carried out in small industries or by craftspeople, where atmospheric levels of dusts can reach very high concentration values. Routine surveillance must be accurate enough to identify hard metal associated pathologies in their earliest stages. Periodic (e.g. annual) questionnaires aimed mainly at temporary symptoms should be administered, along with a medical examination that includes pulmonary function testing and other appropriate medical examinations depending on the clinical manifestations. Since it has been demonstrated that there is a good correlation between cobalt concentrations in the work environment and the urinary excretion of the metal, it is appropriate to carry out periodic (e.g. biannual) measurement of cobalt in urine (CoU) on samples taken at the end of the work week. Pre-exposure medical examinations for the presence of pre-existing respiratory disease and bronchial hypersensitivity can be useful in the counselling and placement of workers. Nonspecific bronchial challenge tests (e.g. with nebulized methacholine) can be useful to identify subjects with bronchial hyperreactivity and potentially use this information in assigning job tasks. The group of experts considered that the following limits of exposure of workplace atmospheric concentrations have been observed to provide a reasonable level of protection for workers' health and to be used in a number of countries: • Cobalt: 0.02 mg/m^3 as 8hr TLV-TWA (when exposed at this level, the biological exposure index for urinary cobalt is estimated to be equal to 15 µg/L). • Tungsten: 3 mg/m^3 as 8hr TLV-TWA.

2.1.5 Bronchopulmonary diseases caused by hard-metal dusts ICD Code J68 +T56.9 +Z57.2

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▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
2.1.5	Toxic effects of exposure to hard-metal dusts	T56.9	NE61& XM3AW0
2.1.5	Bronchopulmonary diseases caused by hard-metal dusts	J68.4+T56.9	CA81.Y
2.1.5	Sensitizer-induced occupational asthma	J45.0	CA23.0
2.1.5	Fibrosing alveolitis	J68.4	CB03.4
2.1.5	Chronic interstitial fibrosis	J68.4	CB03.4
	Occupational exposure to dust	Z57.2	QD84.0

2.1.6 Bronchopulmonary diseases caused by dust of cotton (byssinosis), flax, hemp, sisal or sugar cane (bagassosis) ICD Code J66.0-J66.8, J67.1 +Z57.2

Short profile of the aetio-pathogenesis	Inhalation of dusts and fibres of cotton can give rise to a bronchopulmonary disease ('*byssinosis*'), mainly characterized by cough, chest tightness, and shortness of breath. These symptoms which appear on the first day of the working week after a period of absence from work (e.g. on Mondays after the weekend), tend to decrease until disappearing in the subsequent days. If symptoms become chronic, they persist even when the individual is away from work. Studies of workers exposed to flax (stems), hemp, and sisal have suggested that these dusts have a similar propensity to cause disease. The pathogenic mechanism underlying this disease is still a matter of debate. Research has focused on contamination of vegetable dusts and fibres with Gram-negative bacterial production of endotoxins, whose presence has been clearly demonstrated in occupational settings at risk for byssinosis. Endotoxins can induce release of mediators that are responsible for fever, bronchoconstriction and for sustaining pulmonary inflammatory processes. On the other hand, exposure to the fibrous matter that remains after sugar cane stalks are crushed to extract their juice (i.e., bagasse), has been observed to cause a form of extrinsic allergic alveolitis called '*bagassosis*'. The underlying pathogenic mechanism involves reactions via type III (acute form) and type IV T cell-mediated (subacute and chronic forms) hypersensitivity to *Thermophilic actinomycetes* that contaminate sugar cane dusts.
Occupational exposures	Occupational exposure with inhalation of dusts and vegetable textile fibres occurs primarily in manufacturing textile yarn, thread, or fabric, and it is thus possible during beating, carding, combing, drawing, spinning, twisting and winding of cotton, flax, hemp or sisal. Exposure to cotton dusts can occur during harvesting: cotton bracts are leaves which grow at the base of the cotton flower, become hard once mature, and become brittle and shatter, thus producing dust in the mill where the cotton is yarned. Exposure to bagasse and its contaminants can occur during sugar cane processing. The use of such secondary materials derived from the production of textile fibres and of sugar cane as carbon-neutral biofuels is ever increasing and might represent a novel setting of occupational exposure.

Main health effects and diagnostic criteria

Name of the diseases and ICD code: **Diseases caused by dust of cotton, flax, hemp, or sisal (J66.0-J66.8 +Z57.2)**

Byssinosis (J66.0), Flax-dresser's disease (J66.1), Cannabinosis (J66.2), Airway disease due to other specific organic dusts (J66.8)

Short description of the disease

Inhalation of dusts and fibres of cotton, flax, hemp or sisal can give rise to a pulmonary disorder characterized by respiratory symptoms such as chest tightness and difficulty in breathing, often accompanied by shivering and malaise. The symptoms are more pronounced on the first day of returning to work after a rest period (e.g. a weekend), and gradually lessen with repeated exposure throughout the week. Symptoms of acute forms usually spontaneously disappear in two or three days. If symptoms become chronic, they tend to persist during the working week and remain present even when the individual is away from work. In the chronic forms, shivering and malaise are usually not present or very mild. Clinical examination may be normal or with signs of airflow limitation, chest hyperinflation, prolonged expiration and expiratory wheeze. Radiological signs do not usually accompany the disease.

The prevalence of the disease among workers at risk depends on the quality of the handled materials (those managed in humid and unclean environments yield the highest risk, especially if unwashed) and on the levels of exposure to dusts, airborne concentration and exposure duration. The risk is higher in smokers. The World Health Organization has proposed a classification of clinical manifestations and lung function changes in respiratory disorders from exposure to vegetable dusts (see below), with a description of clinical patterns (i.e., grades), that range from no symptoms to chronic disease. Although it was traditionally accepted that the disease progressed from one grade to another, presumably because of continuing exposure, some studies have shown that this is unlikely, as some individuals have been observed to commence at high grades without passing through the preceding ones.

2.1.6 Bronchopulmonary diseases caused by dust of cotton (byssinosis), flax, hemp, sisal or sugar cane (bagassosis) ICD Code J66.0-J66.8, J67.1 +Z57.2

In addition to classic byssinosis, textile workers have been reported to show clinical manifestations which are similar, but somehow differ from, the classical syndrome:

- *Mill fever* also called cotton or hemp fever, usually follows a worker's first exposure to cotton, flax or hemp dust or a return to work after a prolonged absence. It is characterized by fever, non-productive cough, malaise and sneezing. The symptoms usually disappear in few hours, although exposure to dust is not interrupted.
- *Weaver's cough* is primarily an asthmatic condition characteristically associated with fever; it occurs in both new and senior workers. The symptoms, unlike mill fever, can persist for months. The syndrome has been associated with materials used to treat the yarn, such as tamarind seed powder and locust bean gum.
- *Mattress maker's fever* occurred in workers who were using low-grade cotton and outbreaks have been attributed to contamination of the cotton with *Aerobacter cloacae*; the syndrome was characterized by an acute outbreak of fever, other constitutional including gastrointestinal symptoms, and retrosternal discomfort.

Diagnostic criteria

Clinical manifestations

Classification as proposed by WHO	Signs and symptoms
Grade 0	No symptoms
Byssinosis	
Grade B1	Chest tightness and shortness of breath on most of first days back at work
Grade B2	Chest tightness and shortness of breath on the first and other days of the working week
Respiratory tract irritation (RTI)	
Grade RTI 1	Cough associated with dust exposure
Grade RTI 2	Persistent phlegm (i.e., on most days during three months of the year) initiated or exacerbated by dust exposure
Grade RTI 3	Persistent phlegm initiated or made worse by dust exposure either with exacerbations of chest illness or persisting for two years or more
Lung function	
1. Acute changes	
No effect	Consistent[a] decline in forced expiratory volume in one second (FEV_1) of less than 5% or an increase in FEV_1 during the work shift
Mild effect	Consistent[a] decline in FEV_1 of 5-9% during the work shift
Moderate effect	Consistent[a] decline in FEV_1 of 10-19% during the work shift
Severe effect	Decline of 20% or more in FEV_1 during the work shift
2. Chronic changes	
No effect	FEV_1[b] 80% of predicted value[c]
Mild to moderate effect	FEV_1[b] 60-79% of predicted value[c]
Severe effect	FEV_1[b] less than 60% of predicted value[c]

[a] A decline occurring in at least three consecutive tests made after an absence from dust exposure of two days or more.
[b] Predicted values should be based on data obtained from local populations or similar ethnic and social class groups.
[c] By a pre-shift test after an absence from dust exposure of two days or more.

Exposure assessment

- History of occupational exposure: evidence of exposure to dusts of cotton, flax, hemp, or sisal in the occupational setting or during the work activity, and, if available, workplace air monitoring.
- Minimum duration of exposure: a few hours for the acute forms; five years for the chronic forms.
- Maximum latent period: seven days for the acute forms; five years for the chronic forms.

2.1.6 Bronchopulmonary diseases caused by dust of cotton (byssinosis), flax, hemp, sisal or sugar cane (bagassosis) ICD Code J66.0-J66.8, J67.1 +Z57.2

Name of the diseases and ICD code: **Bagassosis (J67.1) +Z57.2**

Short description of the disease

Bagassosis is a form of extrinsic allergic alveolitis or hypersensitivity pneumonitis, due to the inhalation of *Thermoactinomyces sacchari* (*Thermophilic actinomycetes* species) which grows on stored, crushed sugar cane (bagasse). Extrinsic allergic alveolitis (EAA) is an immune-mediated disease observed as a consequence of the contact with an external antigen. Connecting airways and alveolar walls are affected, with a reduction in gas exchanging capacity. The severity of the disease depends on exposure levels and individual susceptibility. The presentation can be acute, subacute, or chronic; the latter is irreversible.

Acute EAA follows inhalation of high concentrations of antigen and is characterized by flu-like symptoms, such as fever, cough, chills, malaise, muscle pains and headache. The onset occurs several hours after exposure. If exposure is interrupted, recovery is observed in about 48 hours, but symptoms may persist even for a week.

Subacute EAA is observed in intermittent exposures to the causal agent and may follow recurrent acute episodes. The onset is insidious, over a period of weeks in which weight loss, cough and dyspnoea can be observed. Symptoms and signs disappear within days or months after the cessation of exposure.

If subacute EAA is unrecognized, and exposure is not avoided, the onset of a *chronic EAA* may be observed. This disease is characterized by progressive interstitial lung disease in absence of acute attacks. Respiratory impairment is not reversible after the end of exposure, because of the presence of pulmonary fibrosis. Weight loss may be the only systemic symptom. Digital clubbing is unusual, but may be present in the most severe cases. Respiratory crackles and squeaks may be present, together with X-ray findings of interstitial fibrosis or emphysema. In this stage, the disease may progress to severe respiratory impairment.

The diagnosis of EAA is based on the identification of the causal exposure, the presence of the typical signs and symptoms, the presence of specific IgG in serum and the results of clinical, radiographic and functional investigations.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms:
  - *Acute EAA* is characterized by chills, dyspnoea, cough, chest tightness, malaise, fever, and bilateral inspiratory crackles; symptoms appear initially within hours after antigen exposure and disappear when exposure to the causative antigen ceases.
  - *Subacute EAA:* the onset is insidious and progressive over time with dry cough, shortness of breath, weight loss and inspiratory crackles.
  - *Chronic EAA:* symptoms are not reversible, digital clubbing may appear and, in the most severe cases, *cor pulmonale* may occur.
- Examinations:
  - Chest X-rays may show abnormalities consisting, in mild cases, in numerous small opacities (<5 mm) affecting both lungs, often with sparing of the apices and bases, and sometimes with pulmonary oedema. In the advanced disease, ground glass opacities can be observed, in the most severe cases evolving into fibrosis.
  - Pulmonary function tests usually show a reduction in lung volumes and impairment of gas transfer. The main findings are reduction in total lung capacity (TLC), residual volume (RV), vital capacity (VC), and forced expiratory volume in one second (FEV_1), with the ratio between FEV_1 and forced vital capacity (FVC) either unchanged or increased. Diffusing capacity of the lung for carbon monoxide (D_{LCO}) is reduced. The reduction in D_{LCO} is the most sensitive indicator of disease severity. Lung function usually improves 4-6 weeks after cessation of the exposure. When the disease becomes chronic, functional abnormalities are analogous to those of the acute phase but do not show any recovery after exposure cessation.
  - Arterial blood gases: in acute forms, the alveolar-arterial PO_2 gradient is increased at rest and widens with exercise. In severe cases, PO_2 at rest may be sufficiently reduced to produce cyanosis; PCO_2 is either normal or reduced. Increased neutrophil count, erythrocyte sedimentation rate and C-reactive protein in serum can be observed. Chronic forms are characterized by (sometimes severe) reduction of arterial PO_2. In subjects affected by pulmonary fibrosis, pulmonary hypertension can be observed.
  - Bronchoscopy, lung biopsy and histopathological findings: the main pathological finding of this disease is represented by a granulomatous inflammation affecting the peripheral bronchioles and adjacent alveoli. The presence of typical inflammatory exudate can be identified.
  - Immunological findings: the immunological diagnosis is based on the detection of specific IgG antibodies in the serum of affected subjects. In a high proportion of cases, antibodies can be detected in healthy subjects not showing any sign of disease so the utility is in testing those with clinical and radiological signs of disease.
  - Bronchoalveolar lavage (BAL) liquid examination shows lymphocytosis, mainly of the T suppressor subtype (CD8+). Specific antibodies (IgG) can be detected in BAL fluid of affected subjects.

2.1.6 Bronchopulmonary diseases caused by dust of cotton (byssinosis), flax, hemp, sisal or sugar cane (bagassosis) ICD Code J66.0-J66.8, J67.1 +Z57.2

Exposure assessment

- History of occupational exposure: confirmed exposure through inhalation to bagasse and its contaminants, most likely during sugar cane processing.
- Minimum duration of exposure:
  - acute EAA: few minutes;
  - subacute EAA: few hours; and
  - chronic EAA: few months.
- Maximum latent period:
  - acute EAA: 48 hours;
  - subacute EAA: eight days; and
  - chronic EAA: three years (for pulmonary fibrosis, up to 15 years after cessation of exposure).

Key actions for prevention	The main preventive intervention is represented by dust control at the workplace with diverse possible measures, including exposure standards, technology interventions, exhaust ventilation, personal protective equipment, and regulatory enforcement. As regard textile fibres, cotton in particular, industries may need to develop intervention strategies using different blends and synthetic substitutes; the biological activity of dusts can be greatly reduced by either steaming or washing the textile fibres before processing. As regards sugar cane processing, by keeping the moisture content above 20% and spraying the bagasse with 2% propionic acid (a widely used fungicide) bagasse can be rendered safe for manufacturing use. When avoidance of causative antigens cannot be easily achieved, the use of personal protective devices such as appropriate respiratory protection is recommended to protect individual workers from the inhalation of dusts. However, face fitted respirators may provide inadequate protection, and helmet type powered air purifying respirators, although effective, can be cumbersome to wear. As such, care should be taken in the selection and use or respiratory protectives devices to ensure they are adequate in performance, size, weight, and resistance to airflow, as well as appropriate for specific climatic conditions. Regular monitoring of workers' lung function should be undertaken, as part of a respiratory health surveillance program to identify susceptible individuals and early signs of respiratory impairment.

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▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
2.1.6	Byssinosis	J66.0	CA80.0
2.1.6	Flax-dresser's disease	J66.1	CA80.1
2.1.6	Cannabinosis	J66.2	CA80.2
2.1.6	Airway disease due to other specific organic dusts	J66.8	CA80.Y
2.1.6	Bagassosis	J67.1	CA70.1
	Occupational exposure to dust	Z57.2	QD84.0

2.1.7 Asthma caused by recognized sensitizing agents or irritants inherent to the work process ICD Code J45.0, J68.3 +Z57

Short profile of the aetio-pathogenesis

Asthma is a disease characterized by airway inflammation, reversible variable airflow limitation, and airway hyperresponsiveness due to causes and conditions attributable to a particular occupational environment. Occupational or work-related asthma is specifically associated with breathing substances present in the air at the workplace, such as chemical fumes, gases or dust, which are irritating or sensitizing.

The annual population incidence of occupational or work-related asthma ranges from an estimated 12 to 300 cases per million workers. Population attributable risk estimates suggest that the development of 9-15% of asthma cases in adults of working age are directly attributable to workplace exposures.

There are two distinct categories of asthma that can be identified:

(i) Occupational asthma: caused or induced by specific exposures in the working environment. This type of asthma may affect subjects without a previous history of asthma from other causes. This category is subdivided into sensitizer-induced occupational asthma and irritant-induced occupational asthma (reactive airways dysfunction syndrome). Occupational asthmagens are generally categorized as being of either high or low molecular mass, the former being usually glycoproteins that act as complete allergens and the latter being 'chemical' agents, which can be irritant or probably become antigenic only after conjugation with a body protein such as human serum albumin.

(ii) Work aggravated asthma (sometimes referred to as work exacerbated asthma): pre-existing or coincidental new onset of adult asthma, which is worsened by workplace factors, e.g. cold, dry air, irritant fumes or dust and physical exercise [for asthma exacerbated by extremely cold temperatures, refer to item 1.2.6(1)].

Like other types of asthma, occupational or work-related asthma can cause symptoms, such as chest tightness, wheezing and shortness of breath. When diagnosed and treated early, occupational asthma may be reversible. This type of asthma is characteristically associated with symptoms at work and relief on weekends and holidays or other periods away from work exposures. If the work-related exposure is removed within the first six months of symptoms, there is usually complete recovery.

Occupational exposures

Irritant-induced occupational asthma can be caused by any airborne irritating agent present in the workplace at sufficiently high concentrations.

Sensitizer-induced occupational asthma can be caused by both high molecular mass substances, usually glycoproteins of biological origin and chemicals, as well as low molecular mass substances.

The following table reports a non-exhaustive list of the most common asthmagenic agents.

Classification	Subgroups	Sources	Occupational activity
High molecular weight protein antigens	Animal-derived substances	Laboratory animals, crab/seafood, grain mites, insects	Animal handlers, farming and food processing
	Plant-derived substances	Flour, grain dusts, natural rubber latex gloves, bacterial enzymes, castor bean dust, vegetable gums	Bakeries, health workers, food processing, detergent making
Low molecular weight/ chemical sensitizers	Plasticizers, 2-part paints, adhesives, wood dusts, foams, metals, drugs & pharmaceuticals	Isocyanates (e.g. toluene diisocyanate, diphenylmethane diisocyanate); acid anhydrides (e.g. phthalic anhydride, trimellitic anhydride); amines (e.g. ethylene diamine, paraphenylene diamine); fluxes (e.g. colophony); wood dusts (e.g. western red cedar), metals (e.g. platinum salts); drugs (e.g. spiramycin, penicillins, psyllium); plastics (e.g. acrylates)	Auto spray painting, varnishing, sawmill work, woodworking, platinum refineries, metal grinding, pharmaceutical manufacturing and packaging
Other chemicals		Biocides (e.g. glutaraldehyde, chloramine T), polyvinyl chloride fumes, organo-phosphate insecticides	Janitorial work, meat packing

2.1.7 Asthma caused by recognized sensitizing agents or irritants inherent to the work process ICD Code J45.0, J68.3 +Z57

Main health effects and diagnostic criteria

Name of the diseases and ICD code: **Sensitizer-induced occupational asthma (Allergic asthma) (J45.0) +Z57**

Short description of the disease

Sensitizer-induced occupational asthma is characterized by a latency period – which may last from several weeks or months to, very seldom, years – between first exposure to a respiratory sensitizer at work and the development of immunologically mediated symptoms. Once the subject is sensitized, even very low concentrations of the sensitizing agent can provoke asthma attacks. It has been observed that other nonspecific asthma triggers may induce symptoms.

Symptoms and signs of occupational asthma are identical to non-occupational forms. There are many clinical patterns, including progressive worsening of symptoms through the working week with improvement on rest days. Nasal symptoms due to allergic rhinitis are not consistently present but sometimes may either precede the onset of occupational asthma symptoms or commence at the same time, as many allergens involved in occupational asthma can also cause rhinitis. Eye irritation due to conjunctivitis and skin urticaria may be present.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: episodic wheezing, difficulty in breathing, chest tightness and cough. Excess sputum production is common. Pre-existing asthma does not exclude the development of occupational asthma.
- Examinations:
  - Lung function testing may show evidence of airway obstruction. Absence of airway obstruction does not exclude a diagnosis of asthma (or occupational asthma). Bronchodilator response may be seen in certain workers with occupational asthma when given ß2 agonists. Measures of lung function taken before and after a working shift are not sensitive indicators of the presence of occupational asthma and may miss a late asthmatic response.
  - Recording serial peak flow measurements (sPEF) is the initial method of either confirming or refuting a possible occupational cause for asthma. sPEF recording over three weeks with at least four recordings a day has very high specificity and moderately good sensitivity for making a diagnosis of occupational asthma. A comparison of measures collected in conditions of exposure vs the absence of exposure to the suspected causal agent is very useful for reaching a diagnosis.
  - Serum specific IgE to the workplace allergen may be present and may assist in making a diagnosis. IgE is more likely to be present and diagnostically helpful in those workers exposed to allergens with high molecular weight.
  - Skin prick (epicutaneous) testing may be positive to the workplace allergen and should generally be interpreted in a similar way to specific IgE testing.
  - Nonspecific bronchial reactivity to challenge with a variety of agents (including histamine, methacholine, mannitol) may be increased in occupational asthma. Additionally, sequential measures of airway reactivity including periods at work and away from work may assist in making a diagnosis.
  - Specific bronchial challenge to the workplace allergen or allergens (in a specialist facility under carefully controlled conditions) may assist in making a diagnosis. It can generally be interpreted in a similar way of specific IgE testing. Note that a negative test does not exclude this diagnosis.
  - Changes in sputum eosinophilia may be helpful in the diagnosis of allergic asthma.

Exposure assessment

- History of occupational exposure: confirmed occupational exposure to workplace allergen. There is insufficient evidence for exposure thresholds, given the variability in individual susceptibility. Nonetheless, some asthmagens have been shown to be capable of sensitization at levels of tens of ng/m^3.
- Minimum duration of exposure: usually from weeks to years but, in some cases, this period may be as short as a few days.
- Maximum latent period: usually between 3 to 24 months, but may be shorter in atopic subjects and in exceptional cases it may be as short as a few days. In sensitized subjects, the latency between exposure and onset of symptoms is usually no longer than 48 hours.

2.1.7 Asthma caused by recognized sensitizing agents or irritants inherent to the work process ICD Code J45.0, J68.3 +Z57

Name of the diseases and ICD code: **Irritant-induced occupational asthma (Reactive airways dysfunction syndrome, RADS) (J68.3) +Z57**

Short description of the disease

Irritant-induced occupational asthma occurs typically within minutes and no more than 24 hours after exposure to a respiratory irritant (gas, fume or vapour) at work, frequently in an individual without known previous respiratory disease. Irritant-induced asthma affects about one-fifth of workers with the diagnosis of occupational asthma. The lack of latent period between the onset of causative exposure and the development of the condition is a characteristic that makes it differ from sensitizer-induced occupational asthma. Irritant-induced occupational asthma usually develops following a single high level accidental irritant exposure to 'toxic' agents such as chlorine or nitrogen oxides. Cases have been described following repeated irritant exposures. Chemical agents (low molecular mass) cause airway inflammation, epithelial denudation and mucosal oedema. Respiratory symptoms persist for a median time of 13 months following irritant exposure.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: cough, wheezing, and symptoms of 'bronchial irritability'. Chest tightness and breathlessness may be present. The onset of symptoms occurs within 24 hours after a single specific exposure.
- Examinations:
  - Lung function testing may show evidence of airways obstruction (FEV_1/FVC ratio less than 0.7), although the absence of airways obstruction does not exclude a diagnosis of irritant-induced occupational asthma. A positive response to an inhaled bronchodilator may be seen.
  - Chest radiograph is usually normal, although it may show nonspecific signs associated with coexisting respiratory infection or bronchiolitis or evidence of hyperinflation.
  - PEF is not diagnostically specific for irritant-induced occupational asthma; however, an elevated diurnal variation in PEF might suggest the presence of asthma.
  - Serum specific IgE to the workplace allergens (or other agents) and associated skin prick (epicutaneous) testing are not useful when making a diagnosis of irritant-induced occupational asthma.
  - Non-specific bronchial reactivity to challenge with the agents, such as histamine, methacholine, and mannitol, is characteristically abnormal in irritant-induced occupational asthma, with increased nonspecific airway reactivity seen as a typical feature of this condition.
  - Specific bronchial challenge to the workplace agent or agents has no role in making a diagnosis of irritant-induced occupational asthma, as the underlying irritant mechanism is not related to a specific agent (i.e., different from allergic mechanism).
  - When performed, bronchial biopsy in patients with irritant-induced asthma indicates bronchial inflammation with lymphocytes and plasma cells, but not eosinophils, suggesting the clinical response is a manifestation of direct epithelial cell injury.

Exposure assessment

- History of occupational exposure: confirmed occupational exposure to very high concentrations of gas, smoke, fume, or vapour (chemical agents, low molecular mass).
- Minimum duration of exposure: several minutes.
- Maximum latent period: 24 hours.

2.1.7 Asthma caused by recognized sensitizing agents or irritants inherent to the work process ICD Code J45.0, J68.3 +Z57

Key actions for prevention	The prevention of occupational asthma requires environmental interventions and medical management tools such as patient education, behavioural changes to avoid asthma triggers, use of therapies, and frequent medical follow-ups. The reduction or elimination of exposure (*primary prevention*) is the most direct method of reducing the workplace incidence of the disease and can be accomplished by reducing airborne exposure to allergens and irritants. There is little direct evidence that the use of respirators is effective for the primary prevention of occupational asthma. Work aggravated asthma can be generally managed by the identification and avoidance of nonspecific trigger factors. This would include pre-placement evaluation, with education to help the affected worker anticipate and respond to problems in a new job or in a modified work setting at an existing job. Importantly, awareness about sensitizing agents has high utility for control of exposure in the workplace, along with educational programmes for workers. Interventions at the workplace required by legislation and regulations to eliminate or, if not possible, keep the sensitizers, irritants, conditions and the exposure to them at a minimum are essential. Health surveillance programmes, as *secondary prevention*, are necessary, since early detection improves long-term prognosis. Due to the poor positive predictive values of screening criteria, pre-placement examinations should be used to establish a baseline for periodic health surveillance rather than to detect and exclude susceptible individuals from high risk workplaces.

Further reading

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▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
2.1.7	Allergic asthma	J45.0	CA23.0
2.1.7	Irritant-induced acute occupational asthma (reactive airways dysfunction syndrome, RADS)	J68.3	CA81.Y
	Occupational exposure to risk factors	Z57	QD84

2.1.8 Extrinsic allergic alveolitis caused by the inhalation of organic dusts or microbially contaminated aerosols, arising from work activities	ICD Code J67 +Z57.2, Z57.8
Short profile of the aetio-pathogenesis	The term "extrinsic allergic alveolitis" (EAA) or "hypersensitivity pneumonitis" (HP) refers to an inflammatory respiratory syndrome caused by repetitive inhalation of antigenic factors in a susceptible host. It is characterized by diffuse inflammation of the interstitial lung, terminal bronchioles, and alveoli. Inflammation is provoked by prolonged or repeated exposure to inhaled antigens with aerodynamic diameters adequate to allow penetration into the most distal segments of the respiratory tree in the order of 5 µm or less, and characterized by low biodegradability which allows for persistence in the lungs for long periods. Individuals with a greater susceptibility due to genetic predisposition or exposed to high levels of the antigens are at increased risk of developing the disease. Following exposure to the antigens, most individuals do not develop the inflammatory response necessary to provoke the disease. In subjects who develop symptoms, EAA is classified as acute, subacute, or chronic. The acute disease is thought to occur primarily via type III hypersensitivity reaction, while subacute and chronic forms are thought to involve type IV (T cell-mediated) hypersensitivity. Histologically, chronic hypersensitivity pneumonitis is characterized by interstitial inflammation and alveolar destruction (honeycombing), with the formation of noncaseating granulomas.
Occupational exposures	The potential exposures responsible for EAA can derive from microbes or animal proteins. Dust from grain products, plant material such as wood, bark, and compost, or water reservoir vaporizers such as air conditioners or hot tubs, can often be colonized by antigenic microbes and, thereby, cause the condition. High and low molecular weight animal proteins found in feathers, furs, faeces, and other animal products are a common cause of the disease among animal handlers and bird fanciers. Farmers and cattle workers develop the most common form of EAA, as the major causative antigens belong to the *Thermoactinomyces* species. Workers subjected to water-related contamination including ventilation workers may become exposed through microorganism colonized humidifiers, forced airsystems, hot tubs, and whirlpools. In these cases, the antigens are various species of *Thermoactinomyces*, *Cladosporium*, or *Mycobacterium avium* complex (MAC). Poultry and bird handlers, in general, can be easily exposed to feathers, droppings, and serum proteins of pigeons, other birds, and fowl. Veterinarians and animal handlers have significant contact with organic antigens. Grain and flour processors and loaders are exposed to grain that may be colonized with various microorganisms, which can be easily inhaled through aerosols. Lumber mill workers, paper and wallboard manufacturers, can be exposed to wood products that are often colonized with moulds. Metalworking fluid handlers are at risk of developing hypersensitivity pneumonitis, as the fluids are frequently contaminated with microbes. Table 1 at the end of the item lists some of the most common causative agents of EAA, with corresponding sources and typical disease name, when present. Some peculiar clinical presentations, together with their specific causal agents (and ICD codes), are summarised below: - *Farmer's lung* (J67.0): caused by inhalation of *Thermophilic actinomycetes*. - *Bagassosis* (J67.1): consequent to the inhalation of *Thermoactinomyces sacchari* which grows on stored, crushed sugar cane (bagasse). - *Bird fancier's lung* (J67.2): caused by the inhalation of avian serum proteins. - *Suberosis* (J67.3): caused by moulds and fungal spores (especially *Penicillium glabrum*), which can be found in cork stored in hot and humid conditions. - *Maltworker's lung* (J67.4): caused by *Aspergillus clavatus*, a contaminant of barley to which maltmen in whisky distilleries or breweries may be exposed during malting. - *Mushroom-worker's lung* (J67.5): caused by the inhalation of spores generated during the cultivation of mushrooms. - *Maple-bark-stripper's lung* (J67.6): the causal agent is *Cryptostroma corticale*, a fungus whose spores can be inhaled while stripping the bark from maple logs. - *Ventilation pneumonitis or air conditioner and humidifier lung* (J67.7): caused by *Thermofilic actinomycetes* growing in reservoirs of humidification systems. - *Allergic alveolitis caused by metal-working fluids* (J68.0): follows inhalation of aerosols of metalworking fluids contaminated by bacterial, mycobacterial and fungal organisms.

2.1.8 Extrinsic allergic alveolitis caused by the inhalation of organic dusts or microbially contaminated aerosols, arising from work activities ICD Code J67 +Z57.2, Z57.8

Occupational exposures	- *Sequoiosis (J67.8)*: caused by inhalation of fungal spores (*Graphium* species) found on redwood or saw dust. - *Cheese-washer's lung* (J67.8): the involved antigen is *Aspergillus clavatus* or *Penicillium casei* contaminating mouldy cheese. - *Coffee-worker's lung* (J67.8): the involved antigen is coffee dust from beans. - *Fishmeal-worker's lung* (J67.8): caused by inhalation of fish meal particles. - *Furrier's lung* (J67.8): the involved antigen is animal fur dust from animal pelts.

Main health effects and diagnostic criteria

Name of the diseases and ICD code: **Extrinsic allergic alveolitis (J67) +Z57.2, Z57.8**

Short description of the disease

Extrinsic allergic alveolitis (EAA) is an immune-mediated disease observed as a consequence of the contact with an external antigen. Connecting airways and alveolar walls are affected, with a reduction in gas exchanging capacity. The severity of the disease depends on exposure levels and individual susceptibility. The presentation can be acute, subacute, or chronic; the latter is irreversible. The most well known form of EAA is the so-called "Farmer's lung disease".

Acute EAA follows the inhalation of high concentrations of antigen and is characterized by flu-like symptoms, such as fever, cough, chills, malaise, muscle pains and headache. The onset occurs several hours after exposure. If exposure is interrupted, recovery is observed in about 48 hours, but symptoms may persist even for a week.

Subacute EAA is observed in intermittent exposures to the causal agent and may follow recurrent acute episodes. The onset is insidious, over a period of weeks in which weight loss, cough and dyspnoea can be observed. Symptoms and signs disappear within days or months after the cessation of exposure.

If subacute EAA is unrecognized, and exposure is not avoided, the onset of a *chronic EAA* may be observed. This disease is characterized by progressive interstitial lung disease in the absence of acute attacks. Respiratory impairment is not reversible after the end of the exposure, because of the presence of pulmonary fibrosis. Weight loss may be the only systemic symptom. Digital clubbing is unusual but may be present in the most severe cases. Respiratory crackles and squeaks may be present, together with X-ray findings of interstitial fibrosis or emphysema. In this stage, the disease may progress to severe respiratory impairment.

The diagnosis of EAA is based on the identification of the causal exposure, the presence of the typical signs and symptoms, the presence of specific IgG in serum and the results of clinical, radiographic and functional investigations.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms:
  - *Acute EAA* is characterized by chills, dyspnoea, cough, chest tightness, malaise, fever, and bilateral inspiratory crackles; symptoms appear initially within hours after antigen exposure and disappear when exposure to the causative antigen ceases.
  - *Subacute EAA:* the onset is insidious and progressive over time with a dry cough, shortness of breath, weight loss and inspiratory crackles.
  - *Chronic EAA:* symptoms are not reversible, digital clubbing may appear and, in the most severe cases, *cor pulmonale* may occur.
- Examinations:
  - Chest X-rays may show abnormalities, consisting, in mild cases, of numerous small opacities (<5 mm) affecting both lungs, often with sparing of the apices and bases, and sometimes with pulmonary oedema. In the advanced disease, ground glass opacities can be observed, in the most severe cases evolving into fibrosis. In this phase, the picture is similar to one of the other fibroses such as sarcoidosis and differential diagnosis may be difficult.

2.1.8 Extrinsic allergic alveolitis caused by the inhalation of organic dusts or microbially contaminated aerosols, arising from work activities ICD Code J67 +Z57.2, Z57.8

- Pulmonary function tests usually show a reduction in lung volumes and impairment of gas transfer. The main findings are reduction in total lung capacity (TLC), residual volume (RV), vital capacity (VC), and forced expiratory volume in one second (FEV_1), with the ratio between FEV_1 and forced vital capacity (FVC) either unchanged or increased. Diffusing capacity of the lung for carbon monoxide (D_{LCO}) is reduced. The reduction in D_{LCO} is the most sensitive indicator of disease severity. Lung function usually improves 4-6 weeks after cessation of the exposure. When the disease becomes chronic, functional abnormalities are analogous to those of the acute phase but do not show any recovery after exposure cessation.
- Arterial blood gases: in acute forms, the alveolar-arterial PO_2 gradient is increased at rest and widens with exercise. In severe cases, PO_2 at rest may be sufficiently reduced to produce cyanosis; PCO_2 is either normal or reduced. Increase neutrophil count, erythrocyte sedimentation rate and C-reactive protein in serum can be observed. Chronic forms are characterized by sometimes severe reduction of arterial PO_2. In subjects affected by pulmonary fibrosis, pulmonary hypertension can be observed.
- Bronchoscopy, lung biopsy and histopathological findings: the main pathological finding of this disease is represented by a granulomatous inflammation affecting the peripheral bronchioles and adjacent alveoli. The presence of typical inflammatory exudate can be identified.
- Immunological findings: the immunological diagnosis is based on the detection of specific IgG antibodies in the serum of affected subjects. In a high proportion of cases, antibodies can be detected in healthy subjects not showing any sign of disease so the utility is in testing those with clinical and radiological signs of disease.
- Bronchoalveolar lavage (BAL) liquid examination points out lymphocytosis, mainly of the T suppressor subtype (CD8+). Specific antibodies (IgG) can be detected in BAL fluid of affected subjects.

Differential diagnosis

Pneumonitis caused by influenza virus, *Mycoplasma*, and *Legionella*, as well as psittacosis and Q fever are the most important disorders to be considered in differential diagnosis for acute EAA. The chronic form of the disease must be differentiated from other interstitial lung disorders.

Exposure assessment

- History of occupational exposure: confirmed exposure through inhalation to one or more of the mentioned causal antigens at the workplace or during a working activity.
- Minimum duration of exposure:
  - acute EAA: few minutes;
  - subacute EAA: few hours; and
  - chronic EAA: few months.
- Maximum latent period:
  - acute EAA: 48 hours;
  - subacute EAA: eight days; and
  - chronic EAA: three years (for pulmonary fibrosis, up to 15 years after cessation of exposure).

Key actions for prevention	Due to their relevance for the large scale production of food and other consumer items, the working processes providing opportunities for microbial growth and exposure are likely to continue. In most cases, moulds proliferate when their specific substrates are kept in conditions that favour their growth. Whenever this growth is not intrinsic to the production process as it is in the industrial fermentation for production of beer, raised bread, cheese, and animal fodder from pasture grass, hygienic improvements for raw materials storage and goods production can lead to a reduction from spoilage which may also be economically beneficial. In some cases, interventions are as simple as avoiding storage of humid grass. The antigenic burden can be reduced by altering the handling and storage of microbial antigens, wetting compost to decrease aerosolization, and using fungicides to decrease fungal growth. Microbial overgrowth can be discouraged by dehumidification of the environment and elimination of stagnant water. Routine preventive maintenance should be performed on all ventilation, heating, and air-conditioning equipment. Water damaged carpeting and furnishings should be promptly removed from the workplace. The improvement of technologies for handling and storage of raw materials can lead to a reduction of other associated causes of occupational accident or disease, such as the exposure to asphyxiating gases from fermentation (for further details, refer to item 1.1.16) and to some classes of volatile organic compounds. The same holds for allergens of industrial origin, such as cutting fluids, which can be formulated and used in ways that minimize bacterial growth.

2.1.8 Extrinsic allergic alveolitis caused by the inhalation of organic dusts or microbially contaminated aerosols, arising from work activities	ICD Code J67 +Z57.2, Z57.8
Key actions for prevention	When avoidance of causative antigens cannot be easily achieved, the use of personal protective devices such as appropriate respiratory protection is recommended to protect individual workers from the inhalation of dusts. However, face fitted respirators may provide inadequate protection, and helmet type powered air purifying respirators, although effective, can be cumbersome to wear. As such, care should be taken in the selection and use or respiratory protectives devices to ensure they are adequate in performance, size, weight, and resistance to airflow, as well as appropriate for specific climatic conditions. Regular monitoring of workers' lung function should be undertaken, as part of a respiratory health surveillance program to identify susceptible individuals and early signs of respiratory impairment.

Further reading

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▶ Table 1. Some causative agents of extrinsic allergic alveolitis, with corresponding sources and disease name, when present

Antigen	Source	Disease
Thermophilic actinomycetes (Saccharopolyspora rectivirgula), Aspergillus spp., Penicillium spp., Wallemia sebi, Fusarium spp.	Mouldy hay, straw or grain	Farmer's lung
Aspergillus clavatus, Aspergillus fumigatus	Mouldy malting (barley)	Malt worker's lung
Thermophilic actinomycetes, Saccharopolyspora rectivirgula, Aspergillus spp., Penicillium spp., Mushroom spores	Mushroom spores and mouldy compost	Mushroom grower's lung
Cryptostroma corticale	Bark from stored maple	Maple bark stripper's lung
Thermophilic actinomycetes (Saccharopolyspora rectivirgula)	Mouldy bagasse (Pressed sugarcane)	Bagassosis
Penicillium frequentens, Aspergillus spp., Cork	Mouldy cork	Suberosis
Penicillium casei	Mouldy cheese	Cheese washer's lung
Alternaria spp.	Mouldy wood pulp	Wood pulp worker's lung
Bacillus subtilis, Alternaria spp., Pine sawdust	Contaminated wood dust	Wood dust HP
Aspergillus spp.	Mould on tobacco	Tobacco worker's disease
Botrytis cinerea	Mould on grapes	Wine grower's lung
Aureobasidium pullulans	Mouldy redwood sawdust	Sequoiosis
Mucor stolonifer	Mouldy paprika	Paprika splitter's lung
Sacchoromonospora viridis	Mouldy thatch	Roof thatcher's lung
Aspergillus fumigatus, Thermophilic actinomycetes, Esparto grass antigens	Esparto dust (Stipa tenacissima) used to produce plaster	Stipatosis
Cytophaga (gram-negative bacteria)	Biomass in air-conditioning system	Nylon plant lung
Rhizopus spp.	Contaminated tractor cab air conditioner	Tractor lung
Sitophilus granarius protein	Dust-contaminated grain	Miller's lung
Thermoactinomyces candidus, Cladosporium, Thermoactinomyces Vulgaris, Penicillium spp., Cephalosporium spp., Candida spp., Amoebe, Klebsiela spp., Pseudomonas aeruginosa, Faenia rectivirgula, Mucor spp.	Contaminated, water-cooled air conditioning	Ventilation pneumonitis (humidifier lung, hot tub lung)
Unclear (Pseudomonas spp., Acinetobacter spp., Mycobacterium spp.?)	Metal-working fluids (contaminated?)	Metal worker's lung
Unclear	Mollusc (sea snail) shell	(Nacre) Button maker's lung
Saccharomonospora viridis	Dried grass	Thatched roof disease
Aureobasidium, Graphium spp.	Contaminated sauna water	Sauna worker's lung
Rat urine protein	Rat urine	Laboratory worker's HP
Pigeon proteins	Pigeon droppings	Pigeon breeder's disease
Silk worm larvae proteins	Silk worm larvae	Sericulturist's lung
Chicken feather proteins	Chicken feathers	Chicken breeder's lung
Unclear	Fish meal	Fish meal worker's lung
Trichosporon asahii, Cryptococcus albidus	Domestic (Japan) Damp wood and mats	Summer-type EAA (Japanese summer house HP)
Avian serum proteins	Avian bloom and excreta	Bird fancier's lung
Porcine/bovine proteins	Therapeutic 'snuff'	Pituitary snuff taker's lung

▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
2.1.8	Extrinsic allergic alveolitis	J67	CA70.Z
2.1.8	Farmer's lung	J67.0	CA70.0
2.1.8	Bagassosis	J67.1	CA70.1
2.1.8	Bird fancier's lung	J67.2	CA70.2
2.1.8	Suberosis	J67.3	CA70.3
2.1.8	Maltworker's lung	J67.4	CA70.4
2.1.8	Mushroom-worker's lung	J67.5	CA70.5
2.1.8	Maple-bark-stripper's lung	J67.6	CA70.6
2.1.8	Air-conditioner and humidifier lung (ventilation pneumonitis)	J67.7	CA70.7
2.1.8	Sequoiosis	J67.8	CA70.Y
2.1.8	Cheese-washer's lung	J67.8	CA70.Y
2.1.8	Coffee-worker's lung	J67.8	CA70.Y
2.1.8	Fishmeal-worker's lung	J67.8	CA70.Y
2.1.8	Furrier's lung	J67.8	CA70.Y
2.1.8	Metal-working fluids and extrinsic allergic alveolitis	J68.0	CA70.Y
	Occupational exposure to dust	Z57.2	
	Occupational exposure to other risk factors	Z57.8	

2.1.9 Chronic obstructive pulmonary diseases caused by inhalation of coal dust, dust from stone quarries, wood dust, dust from cereals and agricultural work, dust in animal stables, dust from textiles, and paper dust, arising from work activities ICD Code J68.4 + Z57, Z57.2	
Short profile of the aetio-pathogenesis	Chronic obstructive pulmonary disease (COPD), also known as 'chronic obstructive airway disease', is a persistent airflow limitation that is usually progressive and leads to an irreversible decline in lung function. It is caused by a chronic inflammatory response of the airways and the lungs and follows exposure to noxious particles or gases. Various causal agents produce COPD through very different mechanisms, since their chemical composition is usually very complex and variable. In general, chronic bronchitis presents a common response to chronic inhalation of respiratory irritants. This is supported by the causative effect of cigarette smoking which remains the single most potent environmental cause of chronic bronchitis and by the consideration that dustier environments have been associated with a higher prevalence of chronic expectoration: a deleterious effect of lung dust burden is chronic nonspecific bronchial wall inflammation. This type of inflammatory response has been documented in workers exposed to organic dust and its constituents, such as grain and endotoxin both responsible for neutrophilic inflammation. The role of individual susceptibility has to be taken into consideration and known host-related factors include past respiratory infections, the efficiency of clearance mechanisms as well as genetic factors (see below). One disease mechanism which is common to all types of workplace airborne particulate matter is accumulation in the lung parenchyma of those particles that are too fine to be intercepted by the upper airways and too coarse to be exhaled. Although the inhaled particles are chemically unreactive, they are insoluble in biological fluids. They can thus accumulate in the intercellular matrix of the parenchyma (interstitial lung disease), stimulating a foreign-body reaction of the lung tissue which progressively impairs its elasticity and its ability to expand and relax during respiration. The lungs can accommodate for the presence of several grams of inorganic and organic inert dust in the parenchyma, as observed in the past, e.g. in coal miners over a lifetime of work. Other classes of particles generate pulmonary inflammation by various biochemical mechanisms and the long-term consequence is a progressive loss of the gas exchange capacity of the lung tissue. Particulate matter can also host constituent or adsorbed chemical agents capable of exerting toxic effects on the lungs. This is the case, for example, in chronic bronchiolitis obliterans (or obliterative bronchiolitis) caused by spraying of textile garment print dyes: in the early 1990s, the spraying of a paint formula (Acramin F system) had led to severe pulmonary disease in textile printing sprayers in Spain and Algeria (Ardystil syndrome). Exposure to dusts of synthetic polymers, such as nylon fibres, can cause a chronic obliterative bronchiolitis, known as flock worker's lung. Chronic obstructive diseases can appear in different forms, according to the airway component affected and the type of lesions observed: chronic bronchitis, lung emphysema, and obliterative bronchiolitis. A clear separation between the different forms is not always possible, as their patterns of signs and symptoms can overlap. The predominant role of cigarette smoking and the presence of other non-occupational risk factors for COPD such as exposure to environmental airborne agents, viral infections, airway responsiveness, atopy, and obesity have to be taken into account in differential aetiological diagnosis.
Occupational exposures	Although cigarette smoking is the most commonly encountered risk factor for COPD, occupational exposures including organic and inorganic dusts, chemical agents and fumes or aerosols represent an underappreciated independent, and an at least additive, risk factor to smoking. These exposures may account for up to 20% of symptoms or functional impairment consistent with this respiratory disorder. The most well recognised jobs historically linked to the development of a progressive, irreversible obstructive impairment of the workers' lung function are coal mining, iron and steel industry work, textile, construction and agricultural industries. Several airborne particulate agents in workplaces are able to cause COPD, in particular: • inorganic dusts such as those of silica, asbestos, refractory ceramic fibres, coal, and carbon black and fumes generated in smelting, cutting, welding, and machining of iron, steel, other metals, metal alloys, and refractory metal oxides. In chronic bronchitis caused by silica, the intensity of exposure may be below the levels required to induce silicosis. In any case, the disease can occur independently from the specific toxic actions of the soluble chemical forms of the individual metals (for which further details can be found in items 1.1.1, 1.1.2, 1.1.4, 1.1.6, 1.1.8, 1.1.9, 1.1.19, 1.1.20, 1.1.24, 1.1.27, 1.1.28, 1.1.29, 1.1.30, 1.1.31);

2.1.9 Chronic obstructive pulmonary diseases caused by inhalation of coal dust, dust from stone quarries, wood dust, dust from cereals and agricultural work, dust in animal stables, dust from textiles, and paper dust, arising from work activities ICD Code J68.4 + Z57, Z57.2

Occupational exposures	• organic dusts such as flour, cotton, wood, and microbially contaminated aerosols, (for which further details can be found in items 2.1.6 and 2.1.8), agricultural dusts from poultry, animal and arable farming products and practices, and dusts from manufacturing and processing of natural and artificial rubber or other industrial polymers (e.g. latex, for which further details can be found in item 1.1.39); and • some industrial polymers that contain reactive chemical components, such as isocyanates (for which further details can be found in item 1.1.35) and other compounds of major industrial use.

Main health effects and diagnostic criteria

Name of the diseases and ICD code: **Chronic obstructive pulmonary diseases (J68.4 +Z57)**

Short description of the disease

Chronic obstructive pulmonary disease (COPD) is a disease state characterized by limitation of the airflow that is not fully reversible. COPD includes chronic bronchitis, a condition clinically characterized by chronic cough and phlegm; emphysema, a condition anatomically characterized by destruction and enlargement of the lung alveoli; and small airways disease, a condition in which the small bronchioles are narrowed.

Chronic bronchitis

Chronic bronchitis is a clinically defined condition with chronic productive cough which persists for at least three months per year over a period of at least 2 consecutive years. This disease, which is characterized by inflammation of the bronchi, hypertrophy of the mucous glands and in most cases obstruction of the airways, can be co-morbid with occupational fibrotic syndromes.

COPD is very often accompanied by pulmonary emphysema, which represents the most common complication of this disease.

Emphysema

Emphysema is an anatomically defined condition characterized by a permanent destructive enlargement of the airspaces within the lung (alveoli) without any accompanying fibrosis of the lung tissue. This disease is strongly correlated with tobacco smoke, which plays a major role in the genesis or in the worsening of the emphysema even in subjects exposed to occupational risk factors for the disease. Impairment of gas transfer, air trapping in the lung and loss of the elasticity of the smaller airways are often present. Symptoms include dyspnoea on exertion and an expanded chest (barrel chest). Patients may lean forward with arms extended and resting on something to help them breathe.

Chronic obliterative bronchiolitis

In some cases the airway obstruction involves only the small airways. When the obstruction is severe and permanent, as it is the case in intrinsic inflammatory/fibrotic disease of the small airways, the disease takes the name of chronic obliterative bronchiolitis (or *bronchiolitis obliterans*). The main symptoms are shortness of breath, wheezing and dry cough due to inflammation and scarring of the small bronchioles.

Diagnostic criteria

Clinical manifestations of chronic bronchitis

- Productive cough persisting for at least three months per year over a period of at least two consecutive years.
- Chronic progressive breathlessness, cough and sputum production. Barrel chest with decreased airflow, in particular in exhalation.
- Diminished breath sounds, wheezing and prolonged exhalation at physical examination.
- Demonstration of chronic airflow obstruction is the gold standard in the diagnosis of COPD, therefore the accurate and consistent measurement of forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), and their ratio (FEV_1/FVC) using spirometry is crucial. FEV_1/FVC ratio is usually less than 0.7, even after the administration of a bronchial dilatator. High quality serial spirometry showing an increasing rate of decline in lung function indicates early COPD.
- In subjects younger than 45 years, alpha-1 antitrypsin deficiency screening is recommended to highlight a greater vulnerability to the disease, especially if a family history is suggestive.
- Diffusing capacity of the lung for carbon monoxide (D_{LCO}) is a test that measures the ability of gases to diffuse across the alveolar-capillary membrane and is usually normal or increased in chronic bronchitis.

2.1.9 Chronic obstructive pulmonary diseases caused by inhalation of coal dust, dust from stone quarries, wood dust, dust from cereals and agricultural work, dust in animal stables, dust from textiles, and paper dust, arising from work activities ICD Code J68.4 + Z57, Z57.2

Clinical manifestations of emphysema

- The affected subject may exhibit dyspnoea on exercise with variable degrees of severity, symptoms of hypoxia-induced cyanosis, or the appearance of a blue to purplish discolouration of the skin, due to increased levels of deoxyhaemoglobin in the blood.
- On lung auscultation, the respiratory sounds are weak, and chest percussion may reveal hyperresonance.
- Main radiological findings are characterized by the presence of pulmonary bullae on chest X-ray or CT scan.
- Respiratory function evaluation shows elevated total lung capacity (TLC) and FVC, consequent to a loss of the elastic component of the lung. Elevation of the residual volume (RV) and reduction of both FVC and FEV_1 are usually present.
- Arterial blood gases and oximetry may demonstrate resting or exertional hypoxaemia, together with an elevation of the haematocrit value. In the most severe cases, signs of right ventricular hypertrophy can be present.
- In emphysema, D_{LCO} is typically decreased. As such, it may be used to differentiate emphysema from other types of obstructive disorders such as chronic bronchitis and asthma.

Clinical manifestations of chronic obliterative bronchiolitis

- Characteristic symptoms are dry cough, dyspnoea, and wheezing.
- Pulmonary function tests show increased RV/TLC ratio; non-uniform distribution of ventilation and ventilation-perfusion mismatching occur. D_{LCO} is usually normal.
- Chest X-rays show hyperinflation, while HR CT scans of the chest at full inspiration and expiration may reveal heterogeneous air trapping on the expiratory view, as well as haziness and thickened airway walls.
- Lung volume tests may show hyperinflation due to air trapping.
- Lung biopsy may reveal evidence of constrictive obliterative bronchiolitis, such as severe narrowing or complete obstruction of the small airways. In this context, an open lung biopsy such as through thoracoscopy is more likely to be diagnostic than a transbronchial one. Special processing, staining, and review of multiple tissue sections may be necessary for a diagnosis.

Exposure assessment

- History of occupational exposure: confirmed exposure to agents in workplaces able to cause COPD, including organic and inorganic dusts, chemical agents and fumes or aerosols.
- Minimum duration of exposure: five years.
- Maximum latent period: not applicable.

Key actions for prevention	The main action for prevention of this disease at workplaces is to avoid production and dispersion of dust whenever possible and to minimize workers' exposure with the use of personal protective devices, whenever sufficient dust abatement is not ensured. In building, drilling, mining, and quarrying activities, keeping the work surfaces damp or wet is often sufficient to avoid the production and the dispersion of dusts. In agriculture and in transport within yards, on unpaved roads and in fields, wetting the surfaces just before vehicles move minimizes raising dust due to air displacement. Workspace and operations should be organized so that workers find themselves upwind with reference to the production of dust. In several activities, such as underground mining and tunnel drilling, it is possible to integrate prevention measures to confine the areas where dust production occurs such as the mining or drilling front, by fitting separate air exhausts and housing the workers in ventilated enclosures such as the cabins and cockpits of operating machinery, lorries, and dumpers. In other working situations such as close to operating machines and to chemical reactors, localized aspiration of fumes is by far the most effective prevention. Personal protective devices selected according to the physical form of the contaminants gases, vapours, and aerosol, their environmental concentrations and the anticipated exposure time should be adopted whenever workers need to operate outside the ventilated areas.

2.1.9 Chronic obstructive pulmonary diseases caused by inhalation of coal dust, dust from stone quarries, wood dust, dust from cereals and agricultural work, dust in animal stables, dust from textiles, and paper dust, arising from work activities	ICD Code J68.4 + Z57, Z57.2
Key actions for prevention	An adequate health surveillance program should be implemented, aimed to assess the baseline respiratory health of workers before the commencement of an activity that might expose them to occupational risk factors for obstructive lung diseases. An ongoing surveillance of exposed workers would then allow detection of early signs of respiratory impairment enabling withdrawal from exposure and referral for further diagnostic evaluation of those workers with positive findings. Re-evaluation of the workplace risk assessments and exposure mitigation methods should be informed by the health surveillance findings. Prevention of COPD should rely on educational programmes targeting occupational groups at risk. Programmes should provide workers with proper information on respiratory hazards in the workplace, potential respiratory effects of exposures, and pertinent regulations. In parallel there should be promotion of general safe work practices and healthy lifestyles (e.g. anti-smoking campaigns).

Further reading

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▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
2.1.9	Chronic obstructive pulmonary disease (COPD)	J68.4	CA22
2.1.9	Chronic bronchitis	J68.4	CA20.1
2.1.9	Emphysema	J68.4	CA81.Y
2.1.9	Chronic obliterative bronchiolitis	J68.4	CA81.Y
	Occupational exposure to risk factors	Z57	QD84
	Occupational exposure to dust	Z57.2	QD84.0

2.1.10 Diseases of the lung caused by aluminium	ICD Code (J63.0, J63.1, J68.0, J68.9, J68.4) + T56.8 +Z57
Short profile of the aetio-pathogenesis	Aluminium is the most abundant metal element in the earth's crust and can be found in several minerals, very often in combination with oxygen, fluorine, and silicon. Due to its favourable characteristics of lightness, resistance to corrosion, excellent heat and electricity transmission, and wide availability of its mineral source, aluminium is one of the most commonly used non-ferrous metals. Aluminium is among the least toxic elements and has no recognized biological role in any organism. The element is quickly disposed of by the body in the form of several soluble aluminium compounds. Involuntary ingestion of soluble aluminium compounds is unlikely due to the severe astringent taste and sensation starting from the mouth and responsible for the emetic use of alum (aluminium and potassium sulphate) and for its caustic haemostatic domestic use. Aluminium oxides produced as a powder for sintering are highly inert towards dissolution by body fluids. However, inhalation of aluminium (oxide) fumes, dusts and powder has resulted in a wide variety of respiratory effects. Studies on aluminium plant workers have shown increased mortality for chronic obstructive pulmonary disease. Nonetheless, there is no consensus as regards the causal role of aluminium in the occurrence of these effects: concurrent exposures to other agents have been considered, such as silica for the fibrotic disorders and respiratory irritants (e.g. hydrogen or particulate fluoride, chlorine, sulphur dioxide, and mixed inspirable dusts) for the asthmatic syndrome. Occupational exposures during aluminium production have been classified as carcinogenic to humans (Group 1) by IARC for sufficient evidence in humans regarding cancer of the bladder and of the lung. Other substances involved in most aluminium production processes (e.g. polycyclic aromatic hydrocarbons) have been suggested as possible causative agents.
Occupational exposures	Occupational exposure to aluminium and to its compounds can occur in the mining, metallurgical and chemical industry, in the extraction of bauxite and in the preparation of aluminium, in welding, and in the production of synthetic abrasives, glass, heat-resistant materials and fibres, and commodity aluminium compounds for manufacturing uses. Powder production and aluminium welding have been associated with the highest occupational aluminium exposure. Aluminium is alloyed with a variety of other materials, including copper, zinc, silicon, magnesium, manganese and nickel, and may contain small amounts of chromium, lead, bismuth, titanium, zirconium and vanadium for special purposes. Aluminium and aluminium alloy ingots can be extruded or processed in rolling mills, wire-works, forges or foundries. The finished products are used in shipbuilding for internal fittings and superstructures; in the electrical industry for wires and cables; in the building industry for house and window frames, roofs and cladding; in the aircraft industry for airframes and aircraft skin and other components; in the automobile industry for bodywork, engine blocks and pistons; in light engineering for domestic appliances and office equipment; and in the jewellery industry. A major application of aluminium sheets is in beverage or food containers, while aluminium foils are used for packaging; a fine particulate form of aluminium is employed as a pigment in paints and in the pyrotechnics industry. Articles manufactured from aluminium are frequently given a protective and decorative surface finish by anodization. Bauxite mineral containing up to 55% alumina (aluminium oxide) is the principal source of aluminium, while some lateritic ores, which also contain iron oxide, contain up to 35%. Aluminium is produced from these ores with a process that entails purification of alumina from bauxite by dissolution in strong alkalis and re-precipitation by neutralization, baking and electrochemical reduction from a melt with cryolite (synthetic sodium fluoro-aluminate) and calcium fluoride using Joule heating of the flux at approximately 1000°C with synthetic graphite electrodes (Hall-Héroult process). This process takes place in large carbon lined steel vessels called pots, housed in "potrooms". To mitigate costs and environmental impacts, most aluminium is now recycled from metal scraps (secondary production).

2.1.10 Diseases of the lung caused by aluminium — ICD Code (J63.0, J63.1, J68.0, J68.9, J68.4) + T56.8 +Z57

Main health effects and diagnostic criteria

Name of the diseases and ICD code: **Acute chemical pneumonitis caused by aluminium (J68.0) +T56.8 +Z57**

Short description of the disease

Inhalation exposure to aluminium silicate can cause a chemical pneumonitis characterized by eosinophilic pulmonary infiltrates and, commonly, peripheral blood eosinophilia. The acute eosinophilic disease typically follows a rapid course, but the prognosis is usually good. Chemical pneumonitis usually occurs following exposure to airborne aluminium dusts at very high concentrations (e.g. > 50 mg/m^3).

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: the most common symptoms include cough, fever, difficulty in breathing, and sweating at night. In the most severe cases, respiratory failure can be observed.
- Examinations:
  - Blood cell counts reveal eosinophilia.
  - Chest X-rays show pulmonary infiltrates.
  - Pulmonary function tests reveal a restrictive process with reduced diffusion capacity for carbon monoxide
  - Increased eosinophils are usually found in lung tissue biopsy and bronchoalveolar lavage fluid.

Exposure assessment

- History of occupational exposure: evidence of intense inhalation of aluminium oxide fumes.
- Minimum duration of exposure: few hours.
- Maximum latent period: 48 hours.

Name of the diseases and ICD code: **Chronic lung diseases caused by aluminium**
(Specific disease code) **+T56.8 +Z57**

Aluminosis (J63.0)

Short description of the disease

Occupational exposure to aluminium-containing powders in the micron size is associated with a chronic respiratory disease characterized by reduced expiratory flow, sometimes accompanied by a very mild pulmonary fibrosis. Some studies suggest the possibility of a granulomatous reaction, desquamative interstitial pneumonia, and pulmonary alveolar proteinosis.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: exertional dyspnoea and non-productive cough in early stages, together with crackles on auscultation.
- Examinations:
  - Restrictive or mixed impairment of low degree of the lung function, with a severity correlated with the presence of small opacities.
  - Chest X-ray and CT can show a picture of interstitial infiltrates with small round or irregular opacities.

Exposure assessment

- History of occupational exposure: evidence of occupational exposure to a high concentration of aluminium (sub-micron size aluminium powder, non-fibrous and fibrous particles).
- Minimum duration of exposure: three years.
- Maximum latent period: not applicable.

2.1.10 Diseases of the lung caused by aluminium — ICD Code (J63.0, J63.1, J68.0, J68.9, J68.4) + T56.8 +Z57

Bauxite fibrosis (Shaver's disease) (J63.1)

Short description of the disease

Prolonged and high exposure to aluminium fumes contaminated by silicon dioxide causes a rapidly progressive interstitial fibrosis of the lung, also known as Shaver's disease, bauxite fibrosis or pneumoconiosis, corundum smelter's lung. The disease has been attributed to contamination higher than 30% of silicon dioxide in bauxite (the fibrogenic potency of aluminium dust alone has not been proved) and is typically observed in workers involved in the smelting of bauxite to produce corundum, a crystalline form of aluminium oxide with traces of iron, titanium and chromium. The disease appears initially as an alveolitis and then progresses to emphysema. Pneumothorax is a common complication. Nowadays, the preventive interventions introduced in this kind of production have significantly reduced the risk of occurrence of this pulmonary disorder.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: early stages are usually asymptomatic, and then shortness of breath and dry cough can arise. Crepitations on auscultation, when present, are limited to early stages.
- Examinations: restrictive or mixed impairment of low degree of the lung function, with a severity correlated with the presence of radiological opacities. Chest X-ray and CT can show a picture of interstitial infiltrates, alveolitis and emphysema.

Exposure assessment

- History of occupational exposure: evidence of exposure to a high concentration of bauxite fumes contaminated by silica.
- Minimum duration of exposure: 10 years.
- Maximum latent period: not applicable.

Potroom asthma (J68.9), Chronic obstructive pulmonary disease (COPD) (J68.4)

Short description of the disease

The electrolytic production of aluminium from alumina (i.e., Hall-Héroult process) is accompanied by emissions of dust and gases, which are able to cause an asthma-like symptoms known as "potroom asthma", a very relevant health issue among potroom workers, smelters and casters. The most likely causative agents are irritant airborne particulates and fumes containing gaseous hydrogen fluoride, cryolite, and other elements that may be adsorbed onto aluminium. Elicitation of the disease can be observed for low dose exposures.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: wheeze on auscultation, chest tightness, tachypnoea, dyspnoea, tachycardia, non-productive cough and wheeze, occurring during working hours but more typically some hours after leaving work (delayed onset). Symptoms become more frequent with repeated exposure and tend to improve when exposure ceases. Increased bronchial reactivity, once induced, has a tendency to persist.
- Examinations:
  - Reduced forced expiratory volume in the first second (FEV_1) on pulmonary function test, usually reversible by bronchodilators; nonspecific bronchial challenge test (e.g. with methacholine) is often abnormal in this condition, as increased nonspecific airway reactivity is common.
  - If the disease evolves to COPD, bullae on the chest X-ray or CT scan can be seen, together with altered blood gas analyses, showing mild to moderate hypoxaemia without hypercapnia, in the mild forms, or more evident hypoxaemia with the development of hypercapnia, in the most serious forms.

Exposure assessment

- History of occupational exposure: evidence of occupational exposure to complex mixtures such as those occurring in the potrooms of the aluminium electrolytic production industry. Exposures to other aluminium salts such as aluminium fluoride, aluminium sulphate, and potassium aluminium tetrafluoride, as well exposure to aluminium welding fume, foundry fume, aluminium powder, and aluminium chloride have also been associated with asthma.
- Minimum duration of exposure: few weeks.
- Maximum latent period: 10 years but latencies up to 13 years have been reported.

2.1.10 Diseases of the lung caused by aluminium	ICD Code (J63.0, J63.1, J68.0, J68.9, J68.4) + T56.8 +Z57
Key actions for prevention	Aluminium oxides are the compounds more frequently involved in diseases associated with aluminium exposure. These materials are mostly employed in the manufacture of refractories, which involves the machining of sintered raw casts, and are difficult to substitute with other more benign ones. In particular, other refractory metal oxides of comparable performance and use such as zirconia are much less abundant and much more expensive and are therefore used in specialty manufacturing only. For all of the above, the main preventive actions have to be dedicated to control, organizational, and protective measures. Given the potential concurrent exposure to fluorides, other gases, and particulates in potrooms, the principal control is by local exhaust ventilation. Older potrooms (i.e., Søderberg) may have a hood over the cell, while in more recent ones (i.e., pre-bake), local exhaust ventilation is usually able to remove gases and particulates, transferring them to wet or dry scrubbing systems. It is not uncommon for potrooms to have secondary emission controls (e.g. natural ventilation), which contribute to reducing the concentration of airborne pollutants and in decreasing the overall temperature of the potroom. Mechanical lifting devices should be used to enable work as remotely as possible from the hot metal and bath. For workers driving the cranes above the potlines, totally enclosed and air-filtered cabins should be used in order to further reduce exposure to any dusts, fumes and gases not captured by the primary ventilation systems. Appropriate administrative work practices should be considered, such as rotation of workers in various tasks and short residence times when required to work in close proximity to pots. Personal protective equipment for workers in aluminium plants includes the following: appropriate respiratory protection following a risk assessment, overalls, hearing protection devices, gloves, gaiters, safety boots, face shields, and eye protection. Aluminium plant workers should undergo routine periodic health surveillance, preferably including a respiratory symptom questionnaire and pulmonary function tests. The group of experts considered that a workplace atmospheric concentration of aluminium (as 8hr TWA) corresponding to 1 mg/m^3 has been observed to provide a reasonable level of protection for workers' health and used in a number of countries. As regards potential biological markers of exposure, no general consensus has been reached, although occupational biological exposure limits are established in some countries (e.g. Germany has a urinary biological tolerance value for occupational exposure to aluminium of 50 µg/g creatinine, roughly corresponding to 65 µg/L). Samples collected immediately after a work shift are considered to be strongly related with a short-term (i.e., current) exposure, while samples taken later after exposure (e.g. after days off) are more likely to reflect the body burden of aluminium. Given its ubiquitous distribution, aluminium can be found in the general population, with expected concentrations of about 5 µg/L (serum) and <30 µg/L (urine).

2.1.10 Diseases of the lung caused by aluminium — ICD Code (J63.0, J63.1, J68.0, J68.9, J68.4) + T56.8 +Z57

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▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
2.1.10	Acute chemical pneumonitis	J68.0	CA81.0
2.1.10	Aluminosis	J63.0	CA60.4
2.1.10	Bauxite fibrosis (Shaver's disease)	J63.1	CA60.5
2.1.10	Potroom asthma	J68.8	CA81.Y
2.1.10	Chronic obstructive pulmonary disease (COPD), Emphysema	J68.4	CA81.Y
	Toxic effect: other metals	T56.8	NE61
	Occupational exposure to risk factors	Z57	QD84

2.1.11 Upper airways disorders caused by recognized sensitizing agents or irritants inherent to the work process ICD Code (J30.3, J32.8, J31.2, J38.7, J68.2) +Z57

Short profile of the aetio-pathogenesis	Occupational upper airways diseases are characterised by inflammation of the upper airways and can have both allergic and irritant mechanisms. This set of disorders includes rhinitis, sinusitis, pharyngitis, and laryngitis, whose causal agents may be airborne dusts, biological agents, gases, vapours, or fumes. As the clinical picture of these disorders resembles that of the same diseases caused by non-occupational risk factors, the primary criterion for their differentiation is the identification of a specific causal agent in the workplace rather than in the general/domestic environment. In some cases, the diseases belonging to this group are tightly interlinked: this is the case, for example, of occupational rhinitis, which may evolve into occupational asthma especially if a high molecular mass allergen is involved. Nonetheless, although in sensitized subjects the entire upper airways are usually affected, in some cases a specific anatomical site may be predominant.
Occupational exposures	Many chemical substances can lead to the onset of a work-related rhinitis, in different jobs and industries. High molecular mass proteins (≥5,000 Da) can be found in farming and food processing, and represent potential exposures for bakers, health care workers, and detergent manufacturers. Low molecular weight sensitizers (<5,000 Da) can be involved in activities such as auto spray painting, varnishing, woodworking, platinum refining, metal grinding, sawmill work, carpentry, and pharmaceutical manufacturing and packaging. A selection of hazardous exposures for occupational allergic rhinitis, resembling those involved in occupational asthma, is reported in Table 1 at the end of the item. Cases of laryngitis most likely related to work activities have been described for exposure to formaldehyde, acid anhydrides, flour, acrylates, lubricating liquids and coolants, and hairdressing products. Similar exposures such as food processing, acrylics, cleaning products, wood dusts, etc., have been described in the pathogenesis of allergic sinusitis and pharyngitis. Upper airways irritants are involved in a great number of chemical and industrial processes. A selection of respiratory irritants with detailed characteristics is reported in Table 2 at the end of the item. Wood dusts can be causative agents of both allergic and irritant effects: a detailed list of various wood varieties is reported in Table 3 at the end of the item.

Main health effects and diagnostic criteria

Name of the diseases and ICD code: **Upper airways disorders caused by recognized sensitizing agents inherent to the work process (J30.3) +Z57**

Allergic rhinitis (J30.3)

Short description of the disease

Occupational allergic rhinitis follows a sensitization against an occupational antigen; after contact with the antigen, allergic inflammation of the nasal mucosa, congestion, rhinorrhoea and sneezing occur, due to production and release of mediators through IgE-dependent reactions, which produce eosinophilic infiltration and tissue oedema.

The onset is linked with the exposure to airborne occupational allergens. In the case of exposure to high molecular mass allergens, an occupational rhinitis may evolve into occupational asthma.

In general, 40% of rhinitis patients may manifest asthma, and about 70% of asthma patients suffer also from rhinitis.

2.1.11 Upper airways disorders caused by recognized sensitizing agents or irritants inherent to the work process ICD Code (J30.3, J32.8, J31.2, J38.7, J68.2) +Z57

Diagnostic criteria

Clinical manifestations

- Signs and symptoms:
  - Rhinorrhoea, sneezing, lacrimation, red eyes, itchy eyes, nose and throat, nasal cavity obstruction, watery and pale nasal mucosae, congested conjunctivae.
  - Nasal polyps are often present; and indicate an increased likelihood of progression to asthma.
  - In the majority of cases, symptoms appear before the age of 40 years and tend to reduce with aging.
- Examinations:
  - Eosinophils can be found in the nasal secretions of affected subjects, as well as modest peripheral eosinophilia and elevation of serum IgE. Skin prick test represents an in vivo examination aimed at identifying specific IgE antibodies. However many occupational allergens are not available as standard preparations; also the sensitivity and specificity of both serological and skin prick tests varies according to the sensitizing agent.
  - Specific nasal inhalation challenge testing can be used to identify the involved allergen.
  - Anterior rhinoscopy should be used to examine the nasal mucosa.
  - Rhinomanometric measurements can be used to measure nasal obstruction.

Exposure assessment

(see below)

Allergic sinusitis (J32.8)

Short description of the disease

Occupational allergic sinusitis is a disorder characterised by inflammation of the sinuses mucosae, induced by workplace exposure to airborne dust, fungi (e.g. aspergillus), mould, gas, vapour or fume. Sinusitis can be acute, lasting up to 12 weeks, or chronic, lasting more than 12 weeks. Symptoms of allergic sinusitis include: pain, tenderness, swelling and pressure around the forehead, cheeks, and nose and between eyes, headache, reduced sense of smell and taste, irritability, sleep disturbances, together with signs and symptoms of allergies in the nose, throat and eyes. Allergic sinusitis is sometimes confused with non-allergic sinusitis since the clinical picture is the same. However, non-allergic sinusitis is usually not accompanied by typical allergic symptoms, such as itchy nose, eyes or throat. Many of these patients have nasal polyps, and all have congested nasal mucosae and sinuses full of mucoid material.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms:
  - Nasal congestion (sneezing, runny nose) and post nasal drip that persists for more than two weeks are amonget the cardinal symptoms along with facial or dental pain, and reduced sense of smell and taste. Other symptoms include itchy eyes, nose and throat, and headache.
  - Behavioural changes can include irritability, inability to focus, fatigue, and sleep disturbance.
- Examinations:
  - Serum specific IgE antibodies can be found elevated. Skin prick test represents an in vivo examination aimed at identifying specific IgE antibodies. However many occupational allergens are not available as standard preparations; also the sensitivity and specificity of both serological and skin prick tests varies according to the sensitizing agent.
  - Anterior rhinoscopy and nasal endoscopy allow inspection of polyps from the paranasal sinuses and a better appreciation of the anatomy and structures.
  - CT scan of the sinuses can rule out any injury, infection, or other abnormalities.
  - Histological examination of the sinus mucosae may show evidence of local eosinophilia and Charcot-Leyden crystals (breakdown products of eosinophils).

Exposure assessment

(see below)

2.1.11 Upper airways disorders caused by recognized sensitizing agents or irritants inherent to the work process ICD Code (J30.3, J32.8, J31.2, J38.7, J68.2) +Z57

Allergic pharyngitis (J31.2)

Short description of the disease

Occupational allergic pharyngitis is characterized by pharyngeal inflammation in response to inhalation of allergens, such as dust, mould, gas, vapour, fume or other bioaerosols, in the workplace or during a working activity. Symptoms include sore and red throat, and feeling of a "lump in the throat", together with signs and symptoms of allergies in the nose and eyes such as nasal discharge and lacrimation.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: sore, red, dryness and itchy throat, sensation of "lump in the throat", even tonsillitis, together with signs and symptoms of allergies affecting the nose and eyes such as nasal drainage and congestion, difficulty breathing through the nose, excessive sneezing, itchy nose and eyes, red eyes, excessive lacrimation.
- Examinations: serum specific IgE antibodies can be found elevated. Skin prick tests identifying specific IgE antibodies can show positive results.

Exposure assessment

(see below)

Allergic laryngitis (J38.7)

Short description of the disease

Occupational allergic laryngitis is characterized by laryngeal inflammation in response to inhalation of allergens, such as dust, mould, gas, vapour, fume or other bioaerosols, in the workplace or during a working activity. These allergens either bind to surface antibodies in the larynx or are recognized by blood cells in the larynx as foreign. The allergens stimulate the blood cells to release histamine, which then incites an inflammatory response. The allergic inflammatory response causes the increased production of mucous, which is usually thick. The thick, viscous mucous absorbs water and dries the vocal folds. The result is an increase in the shearing forces and friction on the vocal folds during phonation, which causes redness and inflammation of the folds themselves.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: hoarseness, usually worse both during and several hours after exposure to the allergen, itchy throat, excessive phlegm or mucous in the throat, sensation of dry throat, and dry cough, together with signs and symptoms of allergies in the nose and eyes such as nasal drainage and congestion, difficulty breathing through the nose, excessive sneezing, itchy nose and eyes, red eyes, excessive lacrimation.
- Examinations:
  - On physical examinations, the entire larynx may appear red, with mild to moderate swelling. Mucous production is usually increased and thick, resulting in the appearance of an increased amount of phlegm on the vocal folds.
  - Skin prick or serological tests may indicate elevated levels of specific IgE antibodies.
  - Direct laryngoscopy often reveals diffuse laryngeal erythema and oedema, along with vascular engorgement of the vocal folds.

Exposure assessment

(see below).

Exposure assessment criteria for upper airways disorders caused by recognized sensitizing agents inherent to the work process

- History of occupational exposure: confirmed occupational exposure to substances known to induce allergic rhinitis, sinusitis, pharyngitis, or laryngitis. Symptoms typically appear in relation to the exposure, and disappear when exposure ends. Recurrence is thus observed after re-exposure to the same agent.
- Minimum duration of exposure: usually a few weeks, since occupational allergic upper airways disorders require a sensitization period. In exceptional cases, minimum duration of exposure may be as short as a few days.
- Maximum latent period: in sensitized individuals usually no more than 48 hours; however exposure following sensitization and thus producing the symptoms may occur even some years after sensitization itself.

2.1.11 Upper airways disorders caused by recognized sensitizing agents or irritants inherent to the work process ICD Code (J30.3, J32.8, J31.2, J38.7, J68.2) +Z57

Name of the diseases and ICD code: **Upper airways disorders caused by recognized irritants inherent to the work process (J68.2) +Z57**

Short description of the disease

Upper airways irritation can be caused by dusts, gases, fumes and vapours. Very soluble substances in water can affect the upper respiratory tract and cause symptoms, within seconds. The appearance and severity of the irritation can be related to multiple factors e.g. simultaneous exposure to different substances, smoking, medical history of a respiratory disease like asthma, chronic bronchitis. The clinical pictures roughly resembles the plethora of signs and symptoms already described for rhinitis, sinusitis, pharyngitis, and laryngitis due to sensitising agents (see above for further details on clinical manifestations). If exposure to the irritant agent is not interrupted, symptoms of irritation can become chronic.

Exposure assessment criteria for upper airways disorders caused by recognized irritants inherent to the work process

- History of occupational exposure: confirmed occupational exposure to substances known to be irritant for the upper airways.
- Minimum duration of exposure: a single episode for acute irritation; six months for chronic irritation.
- Maximum latent period: 72 hours after cessation of exposure for acute irritation; six months after cessation of exposure for chronic irritation.

Key actions for prevention	The reduction or elimination of exposure (primary prevention) is the most direct method of reducing the workplace incidence of the disease and can be accomplished by reducing airborne exposure to allergens , sensitizing agents and irritants. When elimination of exposure is not possible, secondary and tertiary preventive measures, may be the most feasible actions in some circumstances. In this regard, the measures to prevent asthma in (item 2.1.7) should be implemented.

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▶ Table 1. Examples of sensitizing agents that can cause occupational rhinitis (adapted from the ILO Encyclopaedia of occupational health and safety, 4th edition)

Classification	Sub-groups	Examples of substances	Examples of jobs and industries
High molecular mass protein antigens (5,000 Da, or greater)	Animal-derived substances	Laboratory animals, crab/seafood, mites, insects	Animal handlers, farming and food processing
	Plant-derived substances	Flour and grain dusts, natural rubber latex gloves, bacterial enzymes (e.g. protease, amylase), castor bean dust, vegetable gums	Bakeries, health care workers, detergent making, food processing
Low molecular mass/ chemical sensitizers (less than 5,000 Da)	Plasticizers, 2-part paints, adhesives, foams	Isocyanates, (e.g. toluene diisocyanate, diphenylmethane diisocyanate), acrylates, acid anhydrides (e.g. phthalic anhydride, trimellitic anhydride), amines (e.g. ethylene diamine, paraphenylene diamine)	Auto spray painting, varnishing, woodworking
	Metals	Platinum salts, cobalt	Platinum refineries, metal grinding
	Wood dusts	Cedar (plicatic acid), oak	Sawmill work, carpentry
	Pharmaceuticals, drugs	Psyllium, drug (e.g.spiramycin, penicillins, psyllium)	Pharmaceutical manufacturing and packaging
Other chemicals		Chloramine T, polyvinyl chloride fumes, organophosphate insecticides	Janitorial work, meat packing

▶ Table 2. Respiratory irritants (adapted from the ILO Encyclopaedia of occupational health and safety, 4th edition)

Chemical	Sources of exposure	Important properties	Injury produced	Dangerous exposure level under 15 min
Acetaldehyde	Plastics, synthetic rubber industry, combustion products	High vapour pressure; high water solubility	Upper airway injury; rarely causes delayed pulmonary oedema	
Acetic acid, organic acids	Chemical industry, electronics, combustion products	Water soluble	Ocular and upper airway injury	
Acid anhydrides	Chemicals, paints, and plastics industries; components of epoxy resins	Water soluble, highly reactive, may cause allergic sensitization	Ocular, upper airway injury, bronchospasm; pulmonary haemorrhage after massive exposure	
Acrolein	Plastics, textiles, pharmaceutical manufacturing, combustion products	High vapour pressure, intermediate water solubility, extremely irritating	Diffuse airway and parenchymal injury	
Ammonia	Fertilizers, animal feeds, chemicals, and pharmaceuticals manufacturing	Alkaline gas, very high water solubility	Primarily ocular and upper airway burn; massive exposure may cause bronchiectasis	500 ppm
Beryllium	Alloys (with copper), ceramics; electronics, aerospace and nuclear reactor equipment	Irritant metal, also acts as an antigen to promote a long-term granulomatous response	Acute upper airway injury, tracheobronchitis, chemical pneumonitis	25 μg/m^3
Boranes (diborane)	Aircraft fuel, fungicide manufacturing	Water soluble gas	Upper airway injury, pneumonitis with massive exposure	
Hydrogen bromide	Petroleum refining		Upper airway injury, pneumonitis with massive exposure	
Methyl bromide	Refrigeration, produce fumigation	Moderately soluble gas	Upper and lower airway injury, pneumonitis, CNS depression and seizures	
Calcium oxide, calcium hydroxide	Lime, photography, tanning, insecticides	Moderately caustic, very high doses required for toxicity	Upper and lower airway inflammation, pneumonitis	
Chlorine	Bleaching, formation of chlorinated compounds, household cleaners	Intermediate water solubilty	Upper and lower airway inflammation, pneumonitis and non-cardiogenic pulmonary oedema	5-10 ppm
Chloroacetophenone	Crowd control agent, “tear gas”	Irritant qualities are used to incapacitate; alkylating agent	Ocular and upper airway inflammation, lower airway and parenchymal injury with massive exposure	1-10 ppm
o-Chlorobenzomalonitrile	Crowd control agent, “tear gas”	Irritant qualities are used to incapacitate	Ocular and upper airway inflammation, lower airway injury with massive exposure	
Chloromethyl ethers	Solvents, used in manufacture of other organic compounds		Upper and lower airway irritation, also a respiratory tract carcinogen	
Chloropicrin	Chemical manufacturing, fumigant component	Former First World War gas	Upper and lower airway inflammation	15 ppm
Chromic acid (Cr(IV))	Welding, plating	Water soluble irritant, allergic sensitizer	Nasal inflammation and ulceration, rhinitis, pneumonitis with massive exposure	
Formaldehyde	Manufacture of foam insulation, plywood, textiles, paper, fertilizers, resins; embalming agents; combustion products	Highly water soluble, rapidly metabolized; primarily acts via sensory nerve stimulation; sensitization reported	Ocular and upper airway irritation; bronchospasm in severe exposure; contact dermatitis in sensitized persons	3 ppm
Hydrochloric acid	Metal refining, rubber manufacturing, organic compound manufacture, photographic materials	Highly water soluble	Ocular and upper airway inflammation, lower airway inflammation only with massive exposure	100 ppm

Chemical	Sources of exposure	Important properties	Injury produced	Dangerous exposure level under 15 min
Hydrofluoric acid	Chemical catalyst, pesticides, bleaching, welding, etching	Highly water soluble, powerful and rapid oxidant, lowers serum calcium in massive exposure	Ocular and upper airway inflammation, tracheobronchitis and pneumonitis with massive exposure	20 ppm
Isocyanates	Polyurethane production; paints; herbicide and insecticide products; laminating, furniture, enamelling, resin work	Low molecular weight organic compounds, irritants, cause sensitization in susceptible persons	Ocular, upper and lower inflammation; asthma, hypersensitivity pneumonitis in sensitized persons	0.1 ppm
Mercury	Electrolysis, ore and amalgam extraction, electronics manufacture	No respiratory symptoms with low level, chronic exposure	Ocular and respiratory tract inflammation, pneumonitis, central nervous system, kidney and systemic effects	1.1 μg/m^3
Nitrogen dioxide	Silos after new grain storage, fertilizer making, arc welding, combustion products	Low water solubility, brown gas at	Ocular and upper airway inflammation, non-cardiogenic pulmonary oedema, delayed onset bronchiolitis	50 ppm
Nitrogen mustards (N); sulphur mustards (S)	Military gases	Causes severe injury, vesicant properties	Ocular, upper and lower airway inflammation, pneumonitis	20 mg/m^3 (N) 1 mg/m^3 (S)
Osmium tetroxide	Copper refining, alloy with iridium, catalyst for steroid synthesis and ammonia formation	Metallic osmium is inert, tetraoxide forms when heated in air	Severe ocular and upper airway irritation; transient renal damage	1 mg/m^3
Ozone	Arc welding, copy machines, paper bleaching	Sweet smelling gas, moderate water solubility	Upper and lower airway inflammation; asthmatics more susceptible	1 ppm
Phosgene	Pesticide and other chemical manufacture, arc welding, paint removal	Poorly water soluble, does not irritate airways in low doses	Upper airway inflammation and pneumonitis; delayed pulmonary oedema in low doses	2 ppm
Phosphoric sulphides	Production of insecticides, ignition compounds, matches		Ocular and upper airway inflammation	
Phosphoric chlorides	Manufacture of chlorinated organic compounds, dyes, gasoline additives	Form phosphoric acid and hydrochloric acid on contact with mucosal surfaces	Ocular and upper airway inflammation	10 mg/m^3
Selenium dioxide	Copper or nickel smelting, heating of selenium alloys	Strong vessicant, forms selenious acid on mucosal surfaces	Ocular and upper airway inflammation, pulmonary oedema in massive exposure	
Hydrogen selenide	Copper refining, sulphuric acid production	Water soluble; exposure to selenium compounds gives rise to garlic odour breath	Ocular and upper airway inflammation, delayed pulmonary oedema	
Styrene	Manufacture of polystyrene and resins, polymers	Highly irritating	Ocular, upper and lower airway inflammation, neurological impairments	600 ppm
Sulphur dioxide	Petroleum refining, pulp mills, refrigeration plants, manufacturing of sodium sulphite	Highly water soluble gas	Upper airway inflammation, bronchoconstriction, pneumonitis on massive exposure	100 ppm
Titanium tetrachloride	Dyes, pigments, sky writing	Chloride ions form HCl on mucosa	Upper airway injury	
Uranium hexafluoride	Metal coat removers, floor sealants, spray paints	Toxicity likely from chloride ions	Upper and lower airway injury, bronchospasm, pneumonitis	
Vanadium pentoxide	Cleaning filters of electricty production plants (using oil or coal) exposure to fly ash, oil tanks, metallurgy		Ocular, upper and lower airway symptoms	70 ppm
Zinc chloride	Smoke grenades, artillery	More severe than zinc oxide exposure	Upper and lower airway irritation, fever, delayed onset pneumonitis	200 ppm
Zirconium tetrachloride	Pigments, catalysts	Chloride ion toxicity	Upper and lower airway irritation, pneumonitis	

▶ Table 3. Poisonous, allergenic and biologically active wood varieties that can cause occupational rhinitis (adapted from the ILO Encyclopaedia of occupational health and safety, 4th edition)

Scientific names	Selected commercial names	Family	Health impairment
Abies alba Mill (A. pectinata D.C.)	Silver fir	Pinaceae	Dermatitis; conjunctivitis-rhinitis; asthma
Acacia spp. *A. harpophylla* F. Muell. *A. melanoxylon* R. Br. *A. seyal* Del. *A. shirley* Maiden	Australian blackwood	Mimosaceae	Dermatitis; conjunctivitis-rhinitis; asthma; toxic effects
Afrormosia elata Harms. (*Pericopsis elata* Van Meeuwen)	Afrormosia, kokrodua, asamala, obang, oleo pardo, bohele, mohole	Papilionaceae	Dermatitis; conjunctivitis-rhinitis; asthma
Afzelia africana Smith *A. bijuga* A. Chev. (*Intsia bijuga* A. Cunn.) *A. palembanica Bak. (Intsia palembanica* Bak.)	Doussie, afzelia, aligua, apa, chanfuta, lingue merbau, intsia, hintsy	Caesalpinaceae	Dermatitis; conjunctivitis-rhinitis; asthma
Albizzia falcata Backer *A. ferruginea* Benth. *A. lebbek* Benth *A. toona* F.M. Bail	Iatandza Kokko, siris	Mimosaceae	Dermatitis; conjunctivitis-rhinitis; asthma;
Alnus spp. A. glutinosa Gaertn.	Common alder Black alder	Betulaceae	Dermatitis; conjunctivitis-rhinitis; asthma
Andira araroba Aguiar. (Vataireopsis araroba Ducke) *A. coriacea* Pulle *A. inermis* H.B.K.	Red cabbage tree Partridge wood	Papilionaceae	Dermatitis; conjunctivitis-rhinitis; asthma
Aningeria spp. *A. robusta* Aubr. and Pell. *A. altissima* Aubr. and Pell. *Antiaris africana* Engl. *A. welwitschi* Engl.	Aningeria Antiaris, ako, chen chen	Sapotaceae Moraceae	Dermatitis; conjunctivitis-rhinitis; asthma
Aspidosperma spp. *A. peroba* Fr. All. *A. vargasii* A. DC.	Red peroba Pau marfim, pau amarello, pequia marfim, guatambu, amarilla, pequia	Apocynaceae	Dermatitis; conjunctivitis-rhinitis; asthma; toxic effects
Aucoumea klaineana Pierre	Gabon mahogany	Burseraceae	Dermatitis; conjunctivitis-rhinitis; asthma; allergic extrinsic alveolitis
Blepharocarva involucrigera F. Muell.	Rosebutternut	Anacardiaceae	Dermatitis; conjunctivitis-rhinitis; asthma
Brosimum spp. *B. guianense* Hub. (*Piratinera guianensis* Aubl.)	Snakewood, letterwood, tigerwood	Moraceae	Dermatitis; conjunctivitis-rhinitis; asthma; toxic effects
Buxus sempervirens L. *B. macowani* Oliv.	European boxwood, East London b., Cape b.	Buxaceae	Dermatitis; conjunctivitis-rhinitis; asthma; toxic effects
Callitris columellaris F. Muell.	White cypress pine	Cupressaceae	Dermatitis; conjunctivitis-rhinitis; asthma
Cassia siamea Lamk.	Tagayasan, muong ten, djohar	Caesalpinaceae	Dermatitis; conjunctivitis-rhinitis; asthma
Castanea dentata Borkh *C. sativa* Mill. *C. pumila* Mill.	Chestnut, sweet chestnut	Fagaceae	Dermatitis; conjunctivitis-rhinitis; asthma

Scientific names	Selected commercial names	Family	Health impairment
Cedrela spp. (*Toona* spp.)	Red cedar, Australian cedar	Meliaceae	Dermatitis; conjunctivitis-rhinitis; asthma
Cedrus deodara (Roxb. ex. Lamb.) G. Don (*C. libani* Barrel. lc)	Deodar	Pinaceae	Dermatitis; conjunctivitis-rhinitis; asthma
Chlorophora excelsa Benth. and Hook I. *C. regia* A. Chev. *C. tinctoria* (L.) Daub.	Iroko, gelbholz, yellowood, kambala, mvule, odum, moule, African teak, abang, tatajuba, fustic, mora	Moraceae	Dermatitis; conjunctivitis-rhinitis; asthma; allergic extrinsic alveolitis
Cryptocarya pleurosperma White and Francis	Poison walnut	Lauraceae	Dermatitis; conjunctivitis-rhinitis; asthma; toxic effects
Dacrycarpus dacryoides (A. Rich.) de Laub.	New Zealand white pine	Podocarpaceae	Dermatitis; conjunctivitis-rhinitis; asthma
Dacrydium cupressinum Soland	Sempilor, rimu	Podocarpaceae	Conjunctivitis-rhinitis; asthma
Dalbergia spp. *D. amerimnon* Benth. *D. granadillo* Pitt. *D. hypoleuca* Standl. *D. latifolia* Roxb. *D. melanoxylon* Guill. and Perr. *D. nigra* Fr. All. *D. oliveri* Gamble *D. retusa* Hemsl. *D. sissoo* Roxb. *D. stevensonii* Standl.	Ebony Red foxwood Indian rosewood, Bombay blackwood, African blackwood, pallisander, riopalissandro, Brasilian rosewood, jacaranda Burma rosewood Red foxwood Nagaed wood, Honduras rosewood	Papilionaceae	Dermatitis; conjunctivitis-rhinitis; asthma; toxic effects
Dialium spp. *D. dinklangeri* Harms.	Eyoum, eyum	Caesalpinaceae	Dermatitis; conjunctivitis-rhinitis; asthma
Diospyros spp. *D. celebica* Bakh. *D. crassiflora* Hiern *D. ebenum* Koenig	Ebony, African ebony Macassar ebony, African ebony, Ceylon ebony	Ebenaceae	Dermatitis; conjunctivitis-rhinitis; asthma; toxic effects
Dysoxylum spp. *D. fraseranum* Benth.	Mahogany, stavewood, red bean	Meliaceae	Dermatitis; conjunctivitis-rhinitis; asthma; toxic effects
Echirospermum balthazarii Fr. All. (*Plathymenia reticulata* Benth.)	Vinhatico	Mimosaceae	Dermatitis; conjunctivitis-rhinitis; asthma
Erythrophloeum guineense G. Don *E. ivorense* A. Chev.	Tali, missanda, eloun, massanda, sasswood, erun, redwater tree	Caesalpinaceae	Dermatitis; conjunctivitis-rhinitis; asthma; toxic effects
Eucalyptus spp. *E. delegatensis* R.T. Back *E. hemiphloia* F. Muell. *E. leucoxylon* Maiden *E. maculata* Hook. *E. marginata* Donn ex Sm. *E. microtheca* F. Muell. *E. obliqua* L. Herit. *E. regnans* F. Muell. *E. saligna* Sm.	Alpine ash Grey box Yellow gum Spotted gum Mountain ash	Myrtaceae	Dermatitis; conjunctivitis-rhinitis; asthma
Euxylophora paraensis Hub.	Boxwood	Rutaceae	Dermatitis; conjunctivitis-rhinitis; asthma

Scientific names	Selected commercial names	Family	Health impairment
Excoecaria africana M. Arg. (*Spirostachys africana* Sand) *E. agallocha* L.	African sandalwood, tabootie, geor, aloewood, blind-your-eye	Euphorbiaceae	Dermatitis; conjunctivitis-rhinitis; asthma; toxic effects
Fagara spp. *F. flava* Krug and Urb. (Zanthoxylum flavum Vahl.) *F. heitzii* Aubr. and Pell. *F. macrophylla* Engl.	Yellow sanders, West Indian satinwood, atlaswood, olon, bongo, mbanza	Rutaceae	Dermatitis; conjunctivitis-rhinitis; asthma; toxic effects
Fagus spp. (Nothofagus spp.) *F. sylvatica* L.	Beech	Fagaceae	Dermatitis; conjunctivitis-rhinitis; asthma
Gonioma kamassi E. Mey.	Knysna boxwood, kamassi	Apocynaceae	Dermatitis; conjunctivitis-rhinitis; asthma; toxic effects
Gonystylus bancanus Baill.	Ramin, melawis, akenia	Gonystylaceae	Dermatitis; conjunctivitis-rhinitis; asthma; allergic extrinsic alveolitis
Gossweilerodendron balsamiferum (Verm.) Harms.	Nigerian cedar	Caesalpinaceae	Dermatitis; conjunctivitis-rhinitis; asthma
Guaiacum officinale L.	Gaiac, lignum vitae	Zygophyllaceae	Dermatitis; conjunctivitis-rhinitis; asthma
Guarea spp. *G. cedrata* Pell. *G. laurentii* De Wild. *G. thompsonii* Sprague	Bossé Nigerian pearwood, Cedar mahogany Scented guarea Black guarea	Meliaceae	Dermatitis; conjunctivitis-rhinitis; asthma; toxic effects
Hippomane mancinella L.	Beach apple	Euphorbiaceae	Dermatitis; conjunctivitis-rhinitis; asthma; toxic effects
Juglans spp. *J. nigra* L. *J. regia* L.	Walnut	Juglandaceae	Dermatitis; conjunctivitis-rhinitis; asthma
Juniperus sabina L. *J. phoenicea* L. *J. virginiana* L.	Virginian pencil cedar, Eastern red cedar	Cupressaceae	Dermatitis; conjunctivitis-rhinitis; asthma; toxic effects
Laburnum anagyroides Medic. (Cytisus laburnum L.) *L. vulgare* Gris	Laburnum	Papilionaceae	Dermatitis; conjunctivitis-rhinitis; asthma; toxic effects
Larix spp. *L. decidua* Mill. *L. europea* D.C.	Larch European larch	Pinaceae	Dermatitis; conjunctivitis-rhinitis; asthma
Lovoa trichilioides Harms. (*L. klaineana* Pierre)	Dibetou, African walnut, apopo, tigerwood, side	Meliaceae	Dermatitis; conjunctivitis-rhinitis; asthma; toxic effects
Lucuma spp. (*Pouteria* spp.) *L. procera*	Guapeva, abiurana Massaranduba	Sapotaceae	Dermatitis; conjunctivitis-rhinitis; asthma
Mansonia altissima A. Chev.	Nigerian walnut	Sterculiaceae	Dermatitis; conjunctivitis-rhinitis; asthma; toxic effects
Melanoxylon brauna Schott	Brauna, grauna	Caesalpinaceae	Dermatitis
Microberlinia brazzavillensis A. Chev. *M. bisulcata* A. Chev.	African zebrawood	Caesalpinaceae	Dermatitis; conjunctivitis-rhinitis; asthma; toxic effects
Millettia laurentii De Wild. *M. stuhlmannii* Taub.	Wenge Panga-panga	Papilionaceae	Dermatitis; conjunctivitis-rhinitis; asthma; toxic effects

Scientific names	Selected commercial names	Family	Health impairment
Mimusops spp. (Manilkara spp.) *Mimusops* spp. (*Dumoria* spp.) (*Tieghemella* spp.) *M. congolensis* De Wild. (*Autranella congolensis* A. Chev.) *M. djave Engl.* (Baillonella toxisperma Pierre) *M. heckelii* Hutch. et Dalz. (*Tieghemella heckelii* Pierre) (*Dumoria heckelii* A. Chev.)	Muirapiranga Makoré Mukulungu, autracon Moabi Cherry mahogany	Sapotaceae	Dermatitis; conjunctivitis-rhinitis; asthma; allergic extrinsic alveolitis; toxic effects
Mitragyna ciliata Aubr. and Pell. *M. stipulosa* O. Ktze	Vuku, African poplar Abura	Rubiaceae	Allergic extrinsic alveolitis; toxic effects
Nauclea diderrichii Merrill (Sarcocephalus diderrichii De Wild.) *Nauclea trillessi* Merrill	Bilinga, opepe, kussia, badi, West African boxwood	Rubiaceae	Dermatitis; conjunctivitis-rhinitis; asthma; toxic effects
Ocotea spp. O. *bullata* E. Mey O. *porosa* L. Barr. (*Phoebe porosa* Mez.) O. *rodiaei Mez. (Nectandra rodiaei* Schomb.) O. *rubra* Mez. O. *usambarensis* Engl.	Stinkwood Laurel Brazilian walnut Greenheart Louro vermelho East African camphorwood	Lauraceae	Dermatitis; conjunctivitis-rhinitis; asthma; toxic effects
Paratecoma spp. *P. alba* *P. peroba Kuhlm.*	Brazilian white peroba Peroba white. p.	Bignoniaceae	Dermatitis; conjunctivitis-rhinitis; asthma; toxic effects
Phyllanthus ferdinandi F.v.M.	Lignum vitae, chow way, tow war	Euphorbiaceae	Dermatitis; conjunctivitis-rhinitis; asthma
Picea spp. *P. abies* Karst. *P. excelsa* Link. *P. mariana* B.S.P. *P. polita* Carr.	European spruce, whitewood Black spruce	Pinaceae	Dermatitis; conjunctivitis-rhinitis; asthma; allergic extrinsic alveolitis
Pinus spp. *P. radiata* D. Don	Pine	Pinaceae	Dermatitis; conjunctivitis-rhinitis; asthma
Piptadenia africana Hook f. *Piptadeniastrum africanum Brenan*	Dabema, dahoma, ekhimi agobin, mpewere, bukundu	Mimosaceae	Dermatitis; conjunctivitis-rhinitis; asthma
Pometia spp. *P. pinnata* Forst.	Taun Kasai	Sapindaceae	Dermatitis; conjunctivitis-rhinitis; asthma
Populus spp.	Poplar	Salicaceae	Dermatitis; conjunctivitis-rhinitis; asthma
Prunus spp. *P. serotina* Ehrl.	Cherry Blackcherry	Rosaceae	Dermatitis; conjunctivitis-rhinitis; asthma
Pseudotsuga douglasii Carr. (P. menziesii Franco)	Douglas fir, red fir, Douglas spruce	Pinaceae	Dermatitis; conjunctivitis-rhinitis; asthma
Pterocarpus spp. *P. angolensis* D.C. *P. indicus* Willd. *P. santalinus* L.f. (*Vatairea guianensis* Aubl.)	African padauk, New Guinea rosewood, red sandalwood, red sanders, quassia wood	Papilionaceae	Dermatitis; conjunctivitis-rhinitis; asthma; toxic effects

Scientific names	Selected commercial names	Family	Health impairment
Quercus spp.	Oak	Fagaceae	Dermatitis; conjunctivitis-rhinitis; asthma
Rauwolfia pentaphylla Stapf. O.	Peroba	Apocynaceae	Dermatitis; conjunctivitis-rhinitis; asthma; toxic effects
Sandoricum spp. *S. indicum* Cav.	Sentul, katon, kra-ton, ketjapi, thitto	Meliaceae	Dermatitis; conjunctivitis-rhinitis; asthma; toxic effects
Sequoia sempervirens Endl.	Sequoia, California redwood	Taxodiaceae	Dermatitis; conjunctivitis-rhinitis; asthma; toxic effects
Swietenia spp. S. *macrophylla* King S. *mahogany* Jacq.	Mahogany, Honduras mahogany, Tabasco m., baywood, American mahogany, Cuban mahogany	Meliaceae	Dermatitis; conjunctivitis-rhinitis; asthma; allergic extrinsic alveolitis; toxic effects
Tabebuia spp. *T. ipe* Standl. (T. avellanedae Lor. ex Gris.) *T. guayacan* Hensl. (*T. lapacho* K. Schum)	Araguan, ipé preto, lapacho	Bignoniaceae	Dermatitis; conjunctivitis-rhinitis; asthma; toxic effects
Taxus baccata L.	Yew	Taxaceae	Dermatitis; conjunctivitis-rhinitis; asthma; allergic extrinsic alveolitis; toxic effects
Tecoma spp. *T. araliacea* D.C. *T. lapacho*	Green heart, Lapacho	Bignoniaceae	Dermatitis; conjunctivitis-rhinitis; asthma; toxic effects
Tectona grandis L.	Teak, djati, kyun, teck	Verbenaceae	Dermatitis; conjunctivitis-rhinitis; asthma; allergic extrinsic alveolitis
Terminalia alata Roth. *T.* superba Engl. and Diels.	Indian laurel, limba, afara, ofram, fraké, korina, akom	Combretaceae	Dermatitis; conjunctivitis-rhinitis; asthma
Thuja occidentalis L. *T. plicata* D. Don *T. standishii* Carr.	White cedar Western red cedar	Cupressaceae	Dermatitis; conjunctivitis-rhinitis; asthma; toxic effects
Tieghemella africana A. Chev. (*Dumoria* spp.) *T. heckelii* Pierre	Makoré, douka, okola, ukola, makoré, abacu, baku, African cherry	Sapotaceae	Dermatitis; conjunctivitis-rhinitis; asthma; toxic effects
Triplochiton scleroxylon K. Schum	Obeche, samba, wawa, abachi, African whitewood, arere	Sterculiaceae	Dermatitis; conjunctivitis-rhinitis; asthma
Xylia dolabriformis Benth.		Mimosaceae	Conjunctivitis-rhinitis;

▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
2.1.11	Allergic rhinitis	J30.3	CA08.03
2.1.11	Allergic sinusitis	J32.8	CA0A.Z
2.1.11	Allergic pharyngitis	J31.2	CA09.2
2.1.11	Allergic laryngitis	J38.7	CA0H.Z
2.1.11	Upper airways irritation	J68.2	CA81.2
	Occupational exposure to risk factors	Z57	QD84

2.2. Skin diseases

2.2.1 Allergic contact dermatoses and contact urticaria caused by other recognized allergy provoking agents arising from work activities not included in other items

ICD Code L23, L56.2, L56.8, L50.6 +Z57

Short profile of the aetio-pathogenesis

Allergic occupational dermatoses are classified in two sub-groups, based on the involved causal mechanism: (a) allergic contact dermatitis (ACD), that includes photoallergic contact dermatitis (PACD) and protein contact dermatitis (PCD); and (b) contact urticaria (CU). Occupational ACD is a delayed hypersensitivity reaction (type IV, T cell-mediated) to work-related skin sensitizers. In PACD, a contact agent in the presence of UV or visible light induces or elicits a delayed hypersensitivity skin reaction. Occupational CU caused by an allergen is an immediate-type, immunoglobulin IgE-mediated skin reaction to proteins following external contact. In addition, non-immunological mechanisms of CU exist. PCD combines clinical and pathogenetic features of both ACD and CU.

Causal agents are either proteins, which are per se allergenic or small molecular substances (haptens or incomplete allergens) that can cause sensitization only after having been covalently linked with carrier molecules, mainly proteins. Since sensitization is not dependent on dose, some factors may increase the risk, in detail:

- individual susceptibility;
- chemical structure of the sensitizing agent, its concentration and formulation;
- site and extent of contact; and
- climatic conditions: e.g. temperature, humidity, sunlight (ultraviolet radiation).

The substances responsible for occupationally caused allergic dermatoses are classified as:

- macromolecules: substances of animal (mainly proteins from shellfish, fish, amniotic fluid and milk) or of plant origin (e.g. proteins from fresh fruits, legumes including peanuts, natural rubber latex);
- low molecular mass substances: natural organic substances, such as plant fragrances; synthetic chemicals, such as rubber and plastic accelerators, resins, hardeners; organic dyes and dye intermediates (e.g. p-phenylene-diamine), several drugs (e.g. benzodiazepines, penicillin and cephalosporin antibiotics); metals and their compounds (e.g. nickel, chromate, cobalt); preservatives and disinfectants; and
- photoallergens (e.g. UV-filters, drugs, plants, fragrances), such as halogenated salicylanilides, p-aminobenzoic acid, sandalwood oil, or hexachlorophene.

Examples of photoreactive chemicals are coal tar distillation products, such as creosote, pitch and anthracene. Members of the plant family *Umbelliferae* are well known photoreactants. Family members include cow parsnip, celery, wild carrot, fennel and dill. The reactive agent in these plants are psoralens.

Occupational exposures

Allergic contact dermatoses may occur in workers exposed to antigens and haptens. Below is a non-exhaustive list of occupations at risk:

- ACD: construction workers, painters, workers exposed to resins, dental technicians, florists, forestry workers, gardeners, beauticians, hairdressers, medical personnel, metal workers, printers, rubber workers, textile workers; cleaning/housekeeping.
- PACD: outdoor workers, UV-exposed indoor workers.
- PCD/CU: farmers, veterinarians, cooks, fishermen, workers in food processing.

Main health effects and diagnostic criteria

Name of the diseases and ICD code: **Allergic contact dermatitis (ACD) (L23 +Z57)**

Short description of the disease

Occupational ACD is an eczematous skin reaction due to a delayed type IV hypersensitivity to work-related contact allergens. ACD presents as a pruritic eczema, characterized by erythema and vesicles, which develops within 24-48 hours from exposure at the site of hapten penetration in sensitized individuals. ACD is less common in work places than irritant contact dermatitis. Pre-existing skin irritation promotes the development of ACD. Albeit sensitization can be induced even by a single contact with the compound, in occupational settings it usually takes place after some months of repeated contacts or, in some cases, even after many years.

2.2.1 Allergic contact dermatoses and contact urticaria caused by other recognized allergy provoking agents arising from work activities not included in other items

ICD Code L23, L56.2, L56.8, L50.6 +Z57

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: redness, swelling, vesicles, oozing and crusting (acute eczematous reaction) of the skin. The development of the skin lesions are in direct relationship to the work activities, with a pattern of recurrence of the disease on re-exposure to the same agent. Through a cumulative effect, repeated contact with both weak and moderate allergens/haptens can cause a subacute form of contact dermatitis characterized by dry, red plaques. If the exposure continues, the dermatitis will become chronic. Features of chronic ACD are dry, thickened and scaly skin, cracking and fissuring of the fingers and palms, chronic nail dystrophy (chronic eczematous reaction). Itch (pruritus) is usually present.
- Examinations:
  - Lesions are localized at allergen contact sites, but often spread in the surrounding area or even to other body sites. Occupational ACD is mainly found on the hands. Upon exposure to volatile allergens or by transference from the hands it may occur at the face, neck, arms. The involved areas must be carefully examined. Note should be taken of the severity and stage of the dermatitis, of its precise distribution and of its degree of interference with function. A complete skin examination must be performed, looking for tell-tale stigmata of psoriasis, atopic dermatitis, lichen planus, tinea, etc., which may signify that the dermatitis is not of occupational origin.
  - Patch tests should be performed by a specialized physician, according to relevant guidelines (such as those listed in the 'further reading'), when confronted by suspected skin sensitization. This diagnostic approach might bring about sensitization and the testing concentration should be defined according to specific recommendations. If patch testing a patient's own products, a meticulous decision on the modalities (including concentrations used) is pivotal, together with characterization of components within that product: these aspects have to be kept in mind to avoid the risk of causing active sensitization or irritant effects, which might confound the interpretation of the results.

Exposure assessment

- History of occupational exposure: confirmed previous occupational exposure (at least one episode) to the allergenic substance, and onset of signs and symptoms as a consequence of subsequent exposures. A dose-effect relationship in the onset of allergic contact dermatitis can usually be shown. In general, induction of sensitization needs higher levels of exposure than elicitation.
- Minimum duration of exposure: usually several instances of exposure are required over long periods for sensitization but in exceptional cases even a single contact might be sufficient, in particular for potent sensitizers, such as dinitrochlorobenzene, dinitrofluorobenzene, p-phenylene-diamine, epoxy resins or (meth-) acrylates. For elicitation of ACD in sensitized individuals, a skin contact with the allergen of a few minutes to several hours may give rise to skin reactions.
- Maximum latent period: in sensitized subjects any further exposure to the agent causes the onset of clinical signs usually within 12-72 hours, or even later (up to 1-2 weeks).

The table that follows summarizes some main features of allergic contact dermatitis:

Feature	Allergic contact dermatitis
Mechanism of production	Delayed-type cellular immunity (Gell and Coombs type IV)
Potential victims	A minority of individuals
Onset	Rapid, within 12-48 hours in sensitized individuals
Signs	Acute to subacute eczema with erythema, oedema, bullae and vesicles
Symptoms	Pruritus
Concentration of contactant	Low
Investigation	History and examination / positive patch tests

2.2.1 Allergic contact dermatoses and contact urticaria caused by other recognized allergy provoking agents arising from work activities not included in other items

ICD Code L23, L56.2, L56.8, L50.6 +Z57

Name of the diseases and ICD code: **Photoallergic contact dermatitis (PACD) (L56.8 +Z57)**

Short description of the disease

Most photoreactions on the skin are phototoxic. Either natural or artificial UV-light sources alone or in combination with various chemicals, plants or drugs can induce a phototoxic or photosensitive response. Phototoxic reaction is generally limited to light-exposed areas while photosensitive reaction can develop frequently on non-exposed body surfaces but primarily involves the face and backs of the hands. Photoallergic contact dermatitis (PACD) presents in patients after skin is co-exposed to certain exogenous agents and to ultraviolet and visible light.

Diagnostic criteria

Refer to item 1.2.5.

Name of the diseases and ICD code: **Contact urticaria (CU) (L50.6 +Z57)**

Short description of the disease

Urticaria may appear as a cutaneous manifestation of localized non-pitting oedema and involves only the superficial portion of the dermis. Occupational CU is an immediate itchy wheal and flare reaction at the contact site to proteinaceous material and occasionally chemicals (e.g. metals, preservatives, drugs) which may spread and cause extracutaneous symptoms. Contact urticaria to allergens is a type I allergic response and the reaction is immediate, occurring within about 15 minutes after contact with the relevant substance. Proteins causing occupational CU can be assigned to (1) vegetal proteins, (2) animal proteins, (3) enzymes. The most common sites for urticaria are the extremities and face but may involve any area of the body from the scalp to the soles of the feet. Urticarial eruptions are distinctly pruritic and appear in crops with a variable duration of minutes to 24 hours. By contrast, physical urticarias (cold, cholinergic, dermatographism/friction, pressure), which are not infrequently elicited occupationally, have to be distinguished from (immunologic) contact urticaria.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: acute wheals and flare skin reactions (urticaria) and itch within minutes after exogenous allergen contact. Contact urticaria has a duration of minutes to 24 hours. Occasionally, it may develop into generalized urticaria and affect internal organs such as in anaphylaxis (CU syndrome, grade 2 onward). The pathology of urticaria is characterized by oedema of the superficial dermis. Particular care is needed in the investigation of subjects with systemic symptoms.
- Examinations (it is not necessary to conduct all tests):
  - Open application test on the skin or rubbing test on intact and lesional skin.
  - Skin prick tests with fresh material from the workplace and commercial reagents.
  - Measurement of specific IgE in serum.

Exposure assessment

- History of occupational exposure: confirmed previous occupational exposure (at least one episode) to the allergenic substance (proteinaceous material and occasionally chemicals), and onset of signs and symptoms as a consequence of subsequent exposures.
- Minimum duration of exposure: the sensitization period is generally 10 to 15 days. After sensitization, any further exposure causes the onset of clinical signs in allergic subjects within 15 to 30 min.
- Maximum latent period: in sensitized subjects any further exposure to the agent causes the onset of clinical signs usually within hours, not longer than one day.

Name of the diseases and ICD code: **Protein contact dermatitis (PCD) (L23.8 +Z57)**

Short description of the disease

PCD is an eczematous reaction to protein-containing material often in food handlers. Occupational PCD is a chronic or recurrent dermatitis induced upon skin contact with proteins.

2.2.1 Allergic contact dermatoses and contact urticaria caused by other recognized allergy provoking agents arising from work activities not included in other items

ICD Code L23, L56.2, L56.8, L50.6 +Z57

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: PCD usually presents as a chronic hand dermatitis that may extend to wrists and forearms with eczematous lesions at the allergen contact sites. An urticarial or vesicular exacerbation is often noted in sensitized individuals within minutes after contact with the causative protein on previously affected skin. PCD may cause chronic paronychia.
- Examinations (it is not necessary to conduct all tests):
  - Open application test and rubbing test on intact and lesional skin.
  - Skin prick tests with fresh material from the work place and commercial reagents.
  - Measurement of specific IgE in serum.
  - Patch tests may be negative.

Exposure assessment

- History of occupational exposure: confirmed previous occupational exposure (at least one episode) to the allergenic substance (protein-containing material), and onset of signs and symptoms as a consequence of subsequent exposures. An impaired skin barrier due to endogenous (e.g. atopic dermatitis) and exogenous (e.g. wet work, solvents, detergents and occlusion) factors may promote the penetration of proteins.
- Minimum duration of exposure: normally, several instances of exposure are required over long periods for sensitization. For elicitation of PCD in sensitized individuals a skin contact with the allergen of a few minutes to several hours may give rise to skin reactions.
- Maximum latent period: the sensitization period is generally 10 to 15 days. After sensitization, any further exposure causes the onset of eczematous lesions within 12-48 hours in allergic subjects. Immediate clinical signs (wheals and vesicles) and pruritus may occur within 10 to 30 min.

Key actions for prevention	Primary preventive measures include identification of the materials and activities that may cause allergic dermatoses with elimination or substitution for safer alternatives where possible. Working practices should avoid contact with harmful substances by engineering controls, use of equipment to avoid direct contact and personal protective equipment, including carefully selected gloves. In UV-exposed workplaces, adequate clothing and sunscreens should be made available. Training in glove use and skin care should be provided especially to workers at greater risk. Suitable breaks from work that requires sustained use of gloves should be arranged to avoid skin maceration, since this increases the risk of skin inflammation and sensitization. Pre-work barrier creams must not be relied upon as a substitute for gloves. Washing facilities with mild hand cleaners and skin conditioning cream should be made available. In health care, alcohol rubs should be preferred to hand washing.

2.2.1 Allergic contact dermatoses and contact urticaria caused by other recognized allergy provoking agents arising from work activities not included in other items

ICD Code L23, L56.2, L56.8, L50.6 +Z57

Further reading

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▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
2.2.1	Allergic contact dermatitis (ACD)	L23	EK00
2.2.1	Photoallergic contact dermatitis (PACD)	L56.8	EK01
2.2.1	Contact urticaria (CU)	L50.6	EB01.3
2.2.1	Protein contact dermatitis (PCD)	L23.8	EK11
	Occupational exposure to risk factors	Z57	QD84.Y

2.2.2 Irritant contact dermatoses caused by other recognized irritant agents arising from work activities not included in other items

ICD Code L24, T20-T25, T29-T32, +Z57

Short profile of the aetio-pathogenesis	Irritant contact dermatoses are a group of non-allergic skin reactions of various degrees confined to the areas exposed to the irritant, especially hands and arms. The characteristics of the disease vary according to the type of exposure, its intensity, and the characteristics of the causal agent. The manifestation varies from acute skin burns and erosions to chronic eczematous manifestations. The term "contact irritant" refers to an agent that is capable of causing cell damage (cytotoxicity) if it contacts the skin for sufficient time and in sufficient concentration. Corrosive substances and preparations such as acids (both inorganic and organic), alkali (e.g. sodium hydroxide) or other agents (e.g. wet cement, phenolic compounds, peroxides, halogenated solvents) can cause severe irritant damage on contact with living tissues, including chemical burns. The corrosive potential of substances depends on their chemical properties, concentration, pH, and duration and type of skin contact. Usually these substances can cause irritation at low concentrations and be corrosive at higher concentrations. Some physical agents are intrinsically capable of producing an irritation reaction, such as, for example, dusts in contact with the mucous membranes of the eyes or respiratory tract or even by cutaneous friction. Less concentrated acids and alkalis as well as other non-corrosive irritants (defatting agents, such as solvents, soaps and detergents, cooling fluids, fragrances or proteolytic enzymes in food) cause inflammation, irritant contact dermatitis (ICD) through immediate, prolonged or repeated contact with the skin. However, the most frequent cause of chronic ICD is "wet work", i.e., a regular and sustained contact with fluids or sustained wearing of occlusive gloves. In addition, some physical agents, such as dust or other mechanical stressors (heat, friction, abrasion and pressure), in particular conditions, can cause skin and mucous irritation. Irritant factors are the physical and chemical nature of the contact substance, the concentration, quantity, duration and frequency of skin contact. Individual workers may have characteristics that affect the susceptibility to irritation, these include genetic associations (e.g. filaggrin mutations) and skin type, whilst sex and age also influence irritant resposnses. The skin contact site is relevant to the likelihood of irritant effects (e.g. the thin facial skin relative to the thick epidermis of the soles of the feet). The circumstances of exposure such as seasonal changes may affect the skin barrier (e.g. environmental temperature, humidity and ultraviolet light). Winter weather is in general associated with dry skin and increased susceptibility to skin irritation. By contrast, in warmer weather increased humidity and sweat may aid the penetration of substances in contact with the skin. Similarly occlusive clothing or personal protection such as gloves or footwear may enhance penetration of substances that manage to gain entry inside due to incorrect usage. Direct mechanical friction through microabrasion from irritant dusts or the physical action of hard surface abrasion can elicit skin irritation.
Occupational exposures	The prevalence of occupational dermatoses rises as high as 20% in many high risk occupations. 90–95% of occupational dermatoses consists of contact dermatitis and, among this, irritant contact dermatitis represents the majority. The principal occupational irritants are mainly grouped into soaps and detergents, alkalis and acids, metalworking fluids (cutting oils), organic solvents, other petroleum products, oxidizing agents, reducing agents, pharmaceutical products, cement, fibreglass and wood preservatives, mould release oil, animal and plant products, and physical factors, such as cold weather, friction and low relative humidity, as well as desiccant powders. Irritant contact dermatoses may occur in individuals exposed to irritant agents or irritant work tasks shown in the table below. The list that follows is not intended to be comprehensive: new materials and processes might expose workers to new irritants and risks.

2.2.2 Irritant contact dermatoses caused by other recognized irritant agents arising from work activities not included in other items

ICD Code L24, T20-T25, T29-T32, +Z57

Occupation	Irritant
Agriculture workers	Artificial fertilizers, disinfectants, pesticides, cleaners, gasoline, diesel oil, plants and grains
Artists	Solvents, clay, plaster
Bakers and confectioners	Flour, detergents
Bartenders	Detergents, wet work
Bookbinders	Solvents, glues
Butchers	Detergents, meat, waste
Cabinet makers, and carpenters	Glues, detergents, thinners, solvents, wood preservatives
Cleaners and janitors	Detergents, solvents, wet work
Coal miners	Dust (coal, stone), wet conditions
Construction workers	Cement
Cooks, caterers and food handlers	Detergents, vegetable juices, wet work
Dentists and dental technicians	Detergents, hand cleansers, wet work
Dry cleaners	Solvents
Electricians	Soldering fluxes
Electroplaters	Acids, alkalis
Floor-layers	Solvents
Florists and gardeners	Manure, artificial fertilizers, pesticides, wet work
Hairdressers and beauticians	Permanent wave solutions, shampoos, bleaching agents, wet work
Health workers	Detergents, disinfectants, foods, wet work
Homemakers	Detergents, cleansers, foods, wet work
Jewellers	Detergents, solvents
Machinists, automobile and aircraft industry workers	Solvents, cutting oils, paints, hand cleansers
Mechanics	Oils, greases, gasoline, diesel fuel, cleaners, solvents
Metal workers	Cutting oils, solvents, hand cleansers
Office workers	Solvents (photocopiers, adhesives)
Painters	Solvents, thinners, wallpaper adhesives, hand cleansers
Photography industry workers	Solvents, wet work
Plastics workers	Solvents, acids, oxidizing agents
Printers	Solvents
Rubber workers	Solvents, talc, zinc stearate, uncured rubber
Shoemakers	Solvents, waxes
Tannery workers	Acids, alkalis, reducing and oxidizing agents, wet work
Textile workers	Fibres, bleaching agents, solvents
Veterinarians, farmers and slaughterhouse workers	Disinfectants, wet work, animal entrails and secretions

(Table from: https://www.ccohs.ca/oshanswers/diseases/dermatitis.html)

2.2.2 Irritant contact dermatoses caused by other recognized irritant agents arising from work activities not included in other items

ICD Code L24, T20-T25, T29-T32, +Z57

Main health effects and diagnostic criteria

Name of the diseases and ICD code: **Irritant contact dermatitis (L24) +Z57, Burns and corrosions (T20-T25, T29-T32) +Z57**

Short description of the disease

Occupational irritant contact dermatitis (ICD) is a very common acquired non-allergic eczematous skin reaction of various degrees confined to the areas exposed to the irritant, especially hands and arms. It consists in an inflammation caused by substances found in the workplace that come in direct contact with the skin. A chemical burn is an acute, severe irritant reaction of the skin caused by corrosive substances that severely damage the cells, potentially leading to cell death.

Irritant contact dermatitis can be divided into acute and chronic dermatitis. Acute irritant contact dermatitis is commonly the result of a single short-time, high-intensity exposure to an irritant (e.g. acids like sulphuric acid, or bases such as sodium hydroxide). Chronic irritant dermatitis usually develops as a result of a repeated or prolonged, low-level exposure to a single irritant or to mixtures, resulting in disruption of the skin barrier function (e.g. water, soaps and detergents or cleaning agents in particular solvents). In either case the damage to the skin barrier increases susceptibility to further irritation. The typical features of dermatitis of redness, dryness, scaling, cracking, fissures, vesicles or blisters with weeping, and accompanied by itching are usually present. In the absence of ongoing irritation the skin damage may heal in a few weeks, however with repeated irritant insults chronicity may develop. Secondary infection is a possibility that may aggravate the dermatitis. Chronic irritant dermatitis may show lichenification resulting from rubbing or scratching due to itching.

Damage to the skin barrier results in increased transepidermal water loss and this disruption itself is associated with increased immunological activation and inflammation. The loss of integrity of the skin facilitates further entry of irritants thereby inciting ongoing inflammation. However experimental data have shown that the particular inflammatory response can be specific to the irritant as identified by different cytokine profiles between irritant substances. Typically, an irritant reaction develops within minutes or a few hours from exposure and is at its worst after approximately 24 hours. The table that follows summarises some key features of acute ICD.

Feature	Irritant contact dermatitis
Mechanism of production	Direct cytotoxic effect
Potential victims	Everyone
Onset	Progressive, after repeated or prolonged exposure
Signs	Subacute to chronic eczema with erythema, desquamation and fissures
Symptoms	Pain and burning sensation
Concentration of contactant	High
Investigation	History and examination

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: range from simple irritation (redness, itching, scaling, minor erythema) to severe (third-degree) chemical burns (corrosion), including erythema, swelling, blisters, oozing and crusting. If the disease evolves into chronic dermatitis, its main features are desquamation, thickening and lichenification of the skin with painful fissures. Lesions are confined to the areas exposed to the irritants, mainly the hands and arms. Volatile irritants may cause airborne lesions in uncovered skin areas, like the face and neck. Signs are usually accompanied by pain and burning sensations.

  The clinical manifestations vary according to the intensity of the irritants and the characteristics of the exposure patterns:

  - Exposure to *"strong irritants" and corrosive agents (strong alkalis and acids)* cause local reversible inflammatory reaction immediately following a single application or severe chemical burns that may lead to scarring.
  - Exposure to *"relatively mild irritants" (mild alkali and acids, detergents)* can cause irritation of superficial skin layers. Contact with substances provoking defatting of the skin usually causes dermatitis after prolonged exposure. Physical factors and multiple chemical exposures often play a role.
  - *Repeated long-term exposure* can lead to thickening and lichenification of the skin (with painful fissures) after days or weeks of continuous mild irritation, which can evolve into chronic dermatitis. Account should be taken of the possibility of splashes, and of immersion where occlusion increases the irritation (for instance: under rubber or plastic gloves or soaked clothes).
- Examinations: exclusion of allergic contact dermatitis on appropriate patch testing.

2.2.2 Irritant contact dermatoses caused by other recognized irritant agents arising from work activities not included in other items

ICD Code L24, T20-T25, T29-T32, +Z57

Exposure assessment

- History of occupational exposure: confirmed occupational skin contact with a potentially irritating substance. Water and lipid solubility of the substance, concentration, pH value, duration of exposure, interaction with other substances, sweating, dryness, occlusion, friction, laceration of the skin, ambient temperature and humidity can contribute to the occurrence and severity of the lesion.
- Minimum duration of exposure: extremely variable (from minutes to hours, weeks or even months) depending on the intensity of exposure and the types of irritants.
- Maximum latent period: the symptoms appear immediately or within 48 hours after the exposure.

Key actions for prevention	The application of the hierarchy of controls can be used effectively for the prevention of occupational irritant contact dermatitis: • Elimination of the harmful exposures where substances are not necessary to the work such as abrasive skin cleaning agents; or those soaps containing irritant disinfectants; or the use of a dishwasher rather than washing up by hand in catering work. • Substitution with less harmful substance or agents, the use of non-powdered, non-latex gloves in healthcare and other occupations has been a highly successful intervention. • Engineering controls might include the use of spray booths for spray painting, local exhaust ventilation with dry sanding, control of hand washing water temperature with thermostatic mixer valves. • Administrative and work-practice controls – these can include methods to ensure that workers are provided with tools or equipment that place them at further distance from skin contact irritants (e.g. tongs or scoops rather than only gloved hands). Procedures and controls in place for spillages. Training on work practices, workplace hazardous materials information systems and the recognition and reporting of skin conditions. • Personal protective equipment (PPE) must be chosen with knowledge of the required protection since materials have breakthrough times which in some cases may be shorter than the time spent on a task. The correct donning and doffing, storage and replacement of PPE is essential to avoid contamination and transference to other skin surfaces. So called "barrier creams" are not considered PPE; however skin conditioning creams are useful to maintain skin hydration following handwashing. Secondary prevention measures would include skin health surveillance which may involve the use of questionnaires for workers, self reporting or inspection by a suitably trained person to allow early referral for medical attention and advice. Tertiary prevention should minimise and prevent impairment arising from diagnosed occupational irritant contact dermatitis. In addition to medical treatment and management, prevention will require the implementation of control measures similar to those mentioned above to avoid recurrence of the condition.

2.2.2 Irritant contact dermatoses caused by other recognized irritant agents arising from work activities not included in other items

ICD Code L24, T20-T25, T29-T32, +Z57

Further reading

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▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
2.2.2	Irritant contact dermatitis	L24	EK02
2.2.2	Burns and corrosions	T20-T25, T29-T32	ND9Y,ND9Z,EK5Y, NE10
	Occupational exposure to risk factors	Z57	QD84.Y

2.2.3 Vitiligo caused by other recognized agents arising from work activities not included in other items — ICD Code L81.5 +Z57

Short profile of the aetio-pathogenesis	The aetiology of vitiligo is poorly understood. Investigations so far suggest that a number of factors may contribute to the development of this disease, such as: autoimmune disorders (in which the immune system becomes overactive and destroys the melanocytes), genetic factors that render the melanocyte fragile, stress, sunburns, cuts, some chemicals, neural causes, heredity (as it may run in families), and viruses. Vitiligo is not contagious. When subjected to the above-mentioned instigating factors, susceptible, fragile melanocytes undergo apoptosis. Autoimmune factors then perpetuate the removal of the melanocyte component from the skin. In the majority of cases, the instigating factors are not known (idiopathic vitiligo); however a small subset of individuals develop contact/occupational (or secondary) vitiligo, following exposure to particular chemicals which are cytotoxic to pigmented cells. Many phenolic/catecholic derivatives have been demonstrated to be preferentially cytotoxic to melanocytes, with high-dose exposure resulting in the initiation of apoptosis. The susceptibility of individuals to depigmentation when exposed to these agents shows variation suggesting a genetic predisposition. In the working environment, chemical agents involved in the development of occupational vitiligo belong to the following groups: 1) phenols (e.g. *p*-tert-butyl phenol, *p*-tert-amyl phenol, *p*-cresol, *o*-phenyl phenol, chloro-2 amino-4 phenol); 2) catechols (e.g. catechol or pyrocatechol, menthyl catechol or *o*-hydroxyanisole, 4-isopropyl catechol); and 3) benzoquinone, hydroquinone, 4-benzyloxyphenol (monobenzone).
Occupational exposures	Many chemicals cytotoxic to melanocytes are used in the industrial production of leather, plastics, soap, printing ink, detergents, photographic chemicals, etc. Most of them are used as antioxidants. Exposure may thus take place mainly in the chemical and photographic industries. Moreover, these chemicals are often added to cosmetics, dyes, deodorant, spray perfume, detergents and cleansers, pharmaceuticals, adhesives, neoprene glues, rubber, disinfectants, germicides and insecticides. In the past, skin-decolouring agents were used for cosmetic purposes, especially in the 1920s and '30s by African Americans in the USA, and in some Latin American countries.

Main health effects and diagnostic criteria

Name of the diseases and ICD code: **Leukoderma, not elsewhere classified (L81.5) +Z57**

Short description of the disease

Vitiligo is an acquired depigmentary disorder of the skin that results from the selective destruction of melanocytes. It is characterized by the presence of pale, white patches on the skin (it can affect any area), with low or even no melanin pigment. This disease can be socially devastating for afflicted individuals. In addition, loss of cutaneous pigment increases skin vulnerability to agents such as solar and ultraviolet radiations, both for non-cancer and cancer effects.

Vitiligo is a chronic, persistent and often progressive disorder: as a matter of fact, spontaneous repigmentation is uncommon. Chemical leukoderma is an acquired condition. It may represent the chronic effect of occupational exposure to some chemical substances or to their residues in products. Since systemic absorption of the substance may occur, white patches may appear well beyond sites of direct skin contact, thus closely mimicking idiopathic vitiligo. The symptoms may become evident within few months to several years from the beginning of exposure to these organic chemical agents. The effects of chemicals on melanocytes are thought to be due to their structural similarity to melanin precursor tyrosine. This structural similarity to tyrosine may lead to a mechanism mediated by tyrosinase-related protein-1 (Tyrp1) in which the generation of reactive oxygen species causes melanocyte apoptosis. Death of melanocytes results in depigmentation, which is usually permanent. Associated effects on the liver and thyroid have been reported.

2.2.3 Vitiligo caused by other recognized agents arising from work activities not included in other items — ICD Code L81.5 +Z57

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: hypopigmented or depigmented patches which usually appear on the exposed areas of the hands and forearms, and sometimes on covered areas of the body. Depigmentation on distant sites is often symmetrical. While permanent depigmentation is possible, a slow spontaneous repigmentation is seen when occupational exposure is terminated. It should be noted that facial leukoderma and depigmentation due to steroids, butyl hydroxyanisole or hydroxyquinoline sulphate, are not associated with occupational exposure. Clinico-histopathologically, no absolute criteria can differentiate chemical leukoderma from idiopathic vitiligo. The main differential diagnoses are idiopathic vitiligo and post-inflammatory pigment loss.
- Examinations: Wood's light may help to discover depigmented areas especially in light-skinned individuals.

Exposure assessment

- History of occupational exposure: confirmed history of work-related direct and repeated skin contact with or systemic absorption (e.g. by inhalation) of known depigmenting chemical substances (e.g. phenols, catechols, hydroquinone and monobenzone).
- Minimum duration of exposure: few days to several months.
- Maximum latent period: two years.

Key actions for prevention	Following the implementation of elimination, substitution and engineering controls then the primary endeavour is to achieve adequate control of dermal exposure to the chemicals. personal protective equipment (PPE) adequate to avoid contact; information and training of the workers regarding the hazards and the adequate controls measures (e.g. donning and doffing PPE without contamination). Chemical leukoderma will usually only appear after direct repeated skin contact; occasional accidental contamination with the above named causative agents will not be sufficient to elicit depigmentation. Some individuals seem to be prone to develop such symptoms. Thus, if initial depigmentation has occurred, it has to be decided immediately in each worker if PPE (e.g. suitable protective gloves) is sufficient to ensure prevention of further direct exposure. Essentially, the employer must recognize the circumstances of the work, and bring in the principles of good control practice, i.e., to design and operate processes and activities in order to minimise emission, release and spread of substances hazardous to health. In addition, the exposure through inhalation should be considered, whilst ingestion is less relevant in occupational settings. All these measures should be accompanied by monitoring the effectiveness of the measures adopted and, if necessary, environmental and biological monitoring and dermatological health surveillance.

Further reading

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▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
2.2.3	Leukoderma, not elsewhere specified	L81.5	EK5Y
	Occupational exposure to risk factors	Z57	QD84

2.3. Musculoskeletal disorders

2.3.1 Radial styloid tenosynovitis due to repetitive movements, forceful exertions and extreme postures of the wrist — ICD Code M65.4 + Z57

Short profile of the aetio-pathogenesis	Radial styloid tenosynovitis (de Quervain's disease) is a painful condition which involves tendon entrapment affecting the first dorsal compartment of the wrist. The pain is observed primarily with repetitive gripping and twisting motions. The two tendons most commonly affected are the *extensor pollicis brevis* and the *abductor pollicis longus*, which pass over the distal extremity of the radius (radial styloid) at the wrist. There is epidemiologic evidence of an association between repetition, forceful movements and awkward or unnatural positions of the hand and wrist, even as individual risk factors, and radial styloid tenosynovitis. Job tasks requiring a combination of risk factors (e.g. highly repetitious, forceful hand/wrist exertions, constrained postures, and movements to the extremes of pronation and supination) increase the risk of this disease. It is suggested that mechanical strain on the sheath and tendons within plays a role in causing microruptures, which might in turn entail degenerative or reactive processes.
Occupational exposures	Radial styloid tenosynovitis may be caused by activities involving systematic friction, movements stretching the tendons, repeated active contraction of the muscle moving the tendons, as well as direct injury. Frequent repetitive activities such as opening jars, wringing the hands, sewing, cutting with scissors, driving screws, electronic assembly, peeling vegetables, and playing the piano, have been associated with the disease. Activities involving repeated radio-ulnar deviation, such as hammering, are typically associated with the condition. The combination of both highly repetitive and forceful working activities has been considered to be more than additive, with a rise in the estimated risks.

Main health effects and diagnostic criteria

Name of the diseases and ICD code: **Radial styloid tenosynovitis (de Quervain's disease) (M65.4) + Z57**

Short description of the disease

Radial styloid tenosynovitis is a chronic disease characterized by thickening of the synovial sheath of the *abductor pollicis longus* (APL) and *extensor pollicis brevis* (EPB) tendons, evolving into a stenosing tenosynovitis of the first dorsal compartment of the wrist at the level of the radial styloid. This is the most common tenosynovitis affecting the dorsal tendons of the wrist. It is usually diagnosed in individuals between 30 and 50 years of age, and is more prevalent in females than in men, being associated with pregnancy, the postpartum period, and lactation. Fibrous thickening, restricting movement of the EPB and APL tendons in this compartment, can cause considerable pain and disability. Normally, symptoms improve with rest, and re-appear following return to work or after a change to unfamiliar work requiring new, rapid movements of the wrist.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: the main complaints are usually pain, weakness, and swelling along the radial side of the wrist during activities involving repeated radio-ulnar deviation. An allantoidal (sausage-shaped) swelling is typically present on the radial side of the lower part of the dorsal surface of the forearm, proximal to the radial styloid process.
- Examinations:
  - Physical examination: a nodular thickening may be visible, accompanied by tenderness on palpation. Other typical findings on examination are pain over the radial styloid and on abducting or extending the thumb against resistance. Crepitation can be exacerbated by pressure on the swelling, sometimes extending up the forearm. Local redness and warmth can be noticed.
  - A positive Finkelstein's test (ulnar deviation of the wrist when the patient grasps the thumb in the palm with the other digits of the same hand) is supportive for the diagnosis.
  - Radiographs are useful to exclude alternative pathologies. Hand, wrist, or forearm X-rays may occasionally visualize soft-tissue calcifications at the first dorsal compartment but are often unremarkable.
  - Sonographic and magnetic resonance imaging findings of radial styloid tenosynovitis have been described as consisting of tendon sheath thickening often accompanied by soft-tissue oedema.

Differential diagnosis

Osteoarthritis; entrapment of a superficial branch of the radial nerve, a mononeuropathy with sensory but not motor effects; intersection syndrome, inflammation of the thumb side of the forearm, where the APL and EPB cross over the *extensor carpi radialis longus*, and the *extensor carpi radialis brevis*; wrist sprains or carpal injuries.

2.3.1 Radial styloid tenosynovitis due to repetitive movements, forceful exertions and extreme postures of the wrist — ICD Code M65.4 + Z57

Exposure assessment

- History of occupational exposure: evidence of occupational prolonged repetitive movements, forceful exertions and extreme postures of the wrist. Activities performed with the wrists/hands in awkward positions and using exaggerated hand force increases the risk of the disease.
- Minimum duration of exposure: days.
- Maximum latent period: not longer than 30 days after cessation of exposure.

Key actions for prevention	Primary prevention consists of organizing tasks in a workplace in order to reduce the time spent by the worker in highly repetitive activities involving the wrist, in particular where twisting of the wrist and using high force is frequent. Activities posing significant risk must be alternated with tasks and jobs not involving frequent repetitive wrist movements. Where feasible, mechanised aids can avoid or reduce the risk. Work activity with significant risks can be assessed by using validated ergonomic instruments such as the Assessment of Repetitive Tasks (ART) tool, the Hand Activity Level (HAL) threshold limit value (TLV) tool, the Occupational Repetitive Actions (OCRA) index, the Strain Index (SI) or expert assessment. Measurements of repetition at the workplace (e.g. number of items handled and of hand repetitions), assessment of time spent in awkward positions of wrist/hand and assessment of force exerted (e.g. handled weights, applied forces) can provide valuable information. Secondary prevention consists of monitoring workers identified at risk of work-related upper limb disorders to detect symptoms early. Workers who report symptoms should have an occupational health assessment. Dependent on the findings, a workplace accommodation should allow a short-term re-allocation of work duties if the condition and work circumstances are confirmed or considered likely to aggravate the worker's condition. The affected individuals should not be returned to the same work regime, unless measures to reduce the risks have been considered and implemented accordingly. The occurrence of one or more cases may indicate a 'sentinel' event, highlighting systems of work that may need assessment and implementation of preventive measures to reduce the likelihood of disease occurrence in other workers performing the same job.

2.3.1 Radial styloid tenosynovitis due to repetitive movements, forceful exertions and extreme postures of the wrist ICD Code M65.4 + Z57

Further reading

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▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
2.3.1	Radial styloid tenosynovitis (de Quervain)	M65.4	FB40.5
2.3.1	Occupational exposure to risk factors	Z57	QD84.4

2.3.2 Chronic tenosynovitis of hand and wrist due to repetitive movements, forceful exertions and extreme postures of the wrist — ICD Code M65.8 (*site code 3 or 4*) + Z57

Short profile of the aetio-pathogenesis	Tenosynovitis is an inflammation of the tendon sheaths, which are fluid containing tubular structures surrounding the tendons, providing lubrication and protection. The causal agents of this condition are execution of forceful movements in awkward positions of the hand, highly repetitious, constrained postures, and movements to the extremes of pronation and supination. Other risk factors can be simple repetitive stereotyped movements associated with intensity of effort and speed, single forceful or repetitive wrist strain. Return to the same hazardous activity after prolonged absence can exacerbate the pain. Direct local blunt trauma can cause the condition, a musculoskeletal inflammatory disorder characterized by pain on movement, localized to the tendon sheaths. Infections may also play a role, but this is not usually an occupational risk factor. The wrists extensors are more prone to be affected than the flexors following overuse, strain and injury.
Occupational exposures	The occurrence of tenosynovitis varies widely according to the type of work. High incidences have been reported typically among manufacturing workers, such as food-processing workers, butchers, packers and assemblers. Elevated risks of developing a tenosynovitis of the hand and wrist have been observed in the shoe industry and among automobile workers. Repetitive work with a low cycle time or low-grip-force work with more than half of the cycle time involved in the same fundamental activities have an increased risk of tenosynovitis compared to similar work with low repetition. Works with both high repetition and high grip force may lead to an even greater risk.

Main health effects and diagnostic criteria

Name of the diseases and ICD code: **Other synovitis and tenosynovitis (M65.8) (*site code 3 or 4*) + Z57**

Short description of the disease

The disease is characterized by inflammation of the extensor or flexor tendon sheaths, peritendineum (the fibrous layer around the tendon) or tendon at the wrist, with consequent pain on movement.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: wrist pain on movement, elicited by resisted active movement of the affected wrist tendons. The symptoms are usually more pronounced in the morning, and functional ability improves after some activity.
- Examinations: clinical examination may show tenderness on palpation of the tendon sheath area, and tender nodules may be found. The tendon sheath may be swollen, and bending the wrist back and forth may produce crackling or crepitation. The acute phase is characterized by typical signs of inflammation: redness, swelling, warmth, pain and functional impairment, associated with accumulation of fluid and fibrin in the tendon sheath or between the muscle cells. A classic fusiform swelling is often visible and palpable on the dorsum of the forearm/wrist. The mobility of the tendon is generally affected with different levels of severity, and weakness in gripping is usually observed.

Exposure assessment

- History of occupational exposure: prolonged occupational exposure to highly repetitive hand motions; working with the wrists/hands in awkward positions and using hand force aggravates the exposure.
- Minimum duration of exposure: days.
- Maximum latent period: not longer than 30 days after cessation of exposure.

2.3.2 Chronic tenosynovitis of hand and wrist due to repetitive movements, forceful exertions and extreme postures of the wrist ICD Code M65.8 (*site code 3 or 4*) + Z57

Key actions for prevention

Primary prevention consists of organizing tasks in a workplace in order to reduce the time spent by the worker in highly repetitive activities involving the wrist, in particular where twisting of the wrist and using high force is frequent. Activities posing significant risk must be alternated with tasks and jobs not involving frequent repetitive wrist movements. Where feasible, mechanised aids can avoid or reduce the risk. Work activity with significant risks can be assessed by using validated ergonomic instruments such as the Assessment of Repetitive Tasks (ART) tool, the Hand Activity Level (HAL) threshold limit value (TLV) tool, the Occupational Repetitive Actions (OCRA) index, the Strain Index (SI) or expert assessment. Measurements of repetition) at the work place (e.g. number of items handled and of hand repetitions, assessment of time spent in awkward positions of wrist/hand and assessment of force exerted (e.g. handled weights, applied forces) can provide valuable information.

Secondary prevention consists of monitoring workers identified at risk of work-related upper limb disorders to detect symptoms early. Workers who report symptoms should have an occupational health assessment. Dependent on the findings, a workplace accommodation should allow a short-term re-allocation of work duties if the condition and work circumstances are confirmed or considered likely to aggravate the worker's condition. The affected individuals should not be returned to the same work regime, unless measures to reduce the risks have been considered and implemented accordingly. There is evidence that for those affected workers using computers equipped with modified keyboards are helpful in reducing symptoms. The occurrence of one or more cases may indicate a 'sentinel' event, highlighting systems of work that may need assessment and implementation of preventive measures to reduce the likelihood of disease occurrence in other workers performing the same job.

Further reading

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▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
2.3.2	Other synovitis and tenosynovitis	M65.8 (*site code 3 or 4*)	FB40.Z&XA0WU6
	Occupational exposure to other risk factors	Z57	QD84.4

2.3.3 Olecranon bursitis due to prolonged pressure of the elbow region ICD Code M70.2 +Z57

Short profile of the aetio-pathogenesis	Bursitis is an inflammatory condition of the bursae, i.e., the synovium-like cellular membranes which overlie the bony prominences. Normally, they contain a small amount of fluid. However, that can increase in certain inflammatory conditions. Olecranon bursitis involves the posterior elbow and can follow a single direct trauma to the elbow or, more commonly, repeated minor injuries associated with prolonged pressure on the elbow region, such as rubbing of the olecranon against a desktop during writing, leaning elbows against hard surfaces, and chronic overuse.
Occupational exposures	Occupations where tasks with prolonged pressure to the elbow and repetitive rubbing of olecranon region are common include: polishers, miners, watchmakers, draftsmen, engravers, glass blowers, sportsmen, aero-engineering workers, and textile workers. Cases of olecranon bursitis have been observed among military combat units, most likely because of the frequent crawling required during outdoor training.

Main health effects and diagnostic criteria

Name of the diseases and ICD code: **Olecranon bursitis (M70.2) +Z57**

Short description of the disease

Olecranon bursitis consists of an inflammation of the olecranon bursa, a liquid-filled sac on the dorsal side of the elbow at the proximal part of the ulna. Activities characterized by prolonged pressure of the elbow region may cause symptoms that appear gradually and are mainly characterized by focal swelling at the posterior elbow, possibly accompanied by pain, redness, and functional limitation. If the disorder proceeds, proliferative and degenerative changes in the bursa may occur, with serum secretion and adhesions, villus formation, tags and calcareous deposits.

Synonyms for the disorder are: *"student's elbow", "plumber's elbow", "beat elbow", "draftsman's elbow", "baker's elbow", "swellbow", "water on the elbow"*. Olecranon bursitis has been found to have a higher incidence among males.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms:
  - Pain, when present, is exacerbated or triggered by pressure, and is worse at night.
  - The posterior elbow is typically swollen, often resembling the shape of a golf ball over the olecranon process, usually clearly demarcated, and accompanied by tenderness to palpation and redness. Palpation triggers wavelike motions due to accumulation of fluid in the bursa.
  - Although function may be unaffected, the end range of flexion may be limited due to pain. In the chronic and most severe cases, muscle atrophy and severe limitation of motion can be observed.
  - Skin inspection may reveal contusion or abrasion if there was recent injury.
- Examinations:
  - Diagnosis is mainly based on symptoms and typical focal swelling at the posterior elbow, which can be observed at physical examination more easily with the elbow extended rather than flexed. Laboratory and instrumental examinations are mostly used for differential diagnosis, as other disorders with similar manifestations include: fracture of the olecranon process of the ulna, septic bursitis, crystalline inflammatory arthropathy (e.g. gout, pseudogout), ganglion cyst, tendon cyst, radial neuropathy, epicondylitis, inflammation of tendons surrounding the elbow joint, and rheumatoid arthritis.
  - Ultrasound may detect effusions, synovial proliferation, calcifications, loose bodies, and may be helpful in differential diagnosis by detecting, for example, rheumatoid nodules, gout tophi and septic processes;
  - Laboratory investigations may be used to exclude other disorders, such as rheumatoid arthritis by examining rheumatoid factor, erythrocyte sedimentation rate, and C-reactive protein level or gout by evaluating uric acid concentration.
  - If infection is suspected, the olecranon bursa should be aspirated under sterile conditions and the fluid sent for culture, for a prompt Gram staining for bacteria, and a cell count.
  - An X-ray examination can be done to exclude other conditions like fractures, osteomyelitis or a bony spur.
  - In rare cases, a magnetic resonance imaging study might be used to exclude a triceps tendinitis.

Exposure assessment

- History of occupational exposure: history of repeated direct trauma and pressure on the elbow.
- Minimum duration of exposure: weeks.
- Maximum latent period: not longer than 30 days after cessation of exposure.

2.3.3 Olecranon bursitis due to prolonged pressure of the elbow region ICD Code M70.2 +Z57

Key actions for prevention

Primary prevention consists of organizing tasks in a workplace in order to reduce the time spent by the worker in highly repetitive activities involving prolonged pressure to the elbow and repetitive rubbing of olecranon region. Activities posing significant risk must be alternated with tasks and jobs not involving these frequent repetitive movements. Where feasible, mechanised aids can avoid or reduce the risk. Work activity with significant risks can be assessed by using validated ergonomic instruments such as the Assessment of Repetitive Tasks (ART) tool, the Hand Activity Level (HAL) threshold limit value (TLV) tool, the Occupational Repetitive Actions (OCRA) index, the Strain Index (SI) or expert assessment. Measurements of repetition at the work place (e.g. number of items handled and elbow movements), assessment of time spent in awkward positions of elbow and assessment of force exerted (e.g. handled weights, applied forces) can provide valuable information.

Secondary prevention consists of monitoring workers identified at risk of work-related upper limb disorders to detect symptoms early. Workers who report symptoms should have an occupational health assessment. Dependent on the findings, a workplace accommodation should allow a short-term re-allocation of work duties if the condition and work circumstances are confirmed or considered likely to aggravate the worker's condition. The affected individuals should not be returned to the same work regime, unless measures to reduce the risks have been considered and implemented accordingly. The occurrence of one or more cases may indicate a 'sentinel' event, highlighting systems of work that may need assessment and implementation of preventive measures to reduce the likelihood of disease occurrence in other workers performing the same job.

If the activity entailing exposure to prolonged pressure on the elbow cannot be avoided, then a padded orthosis with a hard exterior can be worn over the elbow. Protective pads should not interfere with range of motion of the elbow.

Further reading

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▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
2.3.3	Olecranon bursitis	M70.2	FB50.1&XA5VA1
	Occupational exposure to risk factors	Z57	QD84.4

2.3.4 Prepatellar bursitis due to prolonged stay in kneeling position ICD Code M70.4 +Z57

Short profile of the aetio-pathogenesis	The prepatellar bursa is a superficial bursa with a thin synovial lining located between the skin and the patella. Normally, it does not communicate with the joint space and contains a minimal amount of fluid which, however, can markedly increase in case of inflammation. The causal circumstances of this disorder are conditions generally requiring prolonged adoption of a kneeling position, such as acute or cumulative traumas related to repetitive rubbing of the patellar region against the floor, repeated friction between skin and patella, and prolonged pressure on the region.
Occupational exposures	Occupational exposures occur in occupations and tasks requiring excessive kneeling or causing local trauma, as is the case for a direct blow or a fall on the knee, repeated physical traumas, friction and prolonged pressure. All these conditions are typical of occupations such as carpet and floor layers, roofers, coal miners, plumbers, domestic workers, cleaners, gardeners, and painters.

Main health effects and diagnostic criteria

Name of the diseases and ICD code: **Prepatellar bursitis (M70.4) +Z57**

Short description of the disease

Prepatellar bursitis is an inflammation of the liquid-filled sac located between the patella and the overlying skin. The onset of prepatellar bursitis can be either acute or gradual over time, with or without an acute starting phase. The incidence of prepatellar bursitis is greater in males than females.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms:
  - Pain, localized swelling and redness of the knee are the typical presentations. Bursal fluctuance may be found. The affected person usually shows difficulty in walking and kneeling.
  - Typical signs are tenderness of the patella to palpation although there is often evidence of a normal, painless range of flexion of the knee, except for extreme flexion when the bursa may be compressed and cause some discomfort.
  - Other possible findings include fluctuant oedema over the lower pole of the patella, crepitation, and decreased extent of flexion, in the most severe cases. Some subjects may show mild peribursal oedema, warmth, and erythema. A skin temperature difference between the contralateral sites may be noted.
- Examinations: soft-tissue changes and synovial fluid in the knee can be detected by ultrasonography; plain radiographs may show soft tissue swelling.

Exposure assessment

- History of occupational exposure: confirmed occupational exposure to conditions such as repetitive rubbing of the patellar region against the floor, repeated friction between skin and patella, and prolonged pressure of the region.
- Minimum duration of exposure: weeks.
- Maximum latent period: not longer than 30 days after cessation of exposure.

Key actions for prevention	Primary prevention consists of organizing tasks in a workplace in order to reduce the time spent by the worker in highly repetitive activities involving prolonged pressure to the knee and repetitive rubbing of the knee region. The main preventive intervention consists of workers' education and training to create awareness regarding the main risk factors and avoiding prolonged or repetitive kneeling or knee trauma. Activities posing significant risk must be alternated with tasks and jobs not involving these frequent repetitive movements. Knee-straining postures seem to vary to a great extent within a job category, and activities should be specifically assessed for preventive purposes. Where feasible, mechanised aids can avoid or reduce the risk. Wearing protective knee-pads may be helpful in protection. Affected workers should be identified at an early stage of the condition, removed from exposure and provided with rehabilitative interventions.

2.3.4 Prepatellar bursitis due to prolonged stay in kneeling position ICD Code M70.4 +Z57

Further reading

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▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
2.3.4	Prepatellar bursitis	M70.4	FB50.1&XA9L17
	Occupational exposure to risk factors	Z57	QD84.4

2.3.5 Epicondylitis due to repetitive forceful work	ICD Code M77.0, M77.1 + Z57
Short profile of the aetio-pathogenesis	The term epicondylitis refers to a painful syndrome which may affect the origins of the extensors of the fingers and wrists on the lateral epicondyle of the humerus (lateral epicondylitis), or the origin of the flexors on the medial epicondyle (medial epicondylitis). Microtears in the muscles, or their insertion, originating at the elbow are thought to be the most likely pathological process underlying the symptoms of both lateral and medial epicondylitis. Histologically tendinosis or degeneration in the tendon is seen rather than acute inflammation. The causal circumstances of this disorder are represented by periods of forceful and repetitive arm movements, associated with overuse of the wrist flexor and extensor tendons that are attached to the humerus at the elbow.
Occupational exposures	Occupational activities associated with epicondylitis include those requiring arms lifted in front of the body, hands bent or twisted, repetitive movements of the arm, and precise movements of the upper limb. Jobs that involve repetitive bending/straightening of the elbow and characterized by tasks with frequent turning and screw driving may pose a hazard. The primary at-risk occupational groups are thus foresters, pipe fitters and water/gas suppliers, meat cutters, construction workers, sausage makers, meat packers, and school cooks. Potentially hazardous tasks include painting, hammering, and professional sport activities such as rowing.

Main health effects and diagnostic criteria

Name of the diseases and ICD code: **Lateral epicondylitis (tennis elbow) (M77.1) + Z57**

Short description of the disease

Lateral epicondylitis is characterized by pain over the lateral epicondyle of the humerus aggravated by loading of the hand extensor muscles at the elbow. The presentation is usually with a complaint of pain during or after elbow flexion and extension. Weakness in gripping and local pain during rest may occur. Pain may radiate into the forearm and dorsum of the wrist. A main finding is tenderness to palpation of the lateral epicondyle and epicondylar pain provoked by resisted movement of the wrist and fingers with the elbow extended. The tendon most often involved is the *extensor carpi radialis brevis*, followed by the *extensor digitorum communis* or the *extensor carpi radialis longus*. The duration of epicondylitis can range from some weeks to six months, but complete recovery is common. Epicondylitis occurs most often in people aged >40 years and it is rare under the age of 30 years.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms:
  - The hallmark of lateral epicondylitis is slow onset of pain and tenderness over the lateral epicondyle. Maximal tenderness is usually found 1-5 cm below the lateral epicondyle midpoint. Chronic pain in the elbow may spread along the forearm and is aggravated by extending the wrist and fingers against resistance. Grip strength is often impaired and reduces work ability. Symptoms may occur at night and at rest, but are usually related to activity during the day, especially grasping or wrist dorsiflexion.
  - Pain is usually felt at the common extensor origin with resisted wrist extension and radial deviation while the forearm is extended and pronated. Pain is thus aggravated when lifting a weight with the palm down, forcefully gripping an object mostly with the elbow extended, extending the wrist, and playing racquet sports (backhand shots) hence the epithet, “tennis elbow”.
  - Pain can be reproduced over the epicondyle with provocative tests, such as resisted wrist extension (Cozen’s test) and third digit extension (Maudsley’s test).
- Examinations:
  - Radiographs are often normal, although enthesopathy and calcifications may be seen in chronic cases.
  - Ultrasound and magnetic resonance imaging can visualize the tendon and confirm tendinosis or tears.
  - In general, investigations other than physical examination are usually not essential for diagnosis, unless other causes of elbow pain need to be ruled out.

Exposure assessment

- History of occupational exposure: evidence of forceful, unaccustomed, and repetitive motions requiring flexion and extension movements of the wrist joint or any work activity characterized by overuse of wrist flexion and extension, performed with the arms lifted in front of the body, and with hands or arms bent or twisted.
- Minimum duration of exposure: days.
- Maximum latent period: not longer than 30 days after cessation of exposure.

2.3.5 Epicondylitis due to repetitive forceful work ICD Code M77.0, M77.1 + Z57

Name of the diseases and ICD code: **Medial epicondylitis (golfer's elbow) (M77.0 + Z57)**

Short description of the disease

Medial epicondylitis is an overuse syndrome characterized by inflammation of the flexor tendons at the medial epicondyle of the humerus. Pain is typically sharp, persistent, and may have an acute or a more typical insidious onset. Pain may radiate along the medial elbow. The causal circumstances are represented by repetitive resisted motions of the wrist through pronation and flexion, which result in microtears and granulation tissue at the origin of the pronator teres and forearm flexors, in particular the *flexor carpi radialis*. This overuse syndrome is usually observed in people older than 40 years of age, is much rarer than lateral epicondylitis, and occurs most often in work-related repetitive activities. Typical signs are tenderness on palpation of the medial epicondyle and epicondylar pain provoked by resisted flexion of the wrist and fingers or forearm pronation with the elbow extended, and pain and weakness in gripping, with local pain during rest and movement. Ulnar neuritis co-exists in 25–50% of patients with medial epicondylitis, associated with tenderness over the ulnar nerve at the elbow accompanied in some cases by hyperesthesia and paraesthesia on the ulnar side of the hand.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms:
  - Symptoms affecting the inner elbow include burning and tenderness on the flexor component of the forearm. Tenderness is present at the medial epicondyle, usually within 1 cm distal and slightly lateral to the medial epicondyle.
  - Resisted pronation or resisted wrist flexion causes discomfort (Mill's test).
- Examinations:
  - Radiographs are often normal, although enthesopathy and calcifications may be seen in chronic cases.
  - Ultrasound and magnetic resonance imaging can visualize the tendon and confirm tendinosis or tears.
  - In general, investigations other than physical examination are usually not essential for diagnosis, unless other causes of elbow pain need to be ruled out.

Exposure assessment

- History of occupational exposure: evidence of forceful, unaccustomed, and repetitive motions requiring flexion and extension movements of the wrist joint or any work activity characterized by overuse of wrist flexion and extension, performed with the arms lifted in front of the body, and with hands or arms bent or twisted.
- Minimum duration of exposure: days.
- Maximum latent period: not longer than 30 days after cessation of exposure.

Key actions for prevention	Primary prevention consists of organizing tasks in a workplace in order to reduce the time spent by the worker in highly repetitive activities involving the wrist, in particular where flexion and extension of the wrist, and using high force is frequent. Activities posing significant risk must be alternated with tasks and jobs not involving frequent repetitive wrist movements. Where feasible, mechanised aids can avoid or reduce the risk. Work activity with significant risks can be assessed by using validated ergonomic instruments such as the Assessment of Repetitive Tasks (ART) tool, the Hand Activity Level (HAL) threshold limit value (TLV) tool, the Occupational Repetitive Actions (OCRA) index, the Strain Index (SI) or expert assessment. Measurements of repetition at the work place (e.g. number of items handled and of hand repetitions), assessment of time spent in awkward positions of arm/wrist/hand and assessment of force exerted (e.g. handled weights, applied forces) can provide valuable information. Secondary prevention consists of monitoring workers identified at risk of work-related upper limb disorders to detect symptoms early. Workers who report symptoms should have an occupational health assessment. Dependent on the findings, a workplace accommodation should allow a short-term reallocation of work duties if the condition and work circumstances are confirmed or considered likely to aggravate the worker's condition. Typically, six weeks of removal from the inciting activity may be required for epicondylitis. The affected individuals should not be returned to the same work regime, unless measures to reduce the risks have been considered and implemented accordingly. The occurrence of one or more cases may indicate a 'sentinel' event, highlighting systems of work that may need assessment and implementation of preventive measures to reduce the likelihood of disease occurrence in other workers performing the same job.

2.3.5 Epicondylitis due to repetitive forceful work ICD Code M77.0, M77.1 + Z57

Further reading

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▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
2.3.5	Lateral epicondylitis (Tennis elbow)	M77.1	FB55.1
2.3.5	Medial epicondylitis (Golfer's elbow)	M77.0	FB55.0
	Occupational exposure to other risk factors	Z57	QD84.4

2.3.6 Meniscus lesions following extended periods of work in a kneeling or squatting position ICD Code M23.2, S83.2 +Z57

Short profile of the aetio-pathogenesis	The menisci of the knee are two crescent-shaped wedges of fibrocartilage (medial and lateral), which act as a structural transition zone between the femoral condyles and the tibial plateau. The menisci provide several integral elements to knee function, such as load transmission, shock absorption, as well as joint lubrication, nutrition, and stability. The circumferential collagen fibres within the meniscus, mostly as type 1 collagen, are uniquely oriented to transmit the compressive load and to protect articular cartilage from high stress. However, the continuity of the collagen fibres can be torn or ruptured during prolonged squatting or kneeling, often in combination with a crouching position, heavy lifting, and be damaged by repeated minor injuries consequent to slipping or tripping with forcible rotation of the knee joint. Lesions of the meniscus may occur during working activities with sudden movements on the knee in a semi-flexed position. Exposures to kneeling tasks at work may predispose to the development of degenerative meniscal tears through multiple micro-trauma or cumulative mechanical strain. Kneeling may be an important factor in the progression from meniscal degeneration to tears among aging workers. The majority of meniscal lesions affects the medial meniscus and tends to involve the posterior horn. A vertical or longitudinal tear may occur in line with the circumferential fibres of the meniscus (bucket-handle tear). It may be detached at either end or transected in the middle with unstable anterior and posterior flaps. A bucket-handle tear may displace into the intercondylar notch, where it can cause locking of the knee joint. The medial meniscus is vulnerable to injury of the anterior cruciate ligament, as it acts to restrain the forces tending to cause anterior tibial displacement. Medial meniscus tear often occurs together with anterior cruciate ligament injury, and damage to the medial collateral ligament of the knee. The posterior oblique ligament attached to the posterior medial meniscus functions to limit displacement and rotation at the knee.
Occupational exposures	Occupational exposure occurs in jobs and tasks requiring prolonged kneeling or squatting, as it is the case for miners, floor layers, electricians, carpet layers, carpenters, roofers, plumbers, domestic workers, cleaners, gardeners, and painters.

Main health effects and diagnostic criteria

Name of the diseases and ICD code: **Meniscal injury of the knee (M23.2), Tear of meniscus (S83.2)**

Short description of the disease

A tear/injury of a meniscus is a rupturing of one of the fibrocartilaginous pads in the knee called menisci. Menisci can be torn by traumatic force encountered during some form of physical exertion: when a stress is exerted, the meniscus tends to extrude from between the articular surfaces of the femur and tibia; this tendency is counteracted by the circumferential tension developed along the collagen fibres of the meniscus itself. In an acute tear, there is immediate severe knee pain at the joint line, sometimes with locking of the knee joint. Internal knee stress is high during kneeling work, and an age-related, degenerative, vulnerable meniscus can easily be torn during such work. Moreover, rising from kneeling to a standing position many times a day may predispose to knee twists and subclinical meniscal tears. Chronic or intermittent knee pain is usually present in case of damage to the meniscal cartilage.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: the affected subject complains of pain at the medial or lateral part of the knee, and may report locking, clicking, and swelling of the knee, or a sensation of the 'knee giving way'. A painful gait and difficulty with squatting may be reported. It may be particularly painful and may cause increased swelling in the knee when twisting, turning, or pivoting on the knee such as getting in and out of a car or walking up or down stairs.
- Examinations: physical findings can include effusion or joint line tenderness. Radiographs are usually normal but may show joint space narrowing or loose bodies. Magnetic resonance imaging is the best diagnostic tool for meniscal lesions and can clearly show meniscal tears. Positive provocation tests may indicate a meniscal lesion, such as (among others):
  - McMurray's test: with the subject supine, the knee flexed at 90°, extension of the leg while the lower extremity is simultaneously turned medially or laterally causes an audible click or pain if there is a meniscal tear (applying to the knee a valgus stress tests the medial meniscus, while a varus stress tests the lateral meniscus).
  - Apley's grind test: with the subject prone and the knee flexed at 90°, downwards force on the foot with internal and external rotation causes pain and crepitus in a meniscal tear (a painful click during inward rotation may be indicative of a lateral meniscus tear, whilst pain during outward rotation may indicate a tear in the medial meniscus).
  - Thessaly's test: a twist of the knee while standing on one leg with the knee slightly flexed can elicit pain.

2.3.6 Meniscus lesions following extended periods of work in a kneeling or squatting position ICD Code M23.2, S83.2 +Z57

Exposure assessment

- History of occupational exposure: evidence of occupational history characterized by prolonged kneeling or squatting.
- Minimum duration of exposure: several weeks.
- Maximum latent period:
  - Acute meniscal tears: days.
  - Cumulative mechanical strain meniscal tears: may present up to two years after cessation of exposure.

Key actions for prevention	The menisci have an integral role for knee function, such as load transmission, shock absorption, joint lubrication, as well as internal and external joint stability. Primary prevention consists of organizing tasks in a workplace in order to reduce the time spent by the worker in activities involving prolonged kneeling or squatting and excessive loading of the knee region whilst twisting and bending. To prevent meniscus injury, the muscles around the knee must be in good condition. Education and training can be useful to prevent a tear in the meniscus by learning and employing proper techniques for manual handling, and for movement at the knee joint. The provision of correct footwear for work is important to minimise slips and falls whilst the knee is loaded. Lifting at work should not require unusual strength and it is noted that knee injury is associated with lifting weights exceeding 25 kg for men, and 20 kg for females. Avoiding excessive compression of the meniscus, using sound techniques for work tasks involving frequent movements at the knees, and exercises to maintain the strength of the leg muscles and working on the flexibility of all the muscle groups in the leg can help stabilize and protect the knee joints. Physiotherapy, simple rest with activity modification, and medication are the tertiary prevention and non-surgical measures for the management of meniscus tears, aiming to minimize effusion and pain, normalize gait and range of motion, prevent muscular atrophy, and maintain proprioception. Most meniscal tears do not heal without intervention, and may therefore require surgical treatment. If not treated promptly, the lesions may increase in size and may abrade the articular cartilage, resulting in further knee complications.

Further reading

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▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
2.3.6	Meniscal injury of the knee (Derangement of meniscus due to old tear or injury)	M23.2	FA33.2
2.3.6	Tear of meniscus, current	S83.2	NC93.3
	Occupational exposure to risk factors	Z57	QD84.4

2.3.7 Carpal tunnel syndrome due to extended periods of repetitive forceful work, work involving vibration, extreme postures of the wrist, or a combination of the three

ICD Code G56.0 +Z57, Z57.7

Short profile of the aetio-pathogenesis	Carpal tunnel syndrome (CTS) arises from the intermittent or continuous compression or entrapment of the median nerve in its passage through the carpal tunnel from the wrist to the hand. Increased pressure on the nerve in the tunnel can result in progressive sensory and motor disturbances in parts of the hand corresponding to the median nerve distribution, eventually leading to pain and, in the most severe cases, loss of function. CTS is multifactorial in aetiology, with recognized non-occupational risk factors as pregnancy, advanced age, female sex, family history, hypothyroidism, diabetes, autoimmune diseases, rheumatologic diseases, arthritis, obesity, renal disease, trauma, and a possible predisposition related to the shape and structure of the carpal tunnel, bones, and tissues, in the wrists and hands. The main occupational risks for the disease are forceful repetitive work, especially repetitive movements of the hands and wrists, hand-transmitted vibration (HTV), direct pressure, and awkward postures of the wrist (i.e., forearm pronation supination, wrist deviation, and metacarpophalangeal and finger flexion). Repetitive hand and wrist movements can be categorized in terms of various elements, such as: the frequency or duration of tasks pertaining to the hand/wrist; the ratio of working time to recovery time; the percentage of the workday spent on repetitive activities; and the quantity of work performed in a given time.
Occupational exposures	Occupational exposures occur in jobs with regular, prolonged activities characterized by repetitive forceful wrist movements or HTV, e.g. fish filleting; meat cutting; manual assembly; sorting of parcels; checkout counters and cash registers operations; hairdressing; knitting and sewing clothes; typing; playing music instruments; playing tennis; baking, manual kneading of dough; farming, in tasks such as milking cows , sheep and gouts, in particular by hand; and gardening, especially doing manual weeding. Excessive use of hand held vibrating tools, in various industries, working with a rock drill, chainsaw, manual work with chisels, polishing, grinding, drilling, or using the hand as a hammer may contribute to CTS development.

Main health effects and diagnostic criteria

Name of the diseases and ICD code: **Carpal tunnel syndrome (G56.0) + Z57, Z57.7**

Short description of the disease

Carpal tunnel syndrome (CTS) is a disease caused by compression of the median nerve, located underneath the *palmaris longus* tendon and anterior to the flexor tendons. Compression may be consequent to a decreased carpal tunnel size, or a swelling of the structures contained within it. In both situations, the median nerve is compressed against the transverse ligament bounding the tunnel's roof. Compression produces ischaemia of the nerve, impaired nerve conduction and consequent symptoms and signs. In females, CTS is three times more frequent than in males, and the condition occurs most often between 45 and 54 years of age. HTV may cause damage to the median nerve with myelin loss and perineural fibrosis. Operative treatment is reported to be less successful in such exposure circumstances.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: impaired nerve conduction is characterized by numbness and tingling in the median nerve distribution of the thumb, index finger, middle finger, and radial half of the ring finger (the palm is not usually involved), and pain. Weakness in the wrist can extend down to the same fingers affected by tingling, and pain may extend up along the arm to the shoulder. Symptoms are usually intermittent and occur often during the night or in the morning at awakening. Symptoms may be relieved by shaking the hand or wrist, and are often reported as associated with certain activities, such as driving, reading the newspaper, and painting. Many affected subjects report sensations of the hands being tight/swollen and cold/hot. If the condition remains untreated, symptoms progress up to muscular dysfunction.

2.3.7 Carpal tunnel syndrome due to extended periods of repetitive forceful work, work involving vibration, extreme postures of the wrist, or a combination of the three

ICD Code G56.0 +Z57, Z57.7

- Examinations:
  - During physical examination, provocative tests such as the Tinel's test (percussion over the flexor retinaculum) and the Phalen's test (sustained complete flexion of the wrist for one minute) can often reproduce symptoms over the median nerve distribution. Clinical tests of sensation such as Semmes Weinstein monofilaments or two point discrimination may show sensory impairment in the affected digits.
  - Electrophysiologic studies, including electromyography and nerve conductions studies, are the most important diagnostic test: a delayed sensory nerve conduction velocity across the carpal tunnel and a prolonged distal motor latency support the diagnosis.
  - Ultrasonography can potentially confirm abnormalities in the median nerve (e.g. increased cross-sectional area) that can be diagnostic of CTS, as well as showing bowing of the flexor retinaculum.

Exposure assessment

- History of occupational exposure: evidence of engagement in activities involving repeated and forceful bending and flexing of the wrist and prolonged exposure to HTV (e.g. for users of vibratory tools or handheld work pieces). The neurological effects of a temporary threshold shift of vibrotactile perception thresholds can be found after normal subjects have 30 minutes exposure to HTV, although dependent on the exposure acceleration amplitude and frequency. It is suggested that levels of HTV exposure less than 1 m/s^2 [A(8)] are not considered likely to cause vascular symptoms related to HTV and this is probably also true of the neurosensory effects.
- Minimum duration of exposure: several months.
- Maximum latent period:
  - For work activities involving repeated and forceful bending and flexing of the wrist 30 days;
  - For work activities involving prolonged exposure to hand-transmitted vibration (e.g. for users of vibrating tools or work pieces), the onset of symptoms is unusual more than 2 years after the cessation of vibration exposure.

Key actions for prevention	Primary prevention consists of organizing tasks in a workplace in order to reduce the time spent by the worker in highly repetitive activities involving the hand and wrist, in particular where twisting of the wrist and using high force is frequent. Activities posing significant risk must be alternated with tasks and jobs not involving frequent repetitive hand and wrist movements. Where feasible, mechanised aids can avoid or reduce the risk. Work activity with significant risks can be assessed by using validated ergonomic instruments such as the Assessment of repetitive tasks (ART) tool, the Hand activity level (HAL) threshold limit value (TLV) tool, the Occupational Repetitive Actions (OCRA) index, the Strain Index (SI) or expert assessment. Measurements of repetition at the work place (e.g. number of items handled and of hand repetitions) assessment of time spent in awkward positions of wrist/hand and assessment of force exerted (e.g. handled weights, applied forces), can provide valuable information. Secondary prevention consists of monitoring workers identified at risk of work-related upper limb disorders and CTS to detect symptoms early. Workers who report symptoms should have an occupational health assessment. Dependent on the findings, a workplace accommodation should allow a short-term re-allocation of work duties if the condition and work circumstances are confirmed or considered likely to aggravate the worker's condition. The affected individuals should not be returned to the same work regime, unless measures to reduce the risks have been considered and implemented accordingly. The occurrence of one or more cases may indicate a 'sentinel' event, highlighting systems of work that may need assessment and implementation of preventive measures to reduce the likelihood of disease occurrence in other workers performing the same job. HTV can be avoided or reduced by using tools equipped with systems addressed at avoiding or minimizing the vibration coupling between the worker and the tool itself (e.g. by means of remotely operated devices) and tools that vibrate less while maintaining a high standard of performance. Some tasks, may require the use of tools with levels of vibration emission considered harmful. A risk assessment may show that use of a tool with higher vibration emission for a short time may enable a task to be completed with less HTV than more prolonged use of a lower emission tool. Job rotation can limit individual worker exposure. Training in correct tool use can limit exposure by ensuring that users do not over grip or force the tool into the work as with road breakers and drills. The proper selection of low vibration tools and their maintenance are key factors; this can be problematic if workers are required to purchase and maintain their own equipment.

2.3.7 Carpal tunnel syndrome due to extended periods of repetitive forceful work, work involving vibration, extreme postures of the wrist, or a combination of the three

ICD Code G56.0 +Z57, Z57.7

Key actions for prevention	Personal protection equipment, such as anti-vibration gloves are not particularly effective at reducing the frequency-weighted vibration associated with risk of HTV associated conditions and some authorities state they can increase the vibration at some frequencies. There is no reliable way of assessing the vibration reduction, if any, that such gloves provide. Gloves and other warm clothing can be useful to protect vibration-exposed workers from cold, and damp conditions helping to maintain circulation. Workers' health surveillance is a useful secondary prevention measure; this allows early detection of HTV associated conditions and indicates the effectiveness of specific preventive measures. We list here some examples of exposure limits (taken from EU directive 2002/44/EC) that, if respected, have been shown to protect the majority of workers from adverse health effects of vibrations: For hand-arm vibration: (a) daily exposure limit value: 5m/s^2 A(8) (note that this value is recommended by the ACGIH as a TLV); and (b) daily exposure action value: 2.5 m/s^2 A(8). If the action values are exceeded, the employer in the EU must implement an action plan to prevent exposure from exceeding limit values.

Further reading

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▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
2.3.7	Carpal tunnel syndrome (CTS)	G56.0	8C10.0
	Occupational exposure to risk factors	Z57	QD84.4
	Occupational exposure to vibration	Z57.7	QD84.3

2.4. Mental and behavioural disorders

2.4.1 Post-traumatic stress disorder	ICD Code F43.1 +Z57
Short profile of the aetio-pathogenesis	Post-traumatic stress disorder (PTSD) occurs in some people as a delayed or protracted response to a stressful event or situation, either brief or long in duration, of an exceptionally threatening or catastrophic nature, such as environmental disasters, war events, civil riots, criminal offences, and any other situation involving threat to life safety and integrity of the affected individuals. Thus, the cause of the condition is any direct or indirect exposure to an extremely threatening or horrific event or series of events. A traumatizing event is defined as one that is outside the normal range of everyday life events and is experienced as overwhelming by the individual. It usually involves a threat to one's own life or to someone close or witnessing an actual death or serious injury, especially when this occurs suddenly, violently, or helplessly. Events and situations which could cause occupational PTSD include: • Workplace violence: incidents where staff members are abused, threatened or assaulted in circumstances related to their work (including commuting to and from work), that involve an explicit or implicit challenge to their safety, well-being or health. • Physical violence: the use of physical force against another person or group that results in physical, sexual or psychological harm. • Psychological violence (emotional abuse): the intentional use of power, including the threat of physical force, against another person or group that can result in harm to physical, mental, spiritual, moral or social development. Such violence includes verbal abuse, bullying or mobbing, harassment, and threats. Although psychological violence does not imply, by definition, a real threat to physical integrity, the onset of PTSD symptoms has been frequently observed in victims of these situations as well.
Occupational exposures	Workplace violence affects many occupations and industries but is more common in service industries, though some are more at risk than others. For example, the exposure of ambulance staff to violence is extremely high in many countries. Nurses and physicians also report very high levels of exposure. Workers in government and private community service agencies, banks and other institutions serving the public are frequently confronted by attacks from individuals who have been kept waiting unduly, have been greeted with disinterest and indifference whether real or perceived, or were thwarted in obtaining the information or services they desired because of complicated bureaucratic procedures or technicalities that made them ineligible. Clerks in retail establishments receiving items being returned, workers staffing airport ticket counters when flights are overbooked, delayed or cancelled, urban bus or trolley drivers and conductors, and others who must deal with customers or clients whose wants cannot immediately be satisfied are often targets for verbal and sometimes even physical abuse. Then, there are those who must contend with impatient and unruly crowds, such as police officers, security guards, ticket takers and ushers at popular sporting and entertainment events. The link between an event of heavy work-related hazard and a defined behavioural disorder was for the first time observed on workers engaged in emergency-facing, rescue, firefighting or any other activity having brought about suffering violence at the workplace, such as for bank employees, police officers, penitentiary officers, bus drivers, etc. People involved in incidents occurring at the workplace, not necessarily as injured but as bystanders, might also develop the condition. These events are particularly relevant for people directly involved because of work, such as police officers, fire-fighters, military personnel, and other emergency responders.

Main health effects and diagnostic criteria

Name of the diseases and ICD code: **Post-traumatic stress disorder (PTSD) (acute/chronic) (F43.1 +Z57)**

Short description of the disease

PTSD is a disorder characterized by features that include:

- re-experiencing the traumatic event or events in the present in the form of vivid intrusive memories, flashbacks, or nightmares. Re-experiencing may occur via one or multiple sensory modalities and is typically accompanied by strong or overwhelming emotions, particularly fear or horror, and strong physical sensations;
- avoidance of thoughts and memories of the event or events, or avoidance of activities, situations, or people reminiscent of the event(s); and
- persistent perceptions of heightened current threat, for example as indicated by hypervigilance or an enhanced startle reaction to stimuli such as unexpected noises. The symptoms persist for at least several weeks and cause significant impairment in personal, family, social, educational, occupational or other important areas of functioning.

2.4.1 Post-traumatic stress disorder ICD Code F43.1 +Z57

Anxiety, depression, and alcohol/substance abuse are commonly associated with the above symptoms and signs, and suicidal ideation is not infrequent. In a small proportion of cases, the condition may follow a chronic course over many years, with an eventual transition to an enduring personality change. The symptoms can cause significant impairment in personal, family, social, educational, occupational or other important areas of functioning.

Most of the time, the symptoms occur within three months from the occurrence of the traumatic event. If symptoms occur six months after the stressor, the onset is defined as delayed. The variability of symptoms is mostly subjective. The severity and duration of the disorder vary and may persist for months or even years, but most patients recover within a year. In some cases, however, recovery can take much longer and lead to profound and prolonged disability. The disease is classified as "acute" if symptoms last for less than three months. Above this limit, it is considered "chronic".

Diagnostic criteria

Clinical manifestations

The diagnosis of occupational PTSD is based on the evidence of the causal association between the symptoms and a well-identified specific event in the occupational context. Below is a summary of diagnostic criteria for PTSD, based on the criteria included in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5).

Criterion A (one required): the person was exposed to: death, threatened death, actual or threatened serious injury, or actual or threatened sexual violence, in the following way(s):

- direct exposure;
- witnessing the trauma;
- learning that a close work colleague was exposed to trauma; and
- indirect exposure to aversive details of the trauma, usually in the course of professional duties (e.g. first responders, medics).

Criterion B (one required): the traumatic event is persistently re-experienced, in the following way(s):

- intrusive thoughts;
- nightmares;
- flashbacks;
- emotional distress after exposure to traumatic reminders; and
- physical reactivity after exposure to traumatic reminders.

Criterion C (one required): avoidance of trauma-related stimuli after the trauma, in the following way(s):

- trauma-related thoughts or feelings; and
- trauma-related reminders.

Criterion D (two required): negative thoughts or feelings that began or worsened after the trauma, in the following way(s):

- inability to recall key features of the trauma;
- overly negative thoughts and assumptions about oneself or the world;
- exaggerated blame of self or others for causing the trauma;
- negative affect;
- decreased interest in activities;
- feeling isolated; and
- difficulty experiencing positive affect.

Criterion E (two required): trauma-related arousal and reactivity that began or worsened after the trauma, in the following way(s):

- irritability or aggression;
- risky or destructive behaviour;
- hypervigilance;
- heightened startle reaction;
- difficulty concentrating; and
- difficulty sleeping.

Criterion F (required): symptoms last for more than one month.

Criterion G (required): symptoms create distress or functional impairment (e.g. social, occupational).

Criterion H (required): symptoms are not due to medication, substance use, or other illness.

Note that predisposing factors, such as the previous history of neurotic illness or personality traits (e.g. compulsive, asthenic), may lower the threshold for the development of the syndrome or aggravate its course, but they are neither necessary nor sufficient to explain the occurrence of the condition.

2.4.1 Post-traumatic stress disorder — ICD Code F43.1 +Z57

Differential diagnosis

Post-traumatic stress disorder is not the only disorder that may be triggered by a traumatic event. Differential diagnoses to be considered are:

- depression;
- specific phobias;
- adjustment disorders;
- enduring personality changes after catastrophic experience;
- dissociative disorders;
- neurological damage due to injuries sustained during the event; and
- psychosis.

Exposure assessment

- History of occupational exposure: confirmed occupational exposure to dramatic events or physical and psychological violence (directly or indirectly).
- Minimum duration of exposure: a single event can cause the condition.
- Maximum latent period: six months, except for delayed onset where symptoms may occur six months after the stressful event.

Key actions for prevention

Awareness of the problem in high risk workplaces and pro-active introduction of measures can prevent, to the extent possible, the occurrence of the traumatic events themselves as well as of job-related PTSD, mitigate its symptoms and long-term consequences, hasten recovery and avoid job withdrawal. This last consequence can lead to the loss of considerable professional experience, especially from older workers, and to significant difficulty in re-employment. Avoiding re-exposure of workers who have already suffered an event of violence or harms to the same high risk situation(s) and, contemporarily, paying attention not to prejudice their employability and career development may ameliorate symptoms. On the contrary, facing re-exposure to the same threat can prolong recovery and lead to withdrawal from occupation. It is therefore fundamental, in the presence of cases, to evaluate the situation where the event happened and verify whether there is the possibility of taking action to prevent its reoccurrence.

People working in occupations where there is a higher probability of experiencing a dramatic incident should be adequately trained.

In detail, the primary preventive methods include:

- Description of potential risks which may occur in the profession (awareness), and training on prevention, avoidance, control and preparedness, including training on possible traumatic reactions.
- Collective preparedness and safety measures by workplace design, appropriate safety precautions and protective measures. Such measures would include "disaster planning" for workplaces where dramatic incidents have a low probability but high consequence.
- Effective training on safety precautions for possible traumatic events, as well as on self-defence and self-protection where appropriate.
- Involvement of workplace occupational health services.
- Safety exercises for the events most likely to occur.

The secondary prevention measures needed are dependent on the type of trauma and on the context of the event. Only a few generic guidelines can be given. Acute stress reactions can be managed by occupational health services or general health care, while PTSD needs specialized psychiatric care (tertiary prevention).

- Earliest possible identification of symptoms by using clinical criteria.
- For acute and short-term reactions (below three months):
  - provide good and trusted therapeutic contact and follow-up;
  - offer an individual trauma-focused cognitive behavioural therapy (CBT) intervention;
  - ensure the presence of a social network, family, friends, other social supporters; and
  - offer help and support in everyday activities.

Note that psychological debriefing may be counterproductive.

2.4.1 Post-traumatic stress disorder	ICD Code F43.1 +Z57
Key actions for prevention	Tertiary prevention requires access to mental health services. When facing manifest PTSD, specific interventions may include: • follow-up of individuals after the traumatic event for the possible onset of symptoms and advised to seek help; • help the person manage any issues that might be a barrier to engaging with trauma-focused therapies, such as substance misuse, dissociation, emotional dysregulation, interpersonal difficulties or negative self-perception; • consider specialized clinical care with trauma-focused cognitive behavioural therapy (CBT), and eye movement desensitization and reprocessing (EMDR); and • pharmacotherapy should be considered for established symptoms following national guidance and best practices.

Further reading

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▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
2.4.1	Post-traumatic stress disorder	F43.1	6B40, 6B41
	Occupational exposure to risk factors	Z57	QD84.Y

3. Occupational cancer

3.1. Cancer caused by the following agents

3.1.1 Occupational cancer caused by asbestos	ICD Code C45, C34, C32, C56 + Z57.2, T57.8
General characteristics of the causal agent	*Asbestos* is a fibrous silicate existing in nature in different forms. Its fibres are long and thin (length-to-diameter ratio > 3) and either curved (serpentine) or straight (amphiboles). The main natural forms are chrysotile among serpentine asbestos and crocidolite, amosite, actinolite, tremolite, and anthophyllite among amphiboles. The species most commonly used in industry are chrysotile (or white asbestos), amosite (or brown asbestos), and anthophyllite. The use of crocidolite (or blue asbestos) has been nowadays drastically reduced due to its ban in many countries of the world.
Occupational exposures	Asbestos was diffusely used since antiquity and in the 20th century for its fireproofing properties and resistance to abrasion and mechanical wear. Among the fields where asbestos was mostly employed are the fireproofing and thermal insulation of boilers, pipes, industrial reactors, buildings with mouldable mixtures of asbestos and inorganic binders or with asbestos-woven fabrics. Mixtures of asbestos fibres with mineral binders, such as concrete, allowed to manufacture lightweight and resistant items for building, especially water pipes and roofing tiles. The chemical resistance of asbestos fibres towards aggressive chemical substances was exploited to manufacture filters and gaskets. The minerals' resistance to mechanical wear was exploited to manufacture brakes. Bans on asbestos use are in place in more than 50 countries of the world, including Australia, South Africa, Japan, and the European Union. But not in Brazil, Canada, China, India, Russia, or the USA. Canada and the USA have laws regarding asbestos use restriction. Brazil accounted for about 10% of asbestos production and consumption, globally, in 2017; however, in the autumn of that same year the Brazilian Supreme Federal Court enacted a ban on extraction, commercialization, and use of asbestos throughout the entire country. Hence, the only remaining commercial producers remain China, Kazakhstan, potentially Zimbabwe, and Russia, with the last being the leading producer. Estimated global consumption of asbestos minerals decreased from about 2 million tons in 2010 to nearly 1.3 million tons in 2016. Where the ban has been successfully enforced, exposure is mostly limited to more or less gradual disposal of existing asbestos, as long as the asbestos containing items are taken out of service when they reach the end of their operative life and are scrapped. This is the case for railway carriages and ships, which can contain as much as 30% of their weight as asbestos-containing insulations. While for government-owned items, such as for military ships, there is very strict control on safe scrapping, privately-owned items, such as commercial ships and industrial equipment, are often cheaply scrapped to recycle metal, while asbestos-containing materials are often discarded and dumped with less attention. The demolition of buildings is another major source of exposure to asbestos and the generation of asbestos-contaminated non-recyclable waste. Occupational exposure to asbestos is possible in countries where the mineral is still used, in the extraction and production of the different asbestos products, as well as in insulation and residual materials. Products containing asbestos cement commonly seen include pipes, clapboards, and shingles, vinyl-asbestos floor tiles, asbestos paper in insulating and filtering products, material in clutch facings and brake linings, spray products used for thermal, fireproofing, and acoustic purposes, and textile products such as yarns, tape, cord, rope, and felt. Occupations potentially associated with asbestos exposure are: insulation workers, boiler makers, plumbers, pipe fitters, welders, steamfitters, and janitors.
Carcinogenic mechanisms, main health effects and diagnostic criteria	
Short profile of the carcinogenic mechanisms	The evidence in humans for the carcinogenicity of all forms of asbestos (chrysotile, crocidolite, amosite, tremolite, actinolite, and anthophyllite) is considered to be sufficient. Asbestos causes mesothelioma (pleural and peritoneal) and cancer of the lung, larynx, and ovary. All forms of asbestos have been classified as carcinogenic to humans (Group 1) by the IARC. Positive associations have been observed with pharyngeal, gastric, and colorectal cancer.

3.1.1 Occupational cancer caused by asbestos — ICD Code C45, C34, C32, C56 + Z57.2, T57.8

Short profile of the carcinogenic mechanisms

Even though all asbestos fibres can cause cancer, their potency and the associated health risks are different. In this respect, the most dangerous compounds are the amphiboles. Most aspects of the physical, chemical and biological mechanisms that take part in the development of asbestos-caused cancers are still a source of active research and debate. The persistence of inhaled fibres in the lung or migration in the body cavities (pleura and peritoneum) is considered basic to the development of asbestos-related neoplasms.

Asbestos fibres have several physicochemical properties that are relevant for their pathogenicity, in detail: the chemistry, reactivity, and surface area, together with the dimension of the fibres and their biopersistence. The multiple mechanisms that have been proposed most likely act at various stages of the development of cancer. Asbestos fibres have been shown to produce free radicals, which are able to induce direct genotoxicity and interfere with the mitotic apparatus of the cells. Tissue injury, genotoxicity, and epigenetic alterations may derive from the generation of reactive oxygen and nitrogen species, producing persistent inflammation and chronic oxidative stress.

Name of the diseases and ICD code: **Malignant mesothelioma (C45) + Z57.2, T57.8**

Short description of the disease

Pleural and peritoneal mesotheliomas are rare malignancies occurring in the mesothelial cells that line these cavities, i.e., serous membranes. The first reported epidemiological evidence of pleural mesothelioma due to occupational exposure to asbestos was in South Africa in 1960. About 80% of mesothelioma patients have had some occupational exposure to asbestos. Amphibole fibres are associated with a higher risk of neoplasms than chrysotile. The latency between first exposure and onset of the disease is usually 20 years or more, up to 40 – 50 years. The prognosis is very poor, and the survival from the point of diagnosis is usually less than 1.5 years (estimated median survival times varies from 4 to 12 months). Smoking does not influence the risk of mesothelioma.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms:
  - Disease onset is often insidious, with chest pain and dyspnoea being very common presenting symptoms. Other accompanying symptoms may include fever, sweats, weight loss, and fatigue.
  - Findings of pleural effusion are usually noted upon percussion and auscultation on physical examination.
- Examinations:
  - Chest X-ray may show a unilateral pleural effusion, in some cases associated with a pleural-based mass or masses. After clinical assessment and chest X-ray or CT imaging, thoracentesis with an aspiration of pleural effusion fluid is generally conducted.
  - Surgical tissue biopsy (e.g. video-assisted thoracoscopic surgery - VATS) could represent the primary investigation for diagnosis, but in those with poor physical condition minimally invasive procedures (e.g. thoracentesis and fine needle aspiration) can be conducted.
  - Cytological features and histology are needed to confirm a diagnosis of mesothelioma. The confirmation can be reached only through immunocytochemistry, which is currently the standard ancillary procedure for distinguishing this malignancy from other types of cancer. This technique relies on the detection of various mesothelial and carcinoma-related antigens in cytology cell block sections or in biopsy tissue; a panel of markers expected to be positive [e.g. calretinin, cytokeratins 5/6 (CK 5/6), Wilms tumour-1 (WT-1) and podoplanin/D2-40] and negative (e.g. TTF1, CEA, Ber-EP4) should be performed to guide the differential diagnosis. Histological subtype (epithelioid, sarcomatoid or biphasic) should be described as well due to its prognostic value, along with age, sex, tumour stage, and Karnofsky score (a method to assess the functional status of a patient).
  - None of the available blood markers to be looked for seems sufficiently reliable to be used currently in the early diagnosis of mesothelioma.

Clinical manifestations of peritoneal mesothelioma

- Signs and symptoms: affected subjects most frequently report abdominal pain and distension. Other symptoms include abdominal mass, anorexia, weight loss, and abdominal wall hernia.
- Examinations:
  - Areas of bowel structures with fixity and loss of peristaltic activity are shown through radiographic studies with barium administration, whilst CT shows tumour mass and related ascites.
  - Laparoscopy can be used to assess the volume and distribution of the disease.
  - Diagnosis is confirmed through histopathological analysis of tissue biopsies (obtained either percutaneously or surgically).
  - Mesothelioma typically stains positive for D2-40, CK 5/6, calretinin, and WT-1 and negative for BerEP4 antibody and thyroid transcription factor 1 (TTF1).

3.1.1 Occupational cancer caused by asbestos ICD Code C45, C34, C32, C56 + Z57.2, T57.8

Exposure assessment

- History of occupational exposure: evidence of occupational exposure to asbestos. Exposure may be confirmed, although not necessary, by the presence of asbestos bodies or fibres in biological samples (sputum, fluid from bronchoalveolar lavage - BAL or lung biopsy); the presence of pleural plaques is indicative of exposure to asbestos.
- Minimum duration of exposure: usually a few years, but shorter exposures can cause the disease. At present, it is not possible to assess whether there is a level of exposure in humans below which an increased risk of cancer would not occur: no threshold level of exposure has been identified. Even very small doses for very short exposure periods may cause the disease.
- Maximum latent period: not applicable.

Name of the diseases and ICD code: **Lung cancer (C34) + Z57.2, T57.8**

Short description of the disease

Asbestos can cause primary bronchial cancer. The presence of asbestosis increases the likelihood of a causal association between asbestos exposure and primary bronchial cancer. The risk shows a dose-response relationship, and it reaches the highest levels for the highest doses of exposure. There is considerable synergy between asbestos exposure and smoke in determining the risk. Lung cancer related to asbestos exposure is clinically similar to lung cancer from other causes. All histological types of bronchial cancer have been linked to asbestos exposure.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms:
  - Anorexia, asthenia, or weight loss.
  - New cough or change in chronic cough, sometimes with haemoptysis.
  - Nonspecific chest pain or pain from bone metastases to the ribs, vertebrae, or pelvis.
  - Local spread may cause obstruction of the bronchi with atelectasis and pneumonia, pleural effusion, superior vena cava syndrome (i.e., a plethora of symptoms following obstruction of blood flow through the superior vena cava, which include facial and arm swelling, nasal congestion, head fullness, headache and lightheadedness, nausea and dysphagia, distorted vision), change in voice (following the involvement of the recurrent laryngeal nerve), and Horner's syndrome (ipsilateral ptosis, miosis, anhidrosis, and enophthalmos following involvement of the inferior cervical ganglion and the paravertebral sympathetic chain).
  - Brain metastases may present with headache, seizures, altered mental status, nausea, and vomiting, while liver metastases might be associated with asthenia and weight loss.
  - Paraneoplastic syndromes including various symptoms related to immunomediated or secretory effects of tumours, such as syndrome of inappropriate antidiuretic hormone secretion, hypercalcaemia, digital clubbing, increased adrenocorticotropin production, anaemia, hypercoagulability, peripheral neuropathy, and myasthenic syndromes.
- Examinations:
  - Chest X-ray: radiologic manifestations of lung cancer are diverse and include lung nodules and pulmonary, cavitated, or apical mass, with or without associated lymphadenopathy.
  - Chest CT provides information on the details of the neoplastic lesion, its relationship to other anatomical structures, the status of the pleural space, and the size of mediastinal lymph nodes.
  - Sputum cytology is highly specific, although not sensitive, with the maximum yield provided when there are lesions in the central airways.
  - Thoracentesis can be used to make a diagnosis when malignant pleural effusions are present.
  - Fine needle aspiration of lymph nodes (supraclavicular or cervical) is frequently diagnostic.
  - Fiberoptic bronchoscopy can help visualisation of the major airways, brush of visible lesions or lung lavage (with cytological specimen evaluation), and assist various biopsy procedures, such as direct biopsy of endobronchial lesions, a transbronchial biopsy of peripheral nodules or of the lung parenchyma, and fine needle aspiration of mediastinal lymph nodes. Other biopsy techniques include percutaneous biopsy using image guidance, and endobronchial ultrasound (EBUS) guided biopsy.

3.1.1 Occupational cancer caused by asbestos ICD Code C45, C34, C32, C56 + Z57.2, T57.8

Exposure assessment

- History of occupational exposure: evidence of occupational exposure to asbestos. The causal attribution to asbestos relies on a reasonable medical certainty, on a probability basis, that asbestos has caused or contributed materially to the disease. In this context, other causes of the disease have to be thoroughly evaluated. The presence of asbestosis is an indicator of high exposure, note that asbestosis may contribute some additional risk of cancer of the lung. The presence of pleural plaques is indicative of exposure to asbestos, although they may be associated with low levels of exposure. At present, it is not possible to assess whether there is a level of asbestos exposure in humans below which risk of lung cancer would not occur. It has been estimated that a cumulative exposure of 25 fibres/years brings about a twofold increase in lung cancer risk. Exposure can be assessed through the determination of the asbestos fibres content in lung tissue, sputum or fluid from BAL.
- Minimum duration of exposure: usually no less than 10 years (but lower in case of very high exposure levels).
- Maximum latent period: not applicable.

Name of the diseases and ICD code: **Laryngeal cancer (C32) + Z57.2, T57.8**

Short description of the disease

Laryngeal cancer has been studied in several cohort and case-control studies, conducted among populations occupationally exposed to asbestos (e.g. insulation workers, asbestos miners and millers, workers in an asbestos-cement industry) in Europe, North and South America, and Asia. These investigations consistently showed a significantly positive association between asbestos exposure and cancer of the larynx.

Clinical manifestations

- Signs and symptoms: symptoms may vary depending on the structures involved by the tumour and the concomitant inflammatory reaction and may include dysphagia (the affected subject may refer to difficulty in swallowing), dysphonia, cough, dyspnoea, blood-stained sputum, together with fatigue and weakness, sore throat, and the presence of a neck mass. Otalgia should be carefully considered as a potential sign of laryngeal cancer.
- Examinations:
  - CT and MRI scans may show the extension of the tumour as well as its potential extension into the surrounding tissue.
  - Flexible laryngoscopy shows the presence of the tumour and provides opportunities for biopsies of the mass (most laryngeal cancers are squamous cell carcinomas).

Exposure assessment

- History of occupational exposure: evidence of occupational exposure to asbestos.
- Minimum duration of exposure: unknown.
- Maximum latent period: not applicable.

Name of the diseases and ICD code: **Cancer of the ovary (C56) + Z57.2, T57.8**

Short description of the disease

Investigations conducted on occupationally exposed female workers (e.g. employed in factories manufacturing asbestos-containing gas masks or asbestos-board insulation, and in asbestos-textile or asbestos-cement plants) showed positive associations with ovarian cancer, further supported by evidence arising among environmentally exposed females. Data are still insufficient to document specific histopathological types of ovarian cancers caused by asbestos exposure.

Clinical manifestations

Symptoms may be uncommon at the early stages of the disease and, when present, can be nonspecific, such as bloating, abdominal distention or discomfort, pelvic and abdominal pain, an effect of pressure on the bladder and rectum, a sense of constipation and early satiety, weight loss, and tiredness. Vaginal bleeding can be present. When the diagnosis is uncertain, imaging investigations such as pelvic ultrasonography and pelvic and abdominal computed tomography (CT) are warranted. If a diagnosis is suspected, laparoscopy might be recommended to confirm the diagnosis and stage the disease.

Exposure assessment

- History of occupational exposure: evidence of occupational exposure to asbestos.
- Minimum duration of exposure: unknown.
- Maximum latent period: not applicable.

3.1.1 Occupational cancer caused by asbestos	ICD Code C45, C34, C32, C56 + Z57.2, T57.8
Key actions for prevention	Due to the perceived and confirmed health hazard posed by asbestos, several substituting materials have been actively researched, developed and marketed to substitute asbestos in its several applications. Different types of heat resistant man-made mineral fibres (MMMF) are spun from molten rock (stone wool), from glass (fibreglass), from furnace slag (slag wool) and mixed with organic and inorganic binders to manufacture insulating materials. High-duty organic polymers and carbon fibres are used in several applications, including those where inorganic materials, such as asbestos, were mostly used before bans were enforced. In all workplaces where there is a residual or authorized presence of asbestos items, such as in insulation, roofing and brakes, encapsulation should avoid dispersion of fibres from the material when it is subject to environmental, mechanical or thermal stress. Workers in extraction, production and use of asbestos-containing materials and items, in the maintenance of brakes, and in the substitution of gaskets in the countries where bans have not yet been enforced should be provided with appropriate personal protective equipment. This also applies to workers involved at all phases of asbestos removal in buildings and equipment, in ship demolition yards, in the disposition of removed asbestos materials at landfills. The very large amount of asbestos-containing materials that were produced in close to one century of manufacturing and use and that is headed for disposal calls for adequate dumping sites, the space for which is at a premium, and that can pose a future threat or limitations to future use of these areas. This is especially true of materials that derive from the demolition of buildings since this is a heavy mixture of concrete, rubble, iron and is little if at all amenable to compacting. To overcome a future shortage of dumping space, asbestos deriving from the demolition of concrete can be recycled as secondary raw materials and re-incorporated as the inert component of concrete ("*geopolymers*") in new buildings. Several processes for thermal inertization of waste asbestos have been devised to this purpose and mostly use existing technologies and plants.

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▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
3.1.1	Malignant mesothelioma	C45	XH0XV0
3.1.1	Lung cancer	C34	2C25.Z
3.1.1	Laryngeal cancer	C32	2C23.Z
3.1.1	Ovarian cancer	C56	2C73.Z
	Occupational exposure to dust	Z57.2	QD84.0
	Other specified inorganic substances	T57.8	XM53B3

3.1.2 Occupational cancer caused by benzidine and its salts — ICD Code C67 +Z57

General characteristics of the causal agent	Benzidine is a greyish-yellow, reddish-grey, or white crystalline powder which darkens on exposure to light and air. Molecular mass 184.2. Density 1.3 gm/cm^3. Melting point 120°C, boiling point 401°C. There is little evaporation at 20°C (i.e., room temperatures). It is an aromatic amine that is soluble in solvents like alcohol and ether (octanol water partition coefficient 1.34 log Pow). Poorly soluble in water (solubility <0.05 g/100 ml water). It reacts violently with strong oxidants, and should be stored separately from these. It is combustible, producing irritant and toxic fumes in a fire.
Occupational exposures	In the past, benzidine was used extensively in the chemical synthesis of azo-dyes and, to a much lesser extent, as a hardener in the rubber industry. It has also been used in specialty applications such as a constituent of chemical laboratory reagents, stains for microscopy, and liquid crystals for electronic applications. Vapours from hot processes and benzidine dust are readily absorbed into the body by inhalation, and skin absorption occurs. It is widely distributed in the body. The carcinogenicity of benzidine and other aromatic amines such as 2-naphthylamine and 4-aminobiphenyl was recognised in the late 19th century. In the chemical industry, co-exposures with other aromatic amines and other carcinogens have proved important in the development of cancers. In developed countries, during the second half of the 20th century, use of benzidine was progressively eliminated or substituted. However, its production and use in dye production have been reported in some developing or in-transition countries. Small quantities may still be used in laboratories in developed countries. Current levels of exposure are unclear.
Carcinogenic mechanisms, main health effects and diagnostic criteria	
Short profile of the carcinogenic mechanisms	Vapours from hot processes and benzidine dust are readily absorbed by inhalation, and skin absorption occurs. It is widely distributed in the body. Once absorbed, it is metabolised to toxic reactive intermediates. Metabolic activation occurs via multiple pathways in different organs, e.g. N-oxidation in the liver, and O-acetylation in the bladder. Studies indicate that it is a genotoxic carcinogen. Metabolic products are mutagenic (damaging DNA), and clastogenic (directly damaging chromosomes). In exposed workers, chromosomal aberrations have been observed in the peripheral lymphocytes. Animal studies have shown DNA lesions in bladder, liver and lung tissues, increased frequency of micronucleated bone marrow cells, unscheduled DNA synthesis, and increased DNA strand breaks. In vivo studies of *S.typhimurium* mutagenicity are also positive. It is subject to phase I metabolism (e.g. by N-acetylation) and phase II metabolism (e.g. by glutathione-S-transferase). It is principally excreted in the urine, so that the urothelium is exposed to carcinogenic products. The International Agency for Research on Cancer (IARC) classifies benzidine as a Group 1 carcinogen, with sufficient evidence of bladder cancer in humans, and of bladder and other cancers in animal models.

Name of the diseases and ICD code: **Bladder cancer (C67)**

Short description of the disease

The association between bladder cancer and aromatic amines like benzidine has been reported since the second half of the 19th century. Since the 1950s, epidemiological studies have demonstrated a very strong association between bladder cancer and benzidine exposure, with extremely high relative risks, odds ratios and standardised mortality ratios. The latent period between exposure and cancer is typically of the order of two decades. IARC classifies benzidine as a Group 1 carcinogen, with sufficient evidence of bladder cancer in humans. In animal models there is sufficient evidence of cancer of the bladder, liver, and mammary glands. More recently, an association with lung cancer has been suggested. Risk is increased if there are co-exposures with other carcinogens such as other aromatic amines, and in particular cigarette smoke.

It has been proposed that individual genetic susceptibility such as acetylator polymorphism may be important in the development of bladder cancer. For example N-acetyltransferase metabolises benzidine to less reactive intermediates, and “slow acetylators” who have lower levels of N-acetyltransferase may be more susceptible to bladder cancer (N.B. “slow acetylators” were first identified because they metabolise the anti-tuberculous drug isoniazid more slowly; this is relatively common in European populations, while “rapid acetylators” are common in Chinese and Japanese populations). Similarly, individuals with lower levels of glutathione-S-transferase may be more susceptible.

3.1.2 Occupational cancer caused by benzidine and its salts — ICD Code C67 +Z57

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: the affected subject may report blood or blood clots in urine, dysuria, urinary frequency, and nocturia. Bleeding and tumour may cause obstruction of the lower urinary tract, accompanied by feeling the need to urinate but being unable to do so. This may lead to hydronephrosis with loin pain. Other symptoms of advanced bladder cancer may include pain in the back or pelvis, unexplained appetite loss, and weight loss.
- Examinations: urinalysis is used to assess the presence of a haematuria; urine cytology and cystoscopy help to reveal cancer cells and detect growths in the bladder that need biopsy or surgery. Computed tomography (CT), magnetic resonance imagining (MRI), positron emission tomography (PET), and ultrasound help to stage the cancer.

Exposure assessment

- History of occupational exposure: evidence of prolonged or repeated exposure to benzidine or its salts, considering all the possible exposure routes (including dermal absorption).
- Minimum duration of exposure: one year, but shorter periods of exposure (months) have been reported.
- Maximum latent period: not applicable.

Key actions for prevention	The hierarchy of controls is normally employed to protect workers from hazardous substances: namely elimination, substitution, engineering controls and personal protective equipment. Since the second half of the 20th century, progressive elimination and substitution of benzidine has been the primary method of controlling occupational exposure. Any residual manufacturing should be performed in enclosed reactors with appropriate engineering and ventilation controls. Any skin, eye and respiratory exposure should be prevented. Workers should be instructed not to eat, drink or smoke in the workplace. Any contaminated work clothing should be bagged and cleaned or disposed of in the workplace, and not taken home. Plant maintenance and management of spillages present risks, and high levels of personal protective equipment may be needed, e.g. self-contained breathing apparatus and chemical protection suits. Because it is a genotoxic agent, causing cancer, with long latent periods following exposure, it is challenging to define safe exposure levels. In consequence, occupational exposure standards for environmental air levels are not quoted for benzidine. In theory, measuring levels of DNA adducts could be used as a form of biological effect monitoring. However, this would be highly unethical, because workers might be exposed to levels of benzidine that could cause cancer. Because of practical and similar ethical issues, screening of workers for N-acetyltransferase and glutathione-S-transferase has not been employed as a preventative measure. Waste disposal is regulated in most countries, and must be carefully controlled. Measurement of benzidine levels in industrial waste has been used as a marker of toxicological hazard.

3.1.2 Occupational cancer caused by benzidine and its salts ICD Code C67 +Z57

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For the chemical entities listed below an entry exists in the collection of International Chemical Safety Cards (ICSC) hosted in the ILO website

Name	Synonyms	ICSC
Benzidine	(1,1'-Biphenyl)-4,4'-diamine; 4,4'-Diaminobiphenyl; p-Diaminodiphenyl; Biphenyl-4,4'-ylenediamine	0224

▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
3.1.2	Bladder cancer	C67	2C94
	Exposure to occupational risk factors	Z57	QD84.Y

3.1.3 Occupational cancer caused by bis-chloromethyl ether (BCME)	ICD Code C34 +Z57
General characteristics of the causal agent	*Bis*-(chloromethyl)-ether (BCME; CAS number 542-88-1) is a volatile colourless liquid with a pungent odour, which forms explosive mixtures with air and decomposes on heating and on contact with water, producing toxic and corrosive fumes of hydrogen chloride and formaldehyde. This chemical attacks many resins and plastics and can corrode metals.
Occupational exposures	BCME can be used as such in the chemical industry or can be generated during chemical reactions aimed at introducing a -CH_2Cl chemical group in the structure of aromatic compounds (chloromethylation). The pure BCME reagent was often used in the past for chloromethylation, especially of styrene-divinylbenzene polymers and resins (Merrifield resins), to manufacture ion exchange resins for water purification and for the extraction of trace metals and the purification of water soluble organic compounds. To avoid the synthesis, purification, storage, and transport of pure BCME, chloromethylation is often performed with a mixture of formaldehyde and hydrochloric acid, catalysed by anhydrous zinc chloride (Blanc and Blanc-Quelet reactions) and often produces an excess of BCME as a reaction by-product. BCME, and chloromethyl methyl ether (CMME), can be formed in the presence of methyl alcohol (that can be present in concentrated solutions of formaldehyde as a product of the spontaneously occurring Cannizzaro reaction). BCME can spontaneously form when mixing formaldehyde and hydrogen chloride solutions, such as in the inadvertent mixing of disinfectant and cleaning products in industrial and household cleaning. Since BCME is a hazardous industrial substance, analytical chemical laboratories measure it in different matrices for control purposes. Therefore, there is a potential for exposure to minute amounts for workers in analytical chemical laboratories who perform chemical measurements of BCME.
Carcinogenic mechanisms, main health effects and diagnostic criteria	
Short profile of the carcinogenic mechanisms	BCME can be readily absorbed by inhalation and skin contact. Due to its chemical reactivity as a strong electrophile, as well as to its decomposition into hydrogen chloride and formaldehyde, it is a strong irritant at the point of contact, mainly the external mucosa and the lung. For the same reason, its toxicity is mostly confined to the site of contact. The mechanisms underlying the carcinogenicity of BCME are not completely understood. The fact that this chemical is a strong alkylating agent provides evidence that it can operate by a genotoxic mechanism of action (i.e., a mechanism similar to that of strong alkylating agents with DNA modifications and resulting mutations). The International Agency for Research on Cancer (IARC) classified BCME as Group 1 human carcinogen.

Name of the diseases and ICD code: **Lung cancer C34 +Z57**

Short description of the disease

Several investigations from different countries indicated an increased risk of lung cancer in workers exposed to BCME. Available histological evaluation documented that exposure resulted mainly in small-cell type lung cancer. In the early stages of the disease, symptoms may be absent.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms:
  - Anorexia, asthenia, or weight loss.
  - New cough or change in chronic cough, sometimes with haemoptysis.
  - Nonspecific chest pain or pain from bone metastases to the ribs, vertebrae, or pelvis.
  - Local spread may cause obstruction of the bronchi with atelectasis and pneumonia, pleural effusion, superior vena cava syndrome (i.e., a plethora of symptoms following obstruction of blood flow through the superior vena cava, which include facial and arm swelling, nasal congestion, head fullness, headache and lightheadedness, nausea and dysphagia, distorted vision), change in voice (following the involvement of the recurrent laryngeal nerve), and Horner's syndrome (ipsilateral ptosis, miosis, anhidrosis, and enophthalmos following involvement of the inferior cervical ganglion and the paravertebral sympathetic chain).
  - Brain metastases may present with headache, seizures, altered mental status, nausea, and vomiting, while liver metastases might be associated with asthenia and weight loss.
  - Paraneoplastic syndromes include various symptoms related to immune-mediated or secretory effects of tumours, such as syndrome of inappropriate antidiuretic hormone secretion, hypercalcaemia, digital clubbing, increased adrenocorticotropin production, anaemia, hypercoagulability, peripheral neuropathy, and myasthenic syndromes.

3.1.3 Occupational cancer caused by bis-chloromethyl ether (BCME) ICD Code C34 +Z57

- Examinations:
  - Chest X-ray: radiologic manifestations of lung cancer are diverse and include lung nodules and pulmonary, cavitated, or apical mass, with or without associated lymphadenopathy.
  - Chest CT provides information on the details of the neoplastic lesion, its relationship to other anatomical structures, the status of the pleural space, and the size of mediastinal lymph nodes.
  - Sputum cytology is highly specific, although not sensitive, with the maximum yield provided when there are lesions in the central airways.
  - Thoracentesis can be used to make a diagnosis when malignant pleural effusions are present.
  - Fine needle aspiration of lymph nodes (supraclavicular or cervical) is frequently diagnostic.
  - Fiberoptic bronchoscopy can help visualisation of the major airways, brush of visible lesions or lung lavage (with cytological specimen evaluation), and assist various biopsy procedures, such as direct biopsy of endobronchial lesions, a transbronchial biopsy of peripheral nodules or of the lung parenchyma, and fine needle aspiration of mediastinal lymph nodes. Other biopsy techniques include percutaneous biopsy using image guidance, and endobronchial ultrasound (EBUS) guided biopsy.

Key actions for prevention	Due to the toxicological hazard of BCME, the production of pure chemicals for chemical manufacturing has been greatly reduced or discontinued. BCME is generated from formaldehyde and hydrogen chloride, and the reaction is performed in batch, in closed vessels, and with a tight control to minimize the formation and dispersion of the compound. Since chloromethylation is a very common chemical reaction used to introduce functional groups and technological properties in several organic materials, there is an ongoing effort to develop alternative techniques to perform the reaction or to obtain the same end products by overcoming the use of toxic reagents. One alternative is to use as reagents some long-chain, non-volatile halomethyl ethers that entail far less carcinogenic risk. Lately, some chemical processes that incorporate chloromethyl-benzene units in non-aromatic polymer resins, such as in polyvinyl chloride, without using chloromethylating reagents have been proposed and patented.

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For the chemical entities listed below an entry exists in the collection of International Chemical Safety Cards (ICSC) hosted in the ILO website

Name	Synonyms	ICSC
Bis-chloromethyl ether (BCME)	sym-Dichloromethyl ether; 1,1'-Dichlorodimethyl ether, Oxybis(chloromethane), Chloro(chloromethoxy)methane	0237
Chloromethyl methyl ether	Dimethylchloro ether, Chloromethoxymethane	0238

▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
3.1.3	Lung cancer	C34	2C25.Z
	Occupational exposure to risk factors	Z57	QD84.Y

3.1.4 Occupational cancer caused by chromium VI compounds	ICD Code C34 +Z57
General characteristics of the causal agent	Chromium (Cr), CAS number 7440-47-3, is the chemical element with atomic number 24 in the periodic table of elements, and belongs to Group 6 (III-B, Transition metals) in the element families. Naturally occurring chromium is composed of three stable isotopes, with ^{52}Cr (83.8%) being the most abundant and has an average atomic mass of 51.9961 Da. Chromium exists in a series of oxidation states from -2 to +6 valence. The most important stable states are 0 (elemental metal), +3 (trivalent), and +6 (hexavalent). This metal occurs in the environment mainly in two oxidation states, i.e., trivalent (III) (chromite ore) and hexavalent (VI) (industry products) chromium. Most chromium is biologically present as transient forms in the physiological reduction of chromium (VI) to chromium (III). Chromium (III) is claimed to be an essential trace element in humans and is much less toxic than chromium (VI). The artificial isotope ^{51}Cr (half-life of 27.7 days) has laboratory applications in diagnostic tests. Elemental chromium is a hard solid, corrosion-resistant metal, blue-white to steel-grey and shiny. In the environment, chromium occurs mostly as compounds, mainly in the stable and less toxic chromium (III) oxidation state and, to a limited extent, in the strongly oxidizing chromium (VI) oxidation state. Chromium (VI) is the chemical form of highest concern for occupational safety. Chromium (VI) compounds may react with reducing (organic) matter to form the most stable chromium (III). According to their solubility in water, hexavalent chromium compounds can be classified into two subgroups: a. w*ater-soluble* hexavalent chromium compounds: chromic acid and its anhydride, and the monochromates and dichromates of sodium, potassium, ammonium, lithium, caesium, and rubidium; and b. w*ater-insoluble* hexavalent chromium compounds: zinc chromate, calcium chromate, lead chromate, barium chromate, strontium chromate, and sintered chromium trioxide.
Occupational exposures	Compounds containing Cr (VI) are used in several industrial operations. The manufacture of relevant inorganic pigments such as lead chromates (used in turn to prepare chrome greens), zinc chromate, molybdate oranges, and chromium oxide green; corrosion inhibition; wood preservation; and coloured glasses and glazes. Basic chromic sulphates are widely used for tanning. Other well-known industrial uses of chromium-containing chemicals include the preparation of many important catalysts containing chromic oxide, the dyeing of textiles, and the production of light-sensitive dichromated colloids for use in lithography. Chromic acid is used for both “decorative” and “hard” chromium plating, where it is deposited in much thicker layers to give an extremely hard surface with a low friction coefficient. Due to the strong oxidizing action of chromates in acid solution, there are many industrial applications, particularly involving organic materials, such as the oxidation of picoline to give nicotinic acid and the oxidation of trinitrotoluene to give phloroglucinol. Chromium oxide is used to produce pure chromium metal that is suitable for incorporation in creep resistant, high temperature alloys and as a refractory oxide. It may be included in a number of refractory compositions (e.g. in magnetite and magnetite-chromate mixtures) with advantages. Occupational exposure to hexavalent chromium can thus be related to activities such as leather tanning, use of anticorrosive pigments for paints, chromium plating, stainless steel welding, use as mordants in dyeing fabrics, in battery production, and in engraving and lithography.

3.1.4 Occupational cancer caused by chromium VI compounds ICD Code C34 +Z57

Carcinogenic mechanisms, main health effects and diagnostic criteria

Short profile of the carcinogenic mechanisms	Hexavalent chromium compounds are well-known human lung carcinogens. Their carcinogenic activity depends, at least in part, on their solubility and chemical reactivity. Chromium (VI) is readily absorbed both by inhalation and oral routes. The respiratory tract is the primary target organ for inhaled chromium, and insoluble inhaled chromium particles can remain in the lung for a long time. Chromium (VI) is unstable in the body and is rapidly reduced to chromium (V), chromium (IV) and ultimately to stable chromium (III) by endogenous reducing agents. Absorbed chromium is distributed to all tissues of the body and is excreted primarily in the urine and to a lesser extent in faeces. Several potential mechanisms for the carcinogenicity of Cr (VI) have been highlighted, mostly due to the induction of mutagenic oxidative DNA lesions, which follow the intracellular reduction of Cr (VI) to Cr (III). This reaction occurs via intermediate chemical forms where the chromium ions are bound to organic ligands such as glutathione and ascorbate and gives rise to the production of several families of reactive intermediates (e.g. the hydroxyl radical). The International Agency for the Research on Cancer (IARC) considered the evidence in humans for the carcinogenicity of chromium (VI) compounds to be sufficient and classified them as carcinogenic to humans (Group 1), as they cause cancer of the lung. Positive associations have been observed with cancer of the nose and nasal sinuses.

Name of the diseases and ICD code: **Lung cancer (C34) +Z57**

Short description of the disease

Lung cancer caused by exposure to chromium (VI) compounds is not different from any other occupational and non-occupational lung cancer. Some data suggest that, among the different histologic subtypes, the one most often associated with chromium exposure is squamous cell carcinoma.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms:
  - Anorexia, asthenia, or weight loss.
  - New cough or change in chronic cough, sometimes with haemoptysis.
  - Nonspecific chest pain or pain from bone metastases to the ribs, vertebrae, or pelvis.
  - Local spread may cause obstruction of the bronchi with atelectasis and pneumonia, pleural effusion, superior vena cava syndrome (i.e., a plethora of symptoms following obstruction of blood flow through the superior vena cava, which include facial and arm swelling, nasal congestion, head fullness, headache and lightheadedness, nausea and dysphagia, distorted vision), change in voice (following the involvement of the recurrent laryngeal nerve), and Horner's syndrome (ipsilateral ptosis, miosis, anhidrosis, and enophthalmos following involvement of the inferior cervical ganglion and the paravertebral sympathetic chain).
  - Brain metastases may present with headache, seizures, altered mental status, nausea, and vomiting, while liver metastases might be associated with asthenia and weight loss.
  - Paraneoplastic syndromes include various symptoms related to immune-mediated or secretory effects of tumours, such as: syndrome of inappropriate antidiuretic hormone secretion, hypercalcaemia, digital clubbing, increased adrenocorticotropin production, anaemia, hypercoagulability, peripheral neuropathy, and myasthenic syndromes.
- Examinations:
  - Chest X-ray: radiologic manifestations of lung cancer are diverse and include lung nodules and pulmonary, cavitated, or apical mass, with or without associated lymphadenopathy.
  - Chest CT provides information on the details of the neoplastic lesion, its relationship to other anatomical structures, the status of the pleural space, and the size of mediastinal lymph nodes.
  - Sputum cytology is highly specific, although not sensitive, with the maximum yield provided when there are lesions in the central airways.
  - Thoracentesis can be used to make a diagnosis when malignant pleural effusions are present.
  - Fine needle aspiration of lymph nodes (supraclavicular or cervical) is frequently diagnostic.
  - Fiberoptic bronchoscopy can help visualisation of the major airways, brush of visible lesions or lung lavage (with cytological specimen evaluation), and assist various biopsy procedures, such as: direct biopsy of endobronchial lesions, a transbronchial biopsy of peripheral nodules or of the lung parenchyma, and fine needle aspiration of mediastinal lymph nodes. Other biopsy techniques include percutaneous biopsy using image guidance, and endobronchial ultrasound (EBUS) guided biopsy.

3.1.4 Occupational cancer caused by chromium VI compounds	ICD Code C34 +Z57
Exposure assessment • History of occupational exposure: evidence of prolonged or repeated exposure to chromium (VI) compounds, primarily via inhalation and, when available, workplace and biological monitoring. • Minimum duration of exposure: six months. • Maximum latent period: not applicable.	
Key actions for prevention	Due to their capacity to cause cancer in humans, the use of chromium (VI) compounds must be eliminated or at least limited. The use of the chromium trioxide-sulphuric acid solution ("*chromium mix*") for the thorough cleaning of laboratory glassware and of glass and crystal for etching and decoration has been eliminated and alternative metal finishing processes to chrome plating have been introduced. Since the exposure route for which there is the soundest evidence of carcinogenicity from chromium (VI) is inhalation and the target organ is the respiratory system, the most convenient prevention is encapsulation of the source and, whenever this does not ensure sufficient protection, the use of personal protective equipment. On the technical side, avoidance of exposure to chromium and its compounds depends on the appropriate design of processes, including adequate exhaust ventilation and the suppression of dust or mist containing chromium. Built-in control measures are necessary, requiring the least possible action by either process operators or maintenance staff. Wet methods of cleaning should be used where possible; at other sites, the only acceptable alternative is vacuum cleaning. Spill of liquids or solids must be removed to prevent dispersion as airborne dust. The concentration in the work environment of chromium-containing dust and fumes should preferably be measured at regular intervals by individual and area sampling. Where unacceptable concentration levels are found by either method, the sources of dust or fumes should be identified and controlled. Respiratory protection preferably with an efficiency of more than 99% in retaining particles of 0.5 µm size, should be worn when air borne exposure is possible, and it may be necessary to provide air-supplied respiratory protective equipment for jobs considered to be hazardous. Management should ensure that dust deposits and other surface contaminants should be removed by washing down or suction, before work begins. Providing laundered overalls daily will help in avoiding skin contamination. Hand and eye protection are generally recommended, as is the routine repair and replacement of all personal protective equipment (PPE). The medical surveillance of workers on processes in which chromium (VI) compounds may be encountered should include education on the toxic and carcinogenic properties of chromium (VI) compounds. The nature of the exposure, hazards, and subsequent risk of disease (e.g. lung cancer) should be described at job entry as well as at regular intervals during employment. The need to observe a high standard of personal hygiene should be emphasized. The group of experts considered that the following limits of exposure of workplace atmospheric concentrations have been observed to provide a reasonable level of protection for workers' health, and to be used in a number of countries: • Most water-soluble chromium (VI) compounds: 0.05 mg/m^3 as 8hr TWA. • Most water-insoluble chromium (VI) compounds: 0.01 mg/m^3 as 8hr TWA.

3.1.4 Occupational cancer caused by chromium VI compounds ICD Code C34 +Z57

Further reading

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For the chemical entities listed below an entry exists in the collection of International Chemical Safety Cards (ICSC) hosted in the ILO website

Group		Name	Synonyms	ICSC
Hexavalent chromium compounds	Water-soluble	Chromium (VI) oxide	Chromic trioxide; Chromic acid; Chromic anhydride	1194
		Ammonium bichromate	Diammonium dichromate (VI); Dichromic acid, diammonium salt; Ammonium bichromate	1368
		Sodium dichromate (anhydrous)	Disodium dichromate (VI); Dichromic acid, disodium salt; Disodium dichromium heptaoxide	1369
		Sodium chromate	Disodium chromate (VI); Chromic acid, disodium salt; Disodium chromium tetraoxide	1370
		Potassium dichromate	Dipotassium dichromate (VI); Dichromic acid, dipotassium salt; Potassium bichromate	1371
		Tert-butyl chromate	bis(tert-Butyl)chromate; Chromic acid, di-tert-butyl ester	1533
		Chromyl chloride	Chromic oxychloride; Dichlorodioxochromium; Chromium dichloride dioxide	0854
	Water-insoluble	Lead chromate	Chromic acid, lead (II) salt (1:1); Plumbous chromate	0003
		Zinc chromate	Chromic acid, Zinc salt (1:1); Chromium zinc oxide; Zinc tetraoxychromate	0811
		Strontium chromate	C.I. Pigment yellow 32; Chromic acid, strontium salt	0957
		Barium chromate	Barium chromate (VI); Barium chromate (1:1); Chromic acid, barium salt 1:1; C.I. 77103; C.I. Pigment Yellow 31	1607

▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
3.1.4	Lung cancer	C34	2C25.Z
	Occupational exposure to risk factors	Z57	QD84.Y

3.1.5 Occupational cancer caused by coal tars, coal tar pitches or soots ICD Code C34, C44 +T65.8 +Z57	
General characteristics of the causal agent	*Coal tar* is a heterogeneous viscous semi-solid material formed as a commercially valuable by-product of thermal treatments of some coals in chemical plants. These treatments aim at obtaining coal gas, a mixture of hydrogen and carbon monoxide used for combustion or as a starting material for the chemical industry, or coke, porous and poorly flammable coal used for the chemical reduction of ferrous and non-ferrous metal ores. *Coal tar pitch* is a black to brown sticky paste with a characteristic odour mainly formed of a complex and poorly characterized mixture of polycyclic aromatic hydrocarbons (PAH), alkyl derivatives, nitrogen and sulphur PAH analogues and derivatives such as aromatic amines, phenols and quinones. Depending on the characteristics of the coal feed and on the temperature of the coking and distillation process, the coal tar mixture contains variable proportions of volatile (anthracene, phenanthrene, pyrene), semivolatile (fluoranthene, benz(a)anthracene, naphthacene) and non-volatile PAH. Coal tar pitches decompose on heating above 400°C producing toxic fumes. *Soot* is a heterogeneous particulate material generated by the incomplete combustion of any type of carbon-containing material and mainly consisting of elemental graphitic carbon, of adsorbed or tightly embedded high molecular weight PAH, and of metal oxides and silicates originally present in the carbonaceous fuel.
Occupational exposures	*Coal tar* is produced in coke or coal gas plants and is nowadays mainly used as a cheap fuel in burners rather than for the extraction and separation of its components, although this activity has not been completely discontinued. It is used as such as a timber preservative, especially for wooden railway sleepers and electric wire poles. Some brands of elemental carbon (carbon blacks) are nowadays industrially prepared to possess more or less broadly defined technological properties by specific processes starting from well-defined raw materials. Occupational exposure can occur in chemical plants for coal distillation and coke manufacture, in briquette making for household heating, and in timber proofing. *Coal tar pitch* is used in the activities of roofing. The exposures associated with roofing are the result of the removal of an old roof by cutting, prying and scraping the existing material from the roof and discarding it. The installation of a new roof follows, by melting solid blocks of coal tar pitch, pumping or carrying buckets of the molten material to the roof, and spreading layers of liquid coal tar pitch and roofing felt upon the surface to produce a cover. Coal tar pitch can also be used in the paving industry; although this use is being gradually discontinued, workers in road paving continue to be potentially exposed to this substance due to the use of recycled coal tar asphalt in some countries. *Soot* is seldom industrially produced or employed as such but is rather the final product of combustion for energy production. Occupational exposure to combustion soot is likely to occur wherever combustion plants are operated, such as in coal or liquid fuel fired power plants, in coke ovens and blast furnaces, in ship engine rooms, and in chimney sweeping.
Carcinogenic mechanisms, main health effects and diagnostic criteria	
Short profile of the carcinogenic mechanisms	Tars and pitches are viscous and semi-solid materials, and occupational exposure occurs mainly through skin contact. Pitches are usually difficult to remove from the skin by washing. Residual material on the surface of the skin penetrates the stratum corneum of the epidermis, or even the dermis, where lipophilic particles can remain embedded for several weeks until the natural turn-over of epithelial cells brings them back to the surface, and they are lost with exfoliated cells. The extent of absorption depends on the permeability of the skin, the duration of exposure and the efficacy of removal. Aggressive washing, particularly with hot water can enhance absorption by increasing skin permeability and blood flow. When tars and pitches are heated, fumes and vapours may cause inhalation exposure. This route of exposure may occur when solid compounds are mechanically processed with the generation of dusts. Once absorbed into the bloodstream, the components of tars and pitches undergo the same biological fate of all large polycyclic aromatic hydrocarbons.

3.1.5 Occupational cancer caused by coal tars, coal tar pitches or soots
ICD Code C34, C44 +T65.8 +Z57

Short profile of the carcinogenic mechanisms	Soot is usually much drier, and therefore less adhesive to skin. Exposure can occur through inhalation, as well as through the dermal route. The extent of respiratory absorption depends on the size distribution of the particles, which in turn determines the depth of penetration into the lung, the systemic absorption of the individual compounds, and the associated extent of toxic damage at the organ and organism level. All classes of these carbon-derived materials are of highly heterogeneous composition, and this influences their toxic properties. Often, the toxic compounds act synergistically, as in the case of partially oxidized PAH (quinones, strained-ring molecules, free radicals), and some metal ions (mostly copper, iron, vanadium), that are able to sustain the production of oxygen-centred free radicals via catalytic reactions (Fenton or Haber-Weiss cycle). The IARC classifies occupational exposures to coal tar during distillation, coal tar pitch as encountered in paving and roofing, and soot (as found in occupational exposure of chimney sweeps) as carcinogenic to humans (Group 1 carcinogens).

Name of the diseases and ICD code: **Lung cancer (C34) +T65.8 +Z57**

Short description of the disease

Exposures to coal tar pitch and soot cause cancer of the lung. Evidences come mainly from studies of pavers, roofers, and chimney sweeps, where increases in lung cancer risk were observed.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms:
  - Anorexia, asthenia, or weight loss.
  - New cough or change in chronic cough, sometimes with haemoptysis.
  - Nonspecific chest pain or pain from bone metastases to the ribs, vertebrae, or pelvis.
  - Local spread may cause obstruction of the bronchi with atelectasis and pneumonia, pleural effusion, superior vena cava syndrome (i.e., a plethora of symptoms following obstruction of blood flow through the superior vena cava, which include facial and arm swelling, nasal congestion, head fullness, headache and lightheadedness, nausea and dysphagia, distorted vision), change in voice (following the involvement of the recurrent laryngeal nerve), and Horner's syndrome (ipsilateral ptosis, miosis, anhidrosis, and enophthalmos following involvement of the inferior cervical ganglion and the paravertebral sympathetic chain).
  - Brain metastases may present with headache, seizures, altered mental status, nausea, and vomiting, while liver metastases might be associated with asthenia and weight loss.
  - Paraneoplastic syndromes include various symptoms related to immune-mediated or secretory effects of tumours, such as syndrome of inappropriate antidiuretic hormone secretion, hypercalcaemia, digital clubbing, increased adrenocorticotropin production, anaemia, hypercoagulability, peripheral neuropathy, and myasthenic syndromes.
- Examinations:
  - Chest X-ray: radiologic manifestations of lung cancer are diverse and include lung nodules and pulmonary, cavitated, or apical mass, with or without associated lymphadenopathy.
  - Chest CT provides information on the details of the neoplastic lesion, its relationship to other anatomical structures, the status of the pleural space, and the size of mediastinal lymph nodes.
  - Sputum cytology is highly specific, although not sensitive, with the maximum yield provided when there are lesions in the central airways.
  - Thoracentesis can be used to make a diagnosis when malignant pleural effusions are present.
  - Fine needle aspiration of lymph nodes (supraclavicular or cervical) is frequently diagnostic.
  - Fibreoptic bronchoscopy can help visualisation of the major airways, brush of visible lesions or lung lavage (with cytological specimen evaluation), and assist various biopsy procedures, such as direct biopsy of endobronchial lesions, a transbronchial biopsy of peripheral nodules or of the lung parenchyma, and fine needle aspiration of mediastinal lymph nodes. Other biopsy techniques include percutaneous biopsy using image guidance and endobronchial ultrasound (EBUS) guided biopsy.

3.1.5 Occupational cancer caused by coal tars, coal tar pitches or soots
ICD Code C34, C44 +T65.8 +Z57

Exposure assessment

- History of occupational exposure: confirmed repeated or prolonged occupational exposure (mainly through inhalation) to coal tar pitches or soots.
- Minimum duration of exposure: unknown (most likely 10 years).
- Maximum latent period: not applicable.

Name of the diseases and ICD code: **Skin cancer (C44) +T65.8 +Z57**

Short description of the disease

Occupational exposures to coal tar and soot cause cancer of the skin. The increased risk of both basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) was primarily observed among coal tar distillers and chimney sweeps who were in the past typically affected by scrotal cancer.

BCC affects skin areas of head, neck or shoulders. The pearly, rolled, telangiectatic border with central ulceration is diagnostic of BCC. Despite being locally invasive, BCC does not metastasize. Crusting and bleeding in the centre of the tumour frequently develop. It is often mistaken for a sore that does not heal. This form of skin cancer only very seldom causes fatalities. Pigmented BCC characterized by the presence of melanin in the cells may be wrongly diagnosed as melanoma.

SCC is a malignant neoplasm of the keratinized epidermal cells characterized by quick growth and metastasizing capacity. The first manifestation is usually a painless, nonhealing, bleeding skin ulceration in the middle of a verrucous papule or plaque, often manifesting on sun-damaged skin.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms of BCC: it may present as pearly nodules (i.e., nodular BCC) or flat, brown or flesh-coloured lesions with a pearly border (superficial BCC).
- Signs and symptoms of SCC: it may present as firm, red nodules or flat lesions with scaly, crusted surfaces; all forms eventually evolve into ulcers, which are typically red with everted edges; skin around the ulcer is usually inflamed and hardened.
- Examinations:
  - Observation of the lesion, supported by dermoscopy, usually prompts the diagnosis.
  - Biopsy of the skin remains the most accurate way of assessing the histologic subtype of the tumour

Exposure assessment

- History of occupational exposure: confirmed repeated or prolonged occupational exposure to coal tars or soots.
- Minimum duration of exposure: six months.
- Maximum latent period: not applicable.

Key actions for prevention	Since coal and oil based fuels will continue to be a source of energy worldwide, it is unlikely that the production and use of secondary by-products such as tars and pitches and the generation of combustion soot will end completely. Technologies that convert carbon and solid hydrocarbons in coal, oil tars and shale into liquid hydrocarbons have been known since the early 1930s (i.e., the Bergius process for coal liquefaction). With the depletion of traditional oil fields, the economic viability of these processes is improving, and pitch and tar in natural shale deposits are being increasingly exploited to produce hydrocarbons for various purposes. In future, exploitation may increase, combined with the generation of hydrogen gas a fuel source. Economic and environmental pressures are driving technological improvements in combustion processes, to increase energy yield, and reduce soot generation. With these advances, the organic content of coal ash also falls. At the same time, environmental regulation is reducing emissions. These trends should progressively reduce worker exposure to coal tars, etc. Nevertheless, the hierarchy of controls will still need to be employed to control exposures: namely elimination, substitution, enclosure, local exhaust ventilation, administrative controls and personal protective equipment. Maintenance workers in combustion plants may still need to use protective clothing, gloves and respiratory protection.

3.1.5 Occupational cancer caused by coal tars, coal tar pitches or soots
ICD Code C34, C44 +T65.8 +Z57

Further reading

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For the chemical entities listed below an entry exists in the collection of International Chemical Safety Cards (ICSC) hosted in the ILO website

Name	Synonyms	ICSC
Creosote	Wash oil; Creosote oil; Coal tar creosote	0572
Coal tar pitch	Pitch	1415

▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
3.1.5	Toxic effect of coal tars, coal tar pitches or soots	T65.8	NE61 & XM2CE3 & XM16M2 & XM6MC4
3.1.5	Lung cancer	C34	2C25.Z
3.1.5	Skin cancer	C44	2C3Z
	Occupational exposure to risk factors	Z57	QD84.Y

3.1.6 Occupational cancer caused by beta-naphthylamine	ICD Code C67 +T65.8 +Z57
General characteristics of the causal agent	Beta-naphthylamine (2-Naphthylamine, 2-Aminonaphthalene, CAS number 91-59-8) is an aromatic amine derived from naphthalene (arylamine). At room temperature, it is in the form of colourless crystals and has a faint aromatic odour. Large amounts of its vapours can be explosive. It is soluble in hot water, alcohol, ether, and in many organic solvents and oxidizes in the presence of air. Beta-naphthylamine was formerly used as an intermediate in the manufacture of dyes, as an antioxidant in the rubber industry, and to produce 2-chloronaphthalene.
Occupational exposures	Beta-naphthylamine is prepared by heating 2-naphthol with ammonium zinc chloride to approximately 200°C; its acetyl derivative can be obtained by heating 2-naphthol with ammonium acetate to ~270°C. As such, it has few industrial uses and is mostly converted into its sulphonic acids (the delta-acid and Bronner's acid are of more technical value and are devoid of the parent amine's toxicity), which are reacted with ortho-tetrazo-ditolyl to produce fine red dyes. A far less toxic product manufactured from beta-naphthylamine is *N*-phenyl-2-naphthylamine. Occupational exposure to *N*-phenyl-2-naphthylamine is possible in industrial manufacturing activities: synthesis of dyes and pigments; in the rubber industry, where the compound has at times been used as antioxidant and vulcanization accelerator, as a stabilizer for silicone-based enamels and lubricants. *N*-phenyl-2-naphthylamine is used as a stabilizer in rocket fuels and in industrial and military explosives, in surgical plaster, and in electroplating baths. Laboratory workers, such as those in analytical and biological research laboratories, may manipulate small amounts of 2-naphthylamine as a pure chemical standard as it is no longer used in commercial applications. Workers can be exposed to pyrolysis fumes containing 2-naphthylamine (e.g. in foundry fumes, in second-hand tobacco smoke and from heated cooking oils) in a complex mixture with other nitro-polycyclic aromatic hydrocarbons (PAH) and non-nitro-PAH. In particular, 2-nitronaphthalene is a nitro-PAH that is metabolized to 2-naphthylamine and thus constitutes a source of the corresponding amine.
Carcinogenic mechanisms, main health effects and diagnostic criteria	
Short profile of the carcinogenic mechanisms	Beta-naphthylamine and its salts are classified by IARC as Group 1 human carcinogens. Cohort studies from the USA, the United Kingdom, Japan, Poland, the Russian Federation, and Italy indicate markedly elevated bladder cancer risks in workers engaged in the manufacture and use of this compound. Mechanistic evidence indicates that the carcinogenicity of 2-naphthylamine operates by a genotoxic mechanism of action that involves metabolic activation, formation of DNA adducts, and induction of mutagenic and clastogenic effects. The excretion of the amine can be enhanced through enzymatic acetylation by *N*-acetyl-transferase (NAT), which converts the basic amine into a neutral metabolite that is excreted in the urine. Oxidative biotransformation of the amine to the corresponding hydroxylamine occurs in the liver; the resulting aryl-hydroxylamine can be (temporarily) detoxified by *O*-acetylation in the bladder and other tissues, and excreted in the urine. A fraction of the acetylated metabolite undergoes activation by acid-catalysed conversion to the corresponding nitrenium transient species. These are highly reactive with carbonyl oxygen and amine functional groups of DNA bases, and this is probably the first step in mutagenic cancer initiation. Since acetylated hydroxylamines are poorly stable in the slightly acidic ambient of urine, their conversion into the active genotoxic species occurs in the bladder, and thus it is this organ in which cancer develops. Amine oxidative activation and acetylation are biotransformation processes subject to a strong effect of genetic polymorphism. In particular, NAT activity shows a strong interindividual variability, which results in a correspondingly large difference in the susceptibility of individuals to cancer from aromatic amines, according to which subjects with a slower N-acetylation rate or efficiency have a higher risk than those with faster acetylation.
Name of the diseases and ICD code: **Bladder cancer (C67) +T65.8 +Z57**	
Short description of the disease Prolonged exposure to 2-naphthylamine has been observed to cause cancer of the bladder. The individual risk of developing the disease also depends on genetic factors, including the efficiency of metabolic acetylation of aromatic amines (see above). The most common type of bladder cancer is urothelial carcinoma, also known as transitional cell carcinoma.	

3.1.6 Occupational cancer caused by beta-naphthylamine ICD Code C67 +T65.8 +Z57

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: the affected subject may report blood or blood clots in the urine, dysuria, feeling the need to urinate many times during the day and at night, feeling the need to urinate but being unable to do so, lower back pain on one side of the body. Other symptoms of advanced bladder cancer may include pain in the back or pelvis, unexplained appetite loss, and weight loss.
- Examinations: urinalysis is used to assess the presence of haematuria; urine cytology and cystoscopy help to reveal cancer cells and detect growths in the bladder that need biopsy or surgery. Computed tomography (CT), magnetic resonance imagining (MRI), positron emission tomography (PET), and ultrasound help to stage cancer.

Exposure assessment

- History of occupational exposure: evidence of prolonged exposure to beta-naphthylamine and, when available, biological monitoring data (considering dermal absorption as a source of exposure).
- Minimum duration of exposures: one year (even less in case of very high exposures).
- Maximum latent period: not applicable.

Key actions for prevention	The manufacture and use of 2-naphthylamine have been prohibited in many countries and therefore, the amine has been replaced by alternative less toxic compounds (e.g. phenyl-β-naphthylamine, which is an even more efficient anti-oxidant). Any industrial use of the compound should be forbidden. In exceptional cases (impossible to find alternatives), only strictly sealed and full time environmentally controlled cycles equipped with warning systems should be allowed.

Further reading

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For the chemical entities listed below an entry exists in the collection of International Chemical Safety Cards (ICSC) hosted in the ILO website

Name	Synonyms	ICSC
2-Naphthylamine	beta-Naphthylamine; 2-Aminonaphthalene	0610

▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
3.1.6.	Toxic effect of beta-naphthylamine	T65.8	NE61& XM60L2
3.1.6.	Bladder cancer	C67	2C94.Z
	Occupational exposure to risk factors	Z57	QD84.Y

3.1.7 Occupational cancer caused by vinyl chloride	ICD Code C22.3, C22.0 +T53.6 +Z57
General characteristics of the causal agent	Vinyl chloride [chloroethylene, vinyl chloride monomer (VCM), CAS number 75-01-4] is a flammable, colourless, slightly lighter-than-air, easily condensable gas with a sweetish odour. It is usually stored as a liquid in low-temperature pressure vessels. Vinyl chloride is classified by IARC as a Group 1 carcinogen, as it causes angiosarcoma of the liver and hepatocellular carcinoma.
Occupational exposures	Occupational exposure to vinyl chloride is primarily via inhalation and occurs mainly during the manufacture of polyvinyl chloride (PVC). VCM is currently mostly used in PVC production and processing plants. Workers employed in the manufacture of industrial chemicals, plastic products, fabricated metal products, and non-electrical machinery are at the greatest risk of exposure. Vinyl chloride is a major chemical commodity, which is produced via ethylene dichloride by a gas-phase catalysed reaction of petrochemical ethylene with chlorine and hydrogen chloride-oxygen mixture or from acetylene and hydrogen chloride. Both production methods raise considerable health and environmental concern and are carried out in large industrial plants and under stringent safety measures. Nowadays, the content of VCM in PVC does not usually exceed one part per million, so that occupational or consumer exposure to VCM in PVC items is considered negligible. Occupational exposure to VCM is nowadays mainly possible in production and polymerization plants. Depolymerisation of PVC to VCM even under severe heating or combustion is considered of negligible concern under real-life circumstances, especially when compared to the production of toxic combustion products such as hydrogen chloride, carbon monoxide, and phosgene and of chlorinated tars containing polychloro-biphenyls, furans and dioxins.
Carcinogenic mechanisms, main health effects and diagnostic criteria	
Short profile of the carcinogenic mechanisms	Vinyl chloride is rapidly metabolized in the liver via a cytochrome P450 enzyme into chloroethylene oxide and chloracetaldehyde, both of which can bind to proteins, DNA, and RNA. Vinyl chloride, via its metabolites, is mutagenic and is able to act as a genotoxic carcinogen by a variety of mechanisms, including increased chromosomal aberration frequency, induction of unscheduled DNA synthesis, and increased frequency of sister chromatid exchange. The binding of vinyl chloride metabolites to DNA is thought to result in mutations affecting the functioning of tumour suppressor genes and proto-oncogenes, causing increased susceptibility to tumour formation. Vinyl chloride and its reactive metabolites bind covalently to hepatic glutathione and are then hydrolysed and excreted in the urine as conjugates of cysteine. Both vinyl chloride and its metabolites produce hyperplasia of mesenchymal sinusoidal lining cells in the liver and hyperplasia of hepatocytes. The IARC classifies vinyl chloride as a Group 1 carcinogen, causing cancer in humans.

Name of the diseases and ICD code: **Liver angiosarcoma (C22.3) +T53.6 +Z57**

Short description of the disease

Hepatic angiosarcoma is a rare, malignant tumour of the liver arising from endothelial and fibroblastic tissues. It has been linked to exposure to carcinogens, including vinyl chloride. The prognosis of this neoplastic disease is very poor.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms:
  - Symptoms may vary and can include abdominal pain, anorexia, fatigue, weight loss, and low back pain.
  - Physical examination may demonstrate jaundice, ascites, hepatomegaly, splenomegaly and other signs of chronic liver disease.
- Examinations:
  - Laboratory examination typically demonstrates nonspecific slight elevation in one or more liver enzymes, most frequently alkaline phosphatase, but in some cases, serologic indicators are normal, differing from hepatocellular carcinoma.
  - Anaemia and thrombocytopaenia are often noted on laboratory testing.
  - Ultrasound and non-contrast CT may demonstrate nonspecific findings, while dynamic CT and MRI are better in depicting the hypervascularity and heterogeneity of the tumour, thus being more useful in establishing the diagnosis.
  - Hepatic angiography may be helpful in establishing the diagnosis.

3.1.7 Occupational cancer caused by vinyl chloride — ICD Code C22.3, C22.0 +T53.6 +Z57

Exposure assessment

- History of occupational exposure: evidence of prolonged/repeated exposure to vinyl chloride monomer.
- Minimum duration of exposure: 10 years.
- Maximum latent period: not applicable.

Name of the diseases and ICD code: **Hepatocellular carcinoma (C22.0) +T53.6 +Z57**

Short description of the disease

Hepatocellular carcinoma (HCC) is a cancer of the hepatic cells, which is one of the most common malignancies worldwide and the most common type of liver cancer.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms:
  - Symptoms may include abdominal pain, abdominal swelling, loss of appetite, fatigue, and weight loss.
  - Physical examination may demonstrate jaundice, ascites, and peripheral oedema.
- Examinations:
  - Laboratory examination commonly yields elevated serum alpha-fetoprotein (AFP) levels.
  - Liver function tests may yield abnormal levels of indicators, in particular serum aminotransferase and alkaline phosphatase.
  - Ultrasound, CT, and MRI are imaging modalities commonly used to diagnose the disease.
  - Percutaneous, image-guided liver biopsy may be utilized if the diagnosis is uncertain from imaging results.

Exposure assessment

- History of occupational exposure: evidence of prolonged/repeated exposure to vinyl chloride monomer.
- Minimum duration of exposure: 10 years.
- Maximum latent period: not applicable.

Key actions for prevention	VCM is the starting monomer for the preparation of PVC and, as long as PVC continues to be used as a main technological polymer, it is not possible to replace VCM. However, implementation of new closed-loop polymerization processes in the manufacture of PVC over the last 40 years has significantly decreased worker exposure to VCM in many factories, resulting in a reduction in the number of cases of hepatic angiosarcoma in these populations. Efforts should be made to encourage universal adoption of these closed loop processes and thus decrease worker exposure to VCM. Appropriate engineering, ventilation controls and working practices should be used with personal protective equipment to avoid skin, eye and respiratory exposure. A full-time working alarm system with continuous environmental monitoring is recommended.

3.1.7 Occupational cancer caused by vinyl chloride ICD Code C22.3, C22.0 +T53.6 +Z57

Further reading

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For the chemical entities listed below an entry exists in the collection of International Chemical Safety Cards (ICSC) hosted in the ILO website

Name	Synonyms	ICSC
Vinyl chloride	Chloroethene; Chloroethylene; Vinylchloride monomer (VCM)	0082

▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
3.1.7	Toxic effect of vinyl chloride	T53.6	NE61&XM6YR0
3.1.7	Liver angiosarcoma	C22.3	2B56.3
3.1.7	Hepatocellular carcinoma	C22.0	2C12.02
	Occupational exposure to risk factors	Z57	QD84.Y

3.1.8 Occupational cancer caused by benzene	ICD Code C92.0 +T52.1 +Z57
General characteristics of the causal agent	Benzene (Benzol, C_6H_6, molecular mass 78.1, CAS number 71-43-2) is the simplest aromatic hydrocarbon. It is a volatile colourless liquid (boiling point 80° C) whose vapours are heavier than air. It belongs to the chemical class of (alkyl)-aromatic hydrocarbons.
Occupational exposures	Benzene occurs naturally in crude petroleum. It is present in coal derivatives and petroleum fractions, and distillates. It is still present in car fuel in variable amounts (in the order of 1-3%), depending on the quality of the gasoline. The presence of benzene in petrol, in several chemical syntesis processes and as a historically widely used industrial solvent can result in significant occupational exposure. Benzene is used as starting material in the chemical synthesis of a great variety of bulk such as styrene, cumene, cyclohexane, nitrobenzene, chlorobenzene, phenol, etc., and speciality products such as detergents, explosives, intermediates for dyes and pharmaceuticals, etc.. Occupational exposure to benzene may hence occur in the chemical industry for the synthesis of a great variety of chemical products, in the production and handling of gasoline fuels, in the production and use of solvents and thinners for fats, waxes, resins, oils, inks, paints, lacquers, adhesives, glues, plastics, rubber, in scouring of metal parts, in dry cleaning, in the extraction of oils from seeds and nuts, and in photogravure printing. Benzene is also used as a chemical intermediate and in the manufacture of detergents, explosives, pharmaceuticals, and dyestuffs. A high level of occupational exposure to benzene may occur in industries involving benzene production (petrochemicals, petroleum refining, and coke and coal chemical manufacturing), rubber manufacturing, and storage or transport of benzene and petroleum products containing benzene. Other workers who may be exposed to benzene because of their occupations include steelworkers, printers, shoemakers, laboratory technicians, firefighters, and gas station employees. Additional occupational exposure to benzene is nowadays possible in the production of benzene via coal tar distillation or from petroleum, in the cleaning of tanks in which benzene has been stored; and through contact with residues of crude oil or with petrol including vehicle emissions.
Carcinogenic mechanisms, main health effects and diagnostic criteria	
Short profile of the carcinogenic mechanisms	Benzene is absorbed by inhalation or through the skin, and is distributed through the bloodstream to the fatty tissues of the body, and in particular the bone marrow. Absorption occurs at a rate of about 1 mg/cm²/h. Benzene undergoes complex biotransformation, which starts with the generation of an arene oxide (epoxide), catalysed by P450 cytochrome (CYP2E1). This chemically reactive intermediate isomerizes to phenol that is further converted to an epoxide and isomerized to hydroquinone. Bone marrow cells, and in particular those of the myeloid cell line, actively express myeloperoxidase, which is able to convert catechol to hydroquinone, which in turn very likely represents the chemically reactive and toxicologically active derivative of benzene. Hydroquinone, its precursor arene oxide, and the metabolites derived from its conjugation with glutathione react with DNA bases and other biological structures. Another biotransformation pathway of benzene leads to the ring-opened cis, cis-muconic acid. These metabolites are cytotoxic and mutagenic to several cell types of haemopoietic cells. Cytotoxicity for totipotent bone marrow stem cells results in pancytopaenia and aplastic anaemia. Transformation and growth promotion of the precursors of the myeloid cell line gives rise to acute myeloid leukaemia. There is strong evidence that benzene metabolites, acting alone or in concert, produce multiple genotoxic effects at the level of the pluripotent haematopoietic stem cell resulting in chromosomal changes consistent with those seen in haematopoietic cancer. Epidemiological studies have confirmed the association of occupational benzene exposure with an increased incidence of acute myeloid leukaemia. While the capacity of benzene to cause other forms of haematological malignancies is less evident, a positive association has been observed with acute lymphocytic leukaemia, chronic lymphoid leukaemia, multiple myeloma, non-Hodgkin lymphoma, chronic myeloid leukaemia, and cancer of the lung. IARC classifies benzene as carcinogenic to humans (Group 1).

3.1.8 Occupational cancer caused by benzene ICD Code C92.0 +T52.1 +Z57

Name of the diseases and ICD code: **Acute myeloid leukaemia (C92.0) +T52.1 +Z57**

Short description of the disease

Acute myeloid leukaemia (AML) is an aggressive myeloid neoplasm characterized by ≥20% myeloblasts in the blood or bone marrow. It is the most common form of acute leukaemia in the general population, with an incidence that increases with age. Benzene-induced AML has a usual latency period of 5-15 years and, in many cases, follows aplastic anaemia.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: fatigue, weight loss, anorexia, increased frequency of bleeding and easy bruising, fever, in some cases accompanied by infections; lymphadenopathy, headache, diaphoresis, bone pain.
- Examinations:
  - Full blood count shows leucocytosis; however, since most blood cells are pathological, the affected subjects end up suffering leukopaenia. Other typical findings are normocytic and normochromic anaemia (with reduced reticulocyte count consequent to reduced erythropoiesis), as well as platelet count usually below 100,000/L (thrombocytopaenia).
  - A peripheral blood smear can detect circulating leukaemic blasts.
  - Bone marrow aspirates and biopsy should be evaluated: light microscopy examination of bone marrow specimens or blood cells, along with flow cytometry and specific cytochemical stains, is helpful to differentiate AML from other types of leukaemia (e.g. acute lymphoblastic leukaemia) and to classify the subtype of the disease.
  - Cytogenetics or fluorescent in situ hybridization (FISH) are carried out to test for chromosomal abnormalities. Additional genetic studies can reveal specific mutations in genes that may influence the outcome of the disease.

Exposure assessment

- History of occupational exposure: confirmed occupational exposure to benzene via inhalation, skin and eye contact, and, if available, workplace air monitoring and biological determinations of benzene metabolites in urine (t,t-muconic and S-phenylmercapturic acids).
- Minimum duration of exposure: in general, at least six months, unless there are antecedents of medullary aplasia.
- Maximum latent period: not applicable.

Key actions for prevention	Due to the carcinogenicity of benzene, its use as a solvent or co-solvent in formulations such as glues, adhesives, paints, lacquers, and degreasers has been mostly eliminated. In the production of fine chemicals, closed-circuit reactors and stringent manufacturing procedures, including the substitution of benzene with alternative starting materials whenever possible, has reduced or completely eliminated exposure. Benzene is generated in the production of gasoline by reforming and aromatization of crude oil fractions, although in most industrial countries its content in the formulated product has been regulated to be well below 5% in volume. What can not be hardly reduced is the generation of benzene from non-aromatic hydrocarbons during combustion of gasoline in combustion engines, a phenomenon that parallels the generation of polycyclic aromatic hydrocarbons in diesel engines. In all industrial activities where benzene is produced, used or generated as a by-product, primary and secondary prevention measures should be applied to the highest possible level. Workplace and biological monitoring of workers should be implemented on a regular basis. Appropriate engineering, ventilation controls and working practices should be used with personal protective equipment to avoid skin, eye and respiratory exposure.

3.1.8 Occupational cancer caused by benzene	ICD Code C92.0 +T52.1 +Z57
Key actions for prevention	The WHO recommends several risk mitigation procedures to be followed; although mainly developed for public health purposes, they can be applied to occupational settings as well. In detail: • Eliminate benzene usage by i) promoting the use of alternative solvents in industrial processes, glues and paints; and ii) developing and implementing policies and legislation to remove benzene from consumer products. • Reduce exposure to benzene by i) minimizing exposure at petrol filling stations as far as possible with the implementation of best practices in location, design and extraction; ii) reducing emissions from vehicle exhausts through means of improved design and regular monitoring of engine settings; iii) separating dwelling spaces from areas where vehicles and benzene-containing products are kept; iv) avoiding as much as possible, the use of benzene-containing products; v) discouraging indoor use of unflued oil and gasoline heating; vi) prohibiting smoking inside buildings. • Educate employers and workers by i) raising their awareness regarding sources of exposure to benzene and risk mitigation measures; and ii) conducting educational activities to discourage the use of benzene or petrol for cleaning and degreasing in industry and domestically. Several scientific bodies and regulatory agencies have suggested occupational exposure limits for benzene. The group of experts considered that the following limits of exposure of workplace atmospheric concentrations have been observed to provide a reasonable level of protection for workers' health and used in a number of countries: • 0.5 ppm as 8hr TWA; and • 2.5 ppm for short-term exposures. Biological exposure indices (BEI) at post-shift sampling should include blood benzene, urinary t,t-muconic acid, and urinary S-phenylmercapturic acid.

Further reading

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For the chemical entities listed below an entry exists in the collection of International Chemical Safety Cards (ICSC) hosted in the ILO website

Name	Synonyms	ICSC
Benzene	Cyclohexatriene; Benzol	0015

▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
3.1.8	Toxic effect of benzene	T52.1	NE61& XM0QY7
3.1.8	Acute myeloid leukaemia (AML)	C92.0	2A60.3Z
	Occupational exposure to risk factors	Z57	QD84.Y

3.1.9 Occupational cancer caused by toxic nitro- and amino-derivatives of benzene or its homologues	ICD Code C67 +T65.3 +Z57
General characteristics of the causal agent	Nitro- and amino-derivatives of benzene or its homologues are a large, heterogeneous class of industrial chemical compounds characterized by the presence in their structure of at least one unit of benzene (or of a benzene alkyl homologue), to which one or more nitro (-NO_2) or/and amino (-NH_2) groups are attached by means of a direct chemical bond. Several of these compounds are considered to be possibly (e.g. nitrobenzene, 2-chloro-nitrobenzene) or probably (e.g. 2-nitrotoluene, 4-chloro-ortho-toluidine) carcinogenic to humans. 4-aminobiphenyl, o-toluidine, and benzidine are among the ones supported by the most consistent evidence for bladder cancer (for further details on the latter, refer to dedicated item 3.1.2) and are all classified as Group 1 carcinogens by the IARC. 4,4′-Methylenebis(2-chloroaniline) (MOCA) is also considered carcinogenic: although the evidence is considered not adequate in humans, it is sufficient in experimental animals where MOCA has been observed as a multiorgan carcinogen and strong as regard the involved carcinogenic mechanisms. *4-Aminobiphenyl* appears as a colourless, crystalline solid (becoming purple if exposed to air), which is slightly soluble in cold water, and soluble in hot water, acetone, chloroform, ethanol, and diethyl ether. In several countries, the production and use of 4-aminobiphenyl have been banned. In the past, it has been used as a rubber antioxidant, as an intermediate for dyes, and for sulfates detection. *o-Toluidine* appears as a light-yellow liquid, that turns reddish brown on exposure to light and air; it is slightly soluble in water, while soluble in dilute acids, alcohol and ether. ortho-Toluidine is used in the manufacture of pigments and dyes and as an intermediate for the synthesis of some herbicides, pesticides, synthetic rubber and rubber-vulcanizing chemicals, pharmaceuticals, and other chemicals. It can also be use in laboratories for glucose analysis and tissue staining. 4,4′-Methylenebis(2-chloroaniline) (MOCA) is a colourless to yellow or light-brown crystalline solid characterized by a vague amine-like odour. It is slightly soluble in water and soluble in ether, alcohol, and dilute acids. MOCA finds use mainly in the manufacture of castable urethane rubber products (e.g. conveyor belts shock-absorption pads) as a curing agent for polyurethane pre-polymers. It is also used in laboratories as a model compound for the study of carcinogens.
Occupational exposures	Occupational exposure to *4-aminobiphenyl* mainly occurred during its production and use as a dye intermediate or as a rubber antioxidant. Workers can be exposed to products contaminated with 4-aminobiphenyl or to benzidine and benzidine-based dyes, which can metabolically release 4-aminobiphenyl. The production of *o-toluidine* and of dyes, pigments and rubber chemicals manufactured from this compound can entail occupational exposure, which can occur by inhalation or skin contact. Health workers, in particular laboratory and medical personnel, may be exposed when using o-toluidine for staining tissues. Tobacco smoke and the use of some hair dyes can represent relevant non-occupational exposure sources of both 4-aminobiphenyl and o-toluidine. In the polyurethane industry, workers can be exposed to 4-4′-methylenebis(2-chloroaniline) (MOCA) during its processing in the form of a liquid emulsion or as solid pellets (with or without dust). The main occupational exposure route is represented by dermal absorption after contact with contaminated surfaces, while inhalation and ingestion configure less usual exposure pathways.
Carcinogenic mechanisms, main health effects and diagnostic criteria	
Short profile of the carcinogenic mechanisms	Most nitro- and amino-derivatives of benzene or its homologues are quickly and largely absorbed by vapour and dust inhalation, and through skin contact. After absorption, they distribute in the body and are extensively bio-transformed (metabolic activation), especially by the liver, lung, kidney, bladder, skin, and gut microorganisms. Nitro-derivatives are biologically transformed by nitrogen reduction into the corresponding toxic reactive intermediates aryl-nitroso- and aryl-hydroxylamine compounds. For this reason, nitro-derivatives share many toxicological effects with amino-derivatives, and their metabolites are often more toxic than the nitro-aromatic precursors themselves.

3.1.9 Occupational cancer caused by toxic nitro- and amino-derivatives of benzene or its homologues — ICD Code C67 +T65.3 +Z57

Short profile of the carcinogenic mechanisms

Amino-derivatives are biologically transformed by nitrogen oxidation to yield toxic reactive intermediates, such as the aryl-hydroxylamine metabolites. The azoic dyes, which contain an Ar(1)-N=N-Ar(2) functional group, are converted especially by gut microorganisms to the aromatic amines Ar(1)-NH_2 and Ar(2)-NH_2, and the entero-hepatic circulation reabsorbs the resulting products for further biotransformation. Aromatic amines and their aryl-hydroxylamine metabolites undergo biological acetylation to neutral compounds, which can be reabsorbed.

Acetylated aryl-hydroxylamines that derive from aromatic amines and aromatic nitro-compounds are easily bio-transformed by deacetylation to the corresponding nitrogen electrophiles (the nitrenes), which are reactive with biological nucleophiles such as the DNA thus possibly initiating genotoxic carcinogenesis.

The biotransformation pathways of aromatic amines and of aromatic nitro compounds are characterized by a strong genotypic modulation of toxicity, e.g. acetylator genotype and phenotype.

Name of the diseases and ICD code: **Bladder cancer (C67) +T65.3 +Z57**

Short description of the disease

Both 4-aminobiphenyl and ortho-toluidine have been observed to cause cancer of the urinary bladder. Bladder cancer is a quite common disease: with over 430,000 prevalent cases estimated in 2018, it is the 7th most frequent cancer worldwide. A well known non-occupational cause of this cancer is represented by tobacco smoke: epidemiological studies show that the risk among smokers is 2-3 times higher than in non-smokers. In persons with a slower acetylation rate the risk is higher, than in those with faster acetylation.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: the affected subject may report blood or blood clots in the urine, dysuria, feeling the need to urinate many times during the day and at night, feeling the need to urinate but being unable to do so, lower back pain on one side of the body. Other symptoms of advanced bladder cancer may include pain in the back or pelvis, unexplained appetite loss, and weight loss.
- Examinations: urinalysis is used to assess the presence of a haematuria; urine cytology and cystoscopy help to reveal cancer cells and detect growths in the bladder that need biopsy or surgery. CT, MRI, PET and ultrasound help to stage the cancer.

Exposure assessment

- History of occupational exposure: evidence of prolonged or repeated exposure to 4-aminobiphenyl or ortho-toluidine, considering all the possible exposure routes (including skin absorption).
- Minimum duration of exposure: one year.
- Maximum latent period: not applicable.

Key actions for prevention

Due to their occupational toxicological hazard, aromatic amines and nitro compounds have been the object of occupational prevention measures since the late nineteenth century. As primary prevention, due to the carcinogenic properties of some compounds of the group and of their chemical derivatives, less toxic substitutes have been developed and, where possible substituted, whilst the more toxic compounds have been banned from production and use in most countries.

Workers and employers should be educated to be aware of the nature and extent of the hazard posed by the production and use of nitro- and amino-aromatic compounds, and work in a clean, safe manner. Adequate plant and equipment design for both operating and maintenance and accurate job analysis are minimum prerequisites to ensure workers' safety and health. In particular, measures include appropriate equipment design, ventilation as close to the point of generation as possible, with air pollution control, adequate handling procedures, and specific measures for the prevention of workers' exposure through spillage. Best available technologies allow performing the chemical reactions involving the most dangerous compounds in closed circuit batch reactors with as much as possible segregation of the reagents, solvents, raw reaction mixtures, purified products and reaction byproducts. In the working phases where this cannot be totally achieved (such as in loading and unloading reactors), workers need to be protected with coveralls, gloves and appropriate respiratory protection.

3.1.9 Occupational cancer caused by toxic nitro- and amino-derivatives of benzene or its homologues	ICD Code C67 +T65.3 +Z57
Key actions for prevention	Work clothing should be changed daily and plants should have facilities for an obligatory bath or shower at the end of the work shift. Protective clothing and equipment must withstand the permeation of chemicals for the expected exposure time. Any contamination of skin or clothing should be washed off immediately and the individual kept under appropriate medical supervision. Routine plant maintenance should include a thorough preliminary cleaning of the machinery before maintenance staff access and appropriate disposal of waste. An effective programme to prevent health impairment due to exposure to nitro- and amino-derivatives should include exposure control and medical supervision. Measurement of airborne or surface contamination is useful to check consistent operation safety and minimal chance of skin contact.

Further reading

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For the chemical entities listed below an entry exists in the collection of International Chemical Safety Cards (ICSC) hosted in the ILO website

Name	Synonyms	ICSC
4-Aminobiphenyl	4-Aminodiphenyl; p-Biphenylamine; Xenylamine; Biphenyl-4-amine; Biphenyl-4-ylamine; (1,1'-Biphenyl)-4-amine	0759
o-Toluidine	1-Amino-2-methylbenzene; 2-Aminotoluene; o-Methylaniline	0341
4,4'-Methylenebis (2-chloroaniline)	Benzenamine, 4,4'-methylenebis(2-chloro-); 2,2'-Dichloro-4,4'-methylenedianiline; 4,4'-Diamino-3,3'-dichlorodiphenylmethane; MOCA; MBOCA	0508

▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
3.1.9	Toxic effects of nitroderivatives and aminoderivatives of benzene and its homologues	T65.3	NE61&XM83H3
3.1.9	Bladder cancer	C67	2C94.Z
	Occupational exposure to risk factors	Z57	QD84.Z

3.1.10 Occupational cancer caused by ionizing radiation	ICD Code C44, C34, C91-C95, C41.9, (C00-C97) +Z57.1
General characteristics of the causal agent	Ionizing radiation is a type of energy released by atoms in the form of electromagnetic waves or particles. Ionizing radiation has so much energy it can cause the separation of electrons from atoms and molecules, a process known as ionization. Ionizing radiation can affect the atoms in living things, and so poses a health risk by damaging tissue and DNA in genes. Some types of radiation of relatively low energy, such as ultraviolet light, can cause ionization under certain circumstances. To distinguish these types of radiation from radiation that always causes ionization, an arbitrary lower energy limit for ionizing radiation is usually set around 10 kiloelectron volts (keV). Ionizing radiations are part of the human environment. There are natural and artificial sources of ionizing radiations. Natural sources are, for example, cosmic rays and naturally occurring radioactive materials, while artificial sources include X-ray machines, radioactive isotopes used in nuclear medicine, gamma cameras, nuclear gauges and nuclear power plants. Ionizing radiations thus include (1) energetic subatomic particulate radiation (e.g. alpha and beta particles emitted from radioactive materials and neutrons from nuclear reactors and accelerators) and (2) electromagnetic radiation (e.g. gamma rays emitted from radioactive materials and X-rays from electron accelerators and X-ray generators). Directly ionizing radiation consists of charged particles. Such particles include energetic electrons, positrons, protons, alpha particles, charged mesons, muons, and heavy ions (ionized atoms). This type of ionizing radiation interacts with matter primarily through the Coulomb force, repelling or attracting electrons from atoms and molecules by virtue of their charges. Indirectly ionizing radiation consists of uncharged particles. The most common kinds of indirectly ionizing radiation are photons above 10 keV (X-rays and gamma rays) and all neutrons. Some essential properties of ionizing radiation are summarised below: *Radioactivity*, i.e., the strength of a radioactive source, is measured in units of Becquerel (Bq): 1 Bq represents one event of radiation emission or disintegration per second. The old unit for this is the Curie (Ci): 1 Bq = 2.7 x 10^{-11} Ci (and 1 Ci = 3.7 x 10^{10} Bq). The *energy* of ionizing radiation is measured in electronvolts (eV); since 1 eV is an extremely small amount of energy, another commonly used unit of measure is the joule, corresponding to 6.24 x 10^{18} eV. When ionizing radiation interacts with the human body, it gives its energy to the body tissues. The biological effects of ionizing radiations are normally classified into deterministic and stochastic. A *deterministic effect* (e.g. cataract) is a biological effect caused by ionizing radiation whose probability of occurrence is zero at small, absorbed doses but will increase steeply to unity (100%) above some level of absorbed dose (i.e., the threshold). A *stochastic effect* (e.g. cancer) is a biological effect caused by ionizing radiation whose probability of occurrence increases with increasing absorbed dose, probably with no threshold, but whose severity is independent of absorbed dose. Regarding the threshold, available biological and biophysical data are in agreement with the hypothesis that the risk would continue in a linear fashion at lower doses without a threshold and that even the smallest dose has the potential to cause a small increase in risk to humans. This assumption is termed the "*linear-no-threshold*" (LNT) model. Radiation damage to tissue and organs depends on the dose of radiation received or the absorbed dose. The potential damage from an absorbed dose depends on the type of radiation and the sensitivity of different tissues and organs. The absorbed dose is the amount of energy absorbed per unit weight of the organ or tissue and is expressed in units of gray (Gy). 1 Gy is defined as 1 joule of energy deposited in 1 kilogram of mass. The old unit of measure for this is the rad: 1 Gy = 100 rad.

3.1.10 Occupational cancer caused by ionizing radiation

ICD Code C44, C34, C91-C95, C41.9, (C00-C97) +Z57.1

General characteristics of the causal agent

Equal doses of all types of ionizing radiation are not equally harmful to human tissue. To account for the way in which different types of radiation cause harm in tissue or an organ, radiation dose is expressed as equivalent dose in units of sievert (Sv). The *equivalent dose* in Sv is equal to the total external and internal absorbed doses multiplied by a 'radiation weighting factor': this is a number that, for a given type and energy of radiation, is representative of values of the relative biological effectiveness of that radiation in inducing stochastic effects at low doses. The values of the radiation weighting factor are related to linear energy transfer (i.e., the energy a charged particle imparts to matter per unit length as it traverses the matter). The *effective dose* (still measured in Sv) is used to measure ionizing radiation in terms of the potential for causing harm: it takes into account the type of radiation and sensitivity of tissues and organs and is the sum of the weighted equivalent doses in all the tissues and organs of the body. Formally, it corresponds to the sum of organ doses multiplied by the 'tissue weighting factor': this represents the contribution of tissue or organ to the total detriment due to all the stochastic effects resulting from uniform irradiation of the whole body, and it is used because the probability of stochastic effects due to an equivalent dose depends on the tissue or organ irradiated. The old unit of measure for equivalent/effective dose is the rem: 1 Sv = 100 rem.

The table below summarises units of measure (u.m.) and conversion factors for some of the abovementioned properties:

Property	Current u.m.	Former u.m.	Conversion factor
Radioactivity	Becquerel (Bq)	Curie (Ci)	1 Bq = 2.7 x 10^{-11} Ci 1 Ci = 3.7 x 10^{10} Bq
Absorbed dose	Gray (Gy)	rad	1 Gy = 100 rad
Equivalent/Effective dose	Sievert (Sv)	rem	1 Sv = 100 rem

Occupational exposures

The use of radioactive sources involves risks due to radiation exposure. Exposure to ionizing radiation occurs in many occupations. Ionizing radiations are present in the use of X-ray machines, used not only in health care activities but also in industry, particle accelerators, gamma radiography sources, nuclear reactors, any activity involving the use of isotopes, uranium and other mines, any other activity conducted underground, and ordinary workplaces in areas that are rich in radon emission. Radon daughters are airborne radioactive isotopes produced in the uranium decay chain. Radiation dose to the lungs due to inhalation of airborne radon daughters is the main concern in underground uranium mines as well as in other underground activities, radon daughters are of concern in some indoor environments where the soil or the building materials are contaminated with radium. Aircrew members are exposed to cosmic radiation, a form of ionizing radiation coming from the outer space that include galactic cosmic radiation and solar particle events, sometimes called "solar flares".

Artificial sources of radiation are commonly used in the manufacturing, service, and defence industries, in research institutions and universities, and in the nuclear power industry. They are extensively used by physicians and health professionals, in the diagnosis and in treatment of diseases.

Carcinogenic mechanisms, main health effects and diagnostic criteria

Short profile of the carcinogenic mechanisms

The ability of ionizing radiations (X-rays) and of the chemical agents that produce ionizing radiations through their own radioactive decay (radionuclides), to cause cancer is documented since the beginning of the 20th century. Experimental animal models and epidemiological studies of numerous and diverse cohorts of humans exposed to ionizing radiations and to radionuclides following diagnostic and medical treatments, as a consequence of the military use of atomic energy, of nuclear accidents and of workplace exposure in several sectors of activity have led to reasonably robust risk estimates.

The currently agreed-upon mechanism for the development of radiogenic cancer is based on the damage to the genetic material of somatic cells exerted by free radicals, generated through direct ionization of cellular fluid by radiation or by direct action on the genome. Mechanisms such as rearrangements of genes and chromosomes and loss of heterozygosity (signalling specific regions of DNA loss) are considered the most likely radiation-induced events that contribute to cancer development.

3.1.10 Occupational cancer caused by ionizing radiation	ICD Code C44, C34, C91-C95, C41.9, (C00-C97) +Z57.1
Short profile of the carcinogenic mechanisms	Latency is the period of time that separates the beginning of exposure from the onset of a clinically diagnosed cancer. In this period, irradiated, damaged, but still viable cells start to grow and stop responding to proliferation-modulating intra- and extra-cellular signals. This general mechanism has paved the way to that accepted for several classes of chemical carcinogens, for which the definition of "*radio-mimetic*" has been coined. The linear no threshold (LNT) response model is accepted as the current basis for radiation protection standards for workers occupationally exposed to ionizing radiation and the general public. This model assumes that there is no threshold dose for the radiation-induced genetic effects (heritable mutations and cancer). A number of factors influence the resistance of individuals to the development of cancer following different doses of radiation and to their fractionation over time. Those most relevant are genetically controlled characteristics, gender, age, physiological state, the coexposure to other noxious agents, such as smoking, some pharmaceutical drugs, specific constituents of food, and various other chemical and physical agents. The cancers caused by different sources of radiation, with or without the contributions of other agents, are indistinguishable from those occurring 'spontaneously' (i.e., when a specific causal agent or exposure has not been identified) or from other identified causes.

Name of the diseases and ICD code: **Skin cancer (C44) +Z57.1**

Short description of the disease

Exposure to X- and gamma radiations has been related to an increased risk of basal cell carcinoma (BCC). In the occupational setting, evidence arose mostly among early day radiologists or radiology technicians, who developed BCC following exposure to high levels of ionizing radiations. In non-occupational settings, this cancer has been observed among atomic-bomb survivors or medical patients exposed to radiations mainly for therapeutic purposes.

BCC affects skin areas of head, neck or shoulders. The pearly, rolled, telangiectatic border with central ulceration is typical of BCC. Despite being locally invasive, BCC does not metastasize. Crusting and bleeding in the centre of the tumour frequently develop. It is often mistaken for a sore that does not heal. This form of skin cancer only very seldom causes fatalities. Pigmented BCC characterized by the presence of melanin in the cells may be wrongly diagnosed as melanoma.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: it may present as pearly nodules (i.e., nodular BCC) or flat, brown or flesh-coloured lesions with a pearly border (superficial BCC).
- Examinations:
  - Observation of the lesion, supported by dermoscopy, usually prompts the diagnosis.
  - Biopsy of the skin remains the most accurate way of assessing the histologic subtype of the tumour.

Exposure assessment

- History of occupational exposure: confirmed occupational exposure to high (or prolonged) doses of ionizing radiations directed towards the skin, with cumulative doses usually exceeding 15 Gy.
- Minimum duration of exposure: variable, depending on the dose.
- Maximum latent period: not applicable.

3.1.10 Occupational cancer caused by ionizing radiation — ICD Code C44, C34, C91-C95, C41.9, (C00-C97) +Z57.1

Name of the diseases and ICD code: **Lung cancer (C34) +Z57.1**

Short description of the disease

Evidence suggests that occupational exposure to ionizing radiations is linked with an increased risk of lung cancer. Increased risk of lung cancer has been observed in some occupational settings, such as among workers of the nuclear industry, underground miners exposed to radon, and plutonium-production workers.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms:
  - Anorexia, asthenia, or weight loss.
  - New cough or change in chronic cough, sometimes with haemoptysis.
  - Nonspecific chest pain or pain from bone metastases to the ribs, vertebrae, or pelvis.
  - Local spread may cause obstruction of the bronchi with atelectasis and pneumonia, pleural effusion, superior vena cava syndrome (i.e., a plethora of symptoms following obstruction of blood flow through the superior vena cava, which include facial and arm swelling, nasal congestion, head fullness, headache and lightheadedness, nausea and dysphagia, distorted vision), change in voice (following the involvement of the recurrent laryngeal nerve), and Horner's syndrome (ipsilateral ptosis, miosis, anhidrosis, and enophthalmos following involvement of the inferior cervical ganglion and the paravertebral sympathetic chain).
  - Brain metastases may present with headache, seizures, altered mental status, nausea, and vomiting, while liver metastases might be associated with asthenia and weight loss.
  - Paraneoplastic syndromes including various symptoms related to immunomediated or secretory effects of tumours, such as syndrome of inappropriate antidiuretic hormone secretion, hypercalcemia, digital clubbing, increased adrenocorticotropin production, anaemia, hypercoagulability, peripheral neuropathy, and myasthenic syndromes.
- Examinations:
  - Chest X-ray: radiologic manifestations of lung cancer are diverse and include lung nodules and pulmonary, cavitated, or apical mass, with or without associated lymphadenopathy.
  - Chest CT provides information on the the details of the neoplastic lesion, its relationship to other anatomical structures, the status of the pleural space, and the size of mediastinal lymph nodes.
  - Sputum cytology is highly specific, although not sensitive, with the maximum yield provided when there are lesions in the central airways.
  - Thoracentesis can be used to make a diagnosis when malignant pleural effusions are present.
  - Fine needle aspiration of lymph nodes (supraclavicular or cervical) is frequently diagnostic.
  - Fiberoptic bronchoscopy can help visualisation of the major airways, brush of visible lesions or lung lavage (with cytological specimen evaluation), and assist various biopsy procedures, such as direct biopsy of endobronchial lesions, a transbronchial biopsy of peripheral nodules or of the lung parenchyma, and fine needle aspiration of mediastinal lymph nodes. Other biopsy techniques include percutaneous biopsy using image guidance, and endobronchial ultrasound (EBUS) guided biopsy.

Exposure assessment

- History of occupational exposure: confirmed occupational exposure to ionizing radiation or from internal exposure to alpha-emitting radionuclides such as radon and plutonium, with cumulative doses, usually exceeding one Sv.
- Minimum duration of exposure: variable, depending on the dose.
- Maximum latent period: not applicable.

3.1.10 Occupational cancer caused by ionizing radiation — ICD Code C44, C34, C91-C95, C41.9, (C00-C97) +Z57.1

Name of the diseases and ICD code: **Leukaemia (C91-C95) +Z57.1**

Short description of the disease

Most kinds of leukaemia (acute lymphoblastic, acute myeloblastic, and chronic myeloid leukaemias) can be induced by irradiation. Chronic lymphocytic leukaemia has shown relatively low to no relationship with ionizing radiations. The association of occupational exposures, even at low levels, with leukaemia was established in studies on pioneer radiologists and radiology technicians. Significant numbers of excess leukaemias have been reported more recently, from 1950 onwards, among medical radiation workers. Below is a summary of the main clinical features of acute lymphoblastic, acute myeloid, and chronic myeloid leukaemias.

Diagnostic criteria

Clinical manifestations of acute lymphoblastic leukaemia (ALL)

- Signs and symptoms: fever is a common presenting sign, together with symptoms of anaemia, e.g. dizziness, fatigue, palpitations, pallor, and dyspnoea (upon even mild exertion). Subjects may present with petechiae (usually at the lower extremities) and ecchymoses because of haemorrhagic and thrombotic complications, following disseminated intravascular coagulation (DIC).
- Examinations:
  - A full blood count with differential can show anaemia and thrombocytopaenia to varying degrees. White blood cell (WBC) count can be high, normal, or low, but neutropaenia is the most usual finding.
  - Circulating blasts are usually observed in the peripheral blood smear, thus confirming the findings of the FBC count. If DIC is present, schistocytes are sometimes seen.
  - The diagnosis can be confirmed by bone marrow aspiration and biopsy (with immunophenotyping helping to clarify the subtype).

Clinical manifestations of acute myeloblastic leukaemia (AML)

- Signs and symptoms: fatigue, weight loss, anorexia, increased frequency of bleeding and easy bruising, fever, in some cases accompanied by infections; lymphadenopathy, headache, diaphoresis, bone pain.
- Examinations:
  - Full blood count shows leucocytosis; however, since most blood cells are pathological, the affected subjects end up suffering leukopaenia. Other typical findings are normocytic and normochromic anaemia (with reduced reticulocyte count consequent to reduced erythropoiesis), as well as platelet count usually below 100,000/L (thrombocytopaenia).
  - A peripheral blood smear can detect circulating leukaemic blasts.
  - Bone marrow aspirates and biopsy should be evaluated: light microscopy examination of bone marrow specimens or blood cells, along with flow cytometry and specific cytochemical stains, is helpful to differentiate AML from other types of leukaemia (e.g. acute lymphoblastic leukaemia) and to classify the subtype of the disease.
  - Cytogenetics or fluorescent in situ hybridization (FISH) are carried out to test for chromosomal abnormalities. Additional genetic studies can reveal specific mutations in genes that may influence the outcome of the disease.

Clinical manifestations of chronic myeloid leukaemia (CML)

- Signs and symptoms:
  - Many subjects affected by CML can have minimal and nonspecific symptoms at presentation, such as fatigue, and are diagnosed on a routine blood test. If access to health care is limited, fatigue can be accompanied by more severe signs and symptoms, such as splenomegaly (which can manifest with a sense of early satiety), anaemia, abdominal pain, and weight loss. Low-grade fever can be present.
  - Less common and more severe presenting findings can follow thrombotic events (from severe leucocytosis or thrombocytosis), such as cardiovascular complications, myocardial infarction, venous thrombosis, visual disturbances, priapism, dyspnoea and pulmonary insufficiency, confusion, drowsiness and loss of coordination, or cerebrovascular accidents.

3.1.10 Occupational cancer caused by ionizing radiation — ICD Code C44, C34, C91-C95, C41.9, (C00-C97) +Z57.1

- Examinations:
  - Leucocytosis (up to 500 x 10^9/L) is a common finding, with a predominance of neutrophils, together with thrombocytosis.
  - Anaemia is present in about 30-40% of cases.
  - The peripheral blood smear shows circulating immature cells from the bone marrow.
  - Bone marrow analysis shows a characteristic hypercellularity, with an expansion of the myeloid cell line (e.g. neutrophils, eosinophils, basophils) and its progenitor cells. Cytogenetic studies of the bone marrow cells, and even peripheral blood, should reveal the typical Philadelphia (Ph1) chromosome.
  - Other laboratory abnormalities include hyperuricemia and elevated serum vitamin B12-binding protein (TC-I).

Exposure assessment

- History of occupational exposure: confirmed occupational exposure to ionizing radiations, with cumulative doses usually exceeding 1 Sv.
- Minimum duration of exposure: variable, depending on the dose.
- Maximum latent period: not applicable.

Name of the diseases and ICD code: **Osteosarcoma (C41.9) +Z57.1**

Short description of the disease

Workers exposed to internal irradiation through the incorporation of radionuclides normally absorbed in bone have shown an increased risk of osteosarcoma. This has been observed in working populations such as plutonium-production workers and watch-dial painters, some of whom ingested radium 226 by the practice of pointing their paintbrush tips with their lips.

Clinical manifestations

- Signs and symptoms: patients typically present with pain (which may be worse at night) and swelling of the affected area; the most common sites of involvement are the distal femur, the proximal tibia, and the proximal humerus.
- Examinations: X-ray is often the first diagnostic test, while surgical biopsy is the gold standard. A plain radiograph reveals a destructive lesion with a moth eaten appearance, a spiculated periosteal reaction "sunburst appearance", and a cuff of periosteal new bone formation at the margin of the soft tissue mass "Codman's triangle". A CT scan of the primary tumour is best for defining bone destruction and the pattern of calcification, whereas MRI is better for defining intramedullary and soft tissue extension.

Exposure assessment

- History of occupational exposure: evidence of internal irradiation through the intake of radionuclides normally absorbed in bone (e.g. Radium, ^{226}Ra, Plutonium, ^{238}Pu) in the occupational setting, with cumulative doses usually exceeding 8 Gy.
- Minimum duration of exposure: variable, depending on the dose.
- Maximum latent period: not applicable.

Name of the diseases and ICD code: **Other cancers caused by ionizing radiation (C00-C97) + Z57.1**

Other cancers were described in workers occupationally exposed to ionizing radiation, such as nasal sinuses and mastoid carcinomas in the radium dial industry, liver cancer in plutonium workers, and multiple myeloma in radiologists. Cancers possibly associated with radiation exposure are those observed in the salivary gland, thyroid, female breast, stomach, colon, oesophagus, urinary bladder, kidney, brain, and central nervous system, mainly among atomic-bomb survivors or medical patients exposed to radiation mostly for therapeutic purposes.

3.1.10 Occupational cancer caused by ionizing radiation	ICD Code C44, C34, C91-C95, C41.9, (C00-C97) +Z57.1
Key actions for prevention	The use of ionizing radiation is unavoidable in most current applications, especially in human health care, in veterinary, and in the quality control of some manufactured items. In health care, some of the diagnostic functions that are performed by X-ray imaging (radioscopy and radiography) now require much less exposure of patients, and post-acquisition digital image processing allows improvement of the quality of radiographic images and avoidance of unnecessary repeated X-rays. Complementary or alternative techniques for diagnostic imaging, such as ultrasonography and nuclear magnetic resonance, do not entail the use of ionizing radiations. In the industrial and manufacturing sector, most use of X-ray and of other nuclear equipment is aimed at detecting undesired metal fragments in goods and in industrial packaged food, at assessing on site the quality of metal welds, and at fast analysis of some complex materials by X-ray fluorescence imaging. For some of these applications, whenever alternatives that do not entail the use of ionizing radiation are made available, they rapidly become preferred to simplify operations and to overcome the regulatory difficulties inherent in the use of ionizing radiations and radioactive materials. The objective of radiation safety is to eliminate or minimize the harmful effects of ionizing radiation and radioactive material on workers, the public and the environment while allowing their beneficial uses. The following principles should guide the use of ionizing radiation and the application of radiation safety standards: • No practice involving exposures to radiation should be adopted unless it produces sufficient benefit to the exposed individuals or to society to offset the radiation detriment it causes (the *justification of a practice*). • In relation to the exposure of workers and members of the public, the magnitude of individual doses, the number of people exposed, and the likelihood of exposure should all be kept as low as reasonably achievable (ALARA), economic and social factors being taken into account, with the restriction that the doses to individuals delivered by the source be subject to dose constraints (the *optimization of protection and safety*). • The exposure of individuals should be restricted so that neither the total effective dose nor the total equivalent dose to relevant tissues or organs caused by possible combinations of exposures due to authorized practices exceeds any relevant dose limit. The limit on effective dose represents the level above which the risk of stochastic effects due to radiation exposure is considered to be unacceptable. For localized exposure of the lens of the eye, the extremities, and the skin, this limit on effective dose is not sufficient to ensure the avoidance of deterministic effects (*individual dose and risk limits*). For occupational exposure of workers over the age of 18 years, the dose limits are: • an effective dose of 20 mSv per year averaged over five consecutive years* (100 mSv in 5 years) and of 50 mSv in any single year; • an equivalent dose to the lens of the eye of 20 mSv per year averaged over five consecutive years* (100 mSv in 5 years) and of 50 mSv in any single year; and • an equivalent dose to the extremities (hands and feet) or to the skin** of 500 mSv in a year. *The start of the averaging period shall be coincident with the first day of the relevant annual period after the date of entry into force of these Standards, with no retrospective averaging. **The equivalent dose limits for the skin apply to the average dose over 1 cm^2 of the most highly irradiated area of the skin. The dose to the skin also contributes to the effective dose, this contribution being the average dose to the entire skin multiplied by the tissue-weighting factor for the skin. The employer, who has been notified of the suspected pregnancy or of breast-feeding, shall adapt the working conditions in respect of occupational exposure so as to ensure that the embryo or foetus or the breastfed infant is afforded the same broad level of protection as is required for members of the public.

3.1.10 Occupational cancer caused by ionizing radiation	ICD Code C44, C34, C91-C95, C41.9, (C00-C97) +Z57.1
Key actions for prevention	For occupational exposure of apprentices of 16 to 18 years of age who are being trained for employment involving radiation and for exposure of students of age 16 to 18 who use sources in the course of their studies, the dose limits are: • an effective dose of 6 mSv in a year; • an equivalent dose to the lens of the eye of 20 mSv in a year; and • an equivalent dose to the extremities (hands and feet) or to the skin of 150 mSv in a year. Radiation doses can be reduced mainly through: • minimizing the time of exposure; • increasing the distance between the body and the radiation source: this will reduce exposure by the square of the distance; and • using absorber (shielding) materials such as Plexiglas® for beta particles and lead for X-rays and gamma rays. In general, the dose limits for occupational exposure apply equally to male and female workers. However, because of the possible relevance of the greater sensitivity of the embryo or foetus or the breastfed infant to radiation, additional controls should be considered for pregnant and breastfeeding workers. Workers who are aware or who suspect that they are pregnant or who are breast-feeding should be encouraged to notify their employer, and they should typically be excluded from tasks in an emergency unless such tasks can be carried out within the requirements for occupational exposure established by the regulatory authority, in accordance with the relevant international radiation protection and safety standards. Areas, where any possibility of exposure has been identified should be restricted to people adequately trained, equipped with dosimeters and with personal protective equipment such as lead aprons, gloves and collar; protective lenses. Admittance into these areas should be forbidden to unauthorized/unequipped persons during irradiations (for example, during X-ray examinations in health care facilities). Doors of X-ray facilities should be equipped with systems able to automatically inhibit any function of the X-ray device when open.

Further reading

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3. Ghissassi FE. et. al. A review of human carcinogens—Part D: Radiation. The Lancet Oncol 2009:10(8);751-752.
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10. IAEA: Radiation protection and safety of radiation sources: international basic safety standards. Vienna: International Atomic Energy Agency, 2014.
11. IAEA/ILO: Occupational radiation protection. Vienna: International Atomic Energy Agency, 2018.

▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
3.1.10	Malignant neoplasms	C00-C97	2D4Z
3.1.10	Skin cancer	C44	2C3Y
3.1.10	Leukaemia	C91-C95	2B33.4
3.1.10	Lung cancer	C34	2C25.Z
3.1.10	Osteosarcoma	C41.9	2B51
	Occupational exposure to radiation	Z57.1	QD84.Y

3.1.11 Occupational cancer caused by tar, pitch, bitumen, mineral oil, anthracene, or the compounds, products or residues of these substances ICD Code C43, C44 +T52.0 +Z57	
General characteristics of the causal agent	All of these products, tar, pitch, bitumen, mineral oil, and anthracene, are very complex natural mixtures of large polycyclic aromatic hydrocarbons (PAH) and of other compounds containing alkyl chains, heterocyclic aromatic hydrocarbons, and organo-metal compounds such as vanadyl porphyrins. Natural tars, pitch and bitumen, originate from geologically very old crude oil, which has undergone extensive polymerization and aromatization, while industrial tars are byproducts of the oil industry. Their physical aspect and properties range from those of blackish green fluorescent viscous liquids to black jelly like substances to black hard waxes with obsidian type conchoid fractures. In principle, the more liquid-like they are, the higher is the content of extractable organic compounds, the higher is the flammability, and the lower is their apparent density. All of these products can burn but are poor ignition sources since they lack a sufficient content of volatile compounds to self-ignite when heated. Nonetheless, large fires are self-sustaining and generate large emissions of thick, black, and toxicologically hazardous smoke. *Tar* is a viscous black liquid derived from the destructive distillation of organic matter. Most tar is produced from coal as a byproduct of coke production, but it can also be produced from petroleum, peat or wood. Tar and pitch are sometimes used interchangeably; however, the *pitch* is considered more of a solid, while tar is more of a liquid. *Bitumen* is a semisolid mixture of high molecular mass hydrocarbons, which may occur naturally or as a residue from the distillation of crude oil. The PAH content of bitumen and its consequent toxicological hazard, varies depending on its origin and technological processing. *Mineral oil* and *anthracene* are the “heavy” fractions of the distillation of natural crude oil and of coal tar derived from cokery, distillation temperature usually above 270°C. These are higher added-value products that are used as industrial lubricants in engines and processing machinery, as water-oil emulsions (in cutting oils for metal-working), and for protection of metal parts from rusting.
Occupational exposures	Tars, pitches and heavy oils are mostly by-products of coal and oil extraction and processing, while natural bitumen is mined on its own. These substances have several industrial uses, mostly as technological materials, and have recently been exploited also as fossil fuels. Intensive chemical and thermal processing of raw materials is necessary to transform them into commodities with the desired properties. The ‘heavy’ fraction of crude oil is subject to destructive distillation under vacuum “cracking”, hydrogenation and hydrodesulfurization to recover as much as possible of the liquid hydrocarbons for fuel production. The tailings of such processes are usually of a very poor industrial value, and their disposal is complicated by toxicological hazard. Crude and heavy oil products stored in large stock tanks settle an oil mud, which gradually transforms into a hard to remove semi-solid mass at the bottom. Occupational exposure to viscous, semi-solid and solid hydrocarbon tars can occur in industrial chemical plants for tar distillation, for coal gas and asphalt production, in the cleaning of tankers and of raw and refined petroleum spillage and in the burning of petroleum and coal tail products for energy production. Other hydrocarbon mixtures, such as natural bitumen, are processed to make materials for road paving, building roofing, waterproofing, and insulation. Bitumen for road paving is a conglomerate material (asphalt) in which gravel is tightly held by a viscous pitch (binder) into a thin mechanically stable layer rolled over the weight-bearing substrate of road pavement. Except for the cheapest and less durable asphalt, the binder is currently a technological material engineered for elasticity, durability and waterproofness. Binders are now increasingly devoid of PAH and pose a significantly less toxicological risk for road pavers.

3.1.11 Occupational cancer caused by tar, pitch, bitumen, mineral oil, anthracene, or the compounds, products or residues of these substances ICD Code C43, C44 +T52.0 +Z57

Occupational exposures	Water-oil emulsions are used to protect metals from air oxidation in processing and in manufacturing. Cutting oils are dripped on metal pieces during boring, shaping, and other metal working processes, which make use of attrition-generating rotating tools. Tool rotation itself generates water and oil mists that contaminate the factory environment and can be absorbed by respiration and through skin contact by the workers. These mists not only contain mineral oils but also oil in water tensides and air oxidation products. The same occurs in textile spinning, where nonvolatile mineral oil is used to lubricate fibres passing at high speed in thread holes, to protect from air oxidation. In addition, oil mists are generated in this manufacture, and fire and explosion hazards often add to the toxicological hazard posed by the PAH contained in the oil. Newspaper printing uses large amounts of lubricating oils to decrease adhesion of paper to printing cylinders.
Carcinogenic mechanisms, main health effects and diagnostic criteria	
Short profile of the carcinogenic mechanisms	Tars, pitches, bitumen, mineral oils, and anthracene are very complex natural mixtures of polycyclic aromatic hydrocarbons (PAH), heterocyclic aromatic hydrocarbons, alkylated PAH and organo-metal compounds, such as vanadyl-porphyrins, each of which has specific toxicological properties. PAH as a group generate the highest health concerns for human cancer. In 2010 the IARC issued a comprehensive list of more than 60 individual PAH with two or more condensed benzene rings. Each was evaluated and classified according to available knowledge. In some countries, there are priority lists of PAH considered to be of highest health concern due to carcinogenic potency, and likelihood of exposures in the environment (e.g. in food and waste) generating health risk. Notwithstanding the hazards posed by PAH, findings on the specific carcinogenicity of tars, pitches, bitumen, mineral oils, and anthracene present a varied picture, as shown by the various evaluations conducted by the IARC. Coal *tar* and coal tar *pitch* are classified as Group 1 carcinogens i.e., carcinogenic to humans for skin (coal tar) and lung (coal tar pitch) cancers. Carcinogenic effects of these two mixtures together with those related to soots, have been thoroughly addressed in dedicated item 3.1.5, which should be referred to for further details. *Bitumen* The IARC classes occupational exposure to oxidized bitumens and their emissions during roofing as probably carcinogenic (2A). Occupational exposure to hard bitumens and their emissions during mastic asphalt work are classed as possibly carcinogenic (2B). Occupational exposure to straight run bitumens and their emissions during road paving are classed as possibly carcinogenic (2B). As regard *mineral oils*, the IARC concluded that there is sufficient evidence in humans for the carcinogenicity of untreated or mildly treated mineral oils as a cause of skin cancer (especially affecting the scrotum), and thus classified them as Group 1 carcinogens. Mineral oils can be hydro-treated to refine the product, but the evidence for carcinogenicity of highly treated mineral oils is insufficient to draw conclusions. Finally, the evidence in humans regarding the carcinogenicity of *anthracene* was considered insufficient.

Name of the diseases and ICD code: **Skin cancer (C43, C44) +T52.0 +Z57**

Short description of the disease

Evidence regarding the carcinogenic potential of mineral oils come from a series of case reports and case series from the early 1900s through the 1960s, where an increased risk of scrotal cancer [epithelioma of the scrotum, whose most common forms are basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)] was observed among mule-spinners i.e., those working on the spinning mule, a machine used to spin cotton and other fibres. More recent studies confirmed an excess in scrotal cancer incidence among metalworkers exposed to oil mists, lathe operators, pressmen, tool setters, and tool fitters. A large study conducted on a cohort of more than 5,000 male aerospace workers found a significantly increased risk of skin melanoma.

3.1.11 Occupational cancer caused by tar, pitch, bitumen, mineral oil, anthracene, or the compounds, products or residues of these substances ICD Code C43, C44 +T52.0 +Z57

Diagnostic criteria

Clinical manifestations

- *Signs and symptoms of BCC:* it affects skin areas of the head, neck or shoulders. Despite being locally invasive, BCC does not metastasize. Crusting and bleeding in the centre of the tumour frequently develops. It is often mistaken for a sore that does not heal. This form of skin cancer only very seldom causes fatalities. Pigmented BCC, characterized by the presence of melanin in the cells may be wrongly diagnosed as melanoma. The tumour may present as pearly nodules, nodular BCC, or flat, brown or flesh-coloured lesions with a pearly border, superficial BCC.
- *Signs and symptoms of SCC:* it is a malignant neoplasm of the keratinized epidermal cells characterized by quick growth and metastasizing capacity. The first manifestation is usually a painless, nonhealing, bleeding skin ulceration in the middle of a verrucous papule or plaque, often manifesting on sun-damaged skin. SCC may present as firm, red nodules or flat lesions with scaly, crusted surfaces; all forms eventually evolve into ulcers, which are typically red with everted edges; the skin around the ulcer is usually inflamed and hardened.
- *Signs and symptoms of melanoma:* it may present in a variety of ways, such as moles that change appearance, large brown spots with darker speckles, or small irregularly bordered lesions with portions that appear red, white, blue, or blue-black.
- Examinations:
  - Observation of the lesion, supported by dermoscopy, usually prompts the diagnosis.
  - Biopsy of the skin remains the most accurate way of assessing the histologic subtype of the tumour.

Exposure assessment

- History of occupational exposure: confirmed occupational exposure to mineral oils or mineral oils mists.
- Minimum duration of exposure: six months.
- Maximum latent period: not applicable.

Key actions for prevention	In the hierarchy of preventive interventions, the first tier is elimination of use, and the second, substitution of the more harmful products with those with no or fewer health risks. In this context, vacuum degassing of bitumen has proved very effective in removing the more volatile PAH and thus greatly reducing the exposure of street workers during paving, while completely retaining and even improving the conglomerating efficacy of bitumen on gravel. Carcinogenic mineral oils have been progressively superseded by more highly refined substitutes. Appropriate engineering of industrial processes, ventilation controls and working practices should be used with personal protective equipment to avoid skin, eye and respiratory exposure in all jobs. Particular attention should be given to control measures in the informal work sector, ship repair and scrapping, and the cleaning of large capacity storage tanks in crude oil tankers and oil terminals.

3.1.11 Occupational cancer caused by tar, pitch, bitumen, mineral oil, anthracene, or the compounds, products or residues of these substances ICD Code C43, C44 +T52.0 +Z57

Further reading

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2. IARC 2012. Monographs on the Evaluation of Carcinogenic Risks to Humans. Vol 100F: Chemical Agents and Related Occupations.
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For the chemical entities listed below an entry exists in the collection of International Chemical Safety Cards (ICSC) hosted in the ILO website

Name	Synonyms	ICSC
Asphalt	Bitumen; Petroleum bitumen	0612
White mineral oil	Paraffin oil; Paraffinum liquidum	1597

▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
3.1.11	Toxic effects of tar, pitch, bitumen, mineral oil, anthracene, or the compounds, products or residues of these substances	T52.0	NE61 &XM4C94 &XM16M2 &XE7CA&XM3SU8 &XM7WM1
3.1.11	Skin cancer	C43, C44	2C3Z
	Occupational exposure to risk factors	Z57	QD84.Y

3.1.12 Occupational cancer caused by coke oven emissions	ICD Code C34 +T59.8 +Z57
General characteristics of the causal agent	Coke ovens are industrial chemical plants where some brands of natural coal are processed to prepare coke carbon, a porous, poorly flammable form of carbon, which is employed as a reducing agent in the extraction of some metals from their ores. The coking process is aimed at stripping from coal its water, volatile constituents, and sulphur content, up to approximately 20% of coal weight in metallurgic-grade coal, which would hamper its metal-reducing properties. Coke oven emissions are thus a mixture of gases mainly hydrogen, methane, carbon monoxide, and nitrogen oxides and airborne volatiles (water, ammonia, aromatic hydrocarbons, volatile polycyclic aromatic hydrocarbons, and heterocyclic aromatic compounds). The gaseous stream is fractionated by condensing the mixture of organic products at room temperature and using the further processed gaseous stream (coal gas) as a raw material for the chemical industry or as a fuel source. The condensed product (coal tar) is a viscous liquid or semisolid coke. The solid airborne particulate matter contained in coke oven emissions is made of graphitized elemental carbon where metals such as arsenic, beryllium, cadmium, chromium, lead, mercury, and nickel are present as embedded oxides, sulphates, or silicates, and non-volatile polycyclic aromatic hydrocarbons are adsorbed. The chemical composition of coke oven emissions depends on the origin and quality of the processed coal and on the process parameters. The condensed fraction of coke oven emissions represented for a long period in the nineteenth and twentieth centuries, the major source of compounds such as ammonia, benzene, and naphthalene. Nowadays, coke is primarily used as a reducing agent to make iron and steel in blast furnaces; coke gases have lost most of their use as raw material for the chemical industry. Therefore, in integrated coking furnaces, the hydrocarbon off-gases produced by the coke-making process are now just purified to be burnt as a cheap energy source for the carbonization process.
Occupational exposures	Occupational exposure to coke oven emissions may occur from the use of coke to extract metals from ores in integrated coke oven blast furnace plants, during the production of coke from coal, in coal gas plants upstream to productions of bulk chemicals such as methyl alcohol, in the synthesis of calcium carbide, and in the manufacture of graphite and of graphite electrodes. Workers at coke ovens and at downstream plants which use coke as a starting material may be exposed to emissions that consist of very complex mixtures of toxic particles, tars, vapours, gases. The main route of workers' exposure to coke oven emissions is the inhalation of dusts and vapours.
Carcinogenic mechanisms, main health effects and diagnostic criteria	
Short profile of the carcinogenic mechanisms	Exposure to coke oven emissions has been observed to cause cancer of the lung. For other cancer sites i.e., skin and bladder, the evidence is considered to be inadequate. Detailed chemical analyses of coke oven emissions have demonstrated the presence of multiple known and potential carcinogens, including polycylic aromatic hydrocarbons (PAH) such as benzo[a]pyrene, nitrosamines, and coal tar. The exact mechanisms by which coke oven emissions induce carcinogenesis have not yet been fully elucidated, in part because of the difficulty of determining the proportional contributions of the different components to genotoxic activity. Nevertheless, there is sufficient evidence for mutagenic and epigenetic modes of action. Much of the literature in this area has focused on the measurement of anti-benzo[a]pyrene-7,8-diol-9,10-epoxide-DNA adducts in peripheral blood lymphocytes in exposed populations as a possible biomarker. Studies suggest that benzo[a]pyrene plays a role in the genotoxic mechanism by which coke oven emissions induce carcinogenesis. The IARC classifies coke production as a Group 1 carcinogen i.e., carcinogenic to humans.

3.1.12 Occupational cancer caused by coke oven emissions ICD Code C34 +T59.8 +Z57

Name of the diseases and ICD code: **Lung cancer (C34) +T59.8 +Z57**

Short description of the disease

Studies conducted on workers exposed occupationally to coke oven emissions during coke production have documented an excess of lung cancer, and some reported a trend of increasing risk for this cancer with increasing duration of exposure.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms:
  - Anorexia, asthenia, or weight loss.
  - New cough or change in chronic cough, sometimes with haemoptysis.
  - Nonspecific chest pain or pain from bone metastases to the ribs, vertebrae, or pelvis.
  - Local spread may cause obstruction of the bronchi with atelectasis and pneumonia, pleural effusion, superior vena cava syndrome (i.e., a plethora of symptoms following obstruction of blood flow through the superior vena cava, which include facial and arm swelling, nasal congestion, head fullness, headache and lightheadedness, nausea and dysphagia, distorted vision), change in voice (following the involvement of the recurrent laryngeal nerve), and Horner's syndrome (ipsilateral ptosis, miosis, anhidrosis, and enophthalmos following involvement of the inferior cervical ganglion and the paravertebral sympathetic chain).
  - Brain metastases may present with headache, seizures, altered mental status, nausea, and vomiting, while liver metastases might be associated with asthenia and weight loss.
  - Paraneoplastic syndromes include various symptoms related to immune-mediated or secretory effects of tumours, such as syndrome of inappropriate antidiuretic hormone secretion, hypercalcaemia, digital clubbing, increased adrenocorticotropin production, anaemia, hypercoagulability, peripheral neuropathy, and myasthenic syndromes.
- Examinations:
  - Chest X-ray: radiologic manifestations of lung cancer are diverse and include lung nodules and pulmonary, cavitated, or apical mass, with or without associated lymphadenopathy.
  - Chest CT provides information on the details of the neoplastic lesion, its relationship to other anatomical structures, the status of the pleural space, and the size of mediastinal lymph nodes.
  - Sputum cytology is highly specific, although not sensitive, with the maximum yield provided when there are lesions in the central airways.
  - Thoracentesis can be used to make a diagnosis when malignant pleural effusions are present.
  - Fine needle aspiration of lymph nodes (supraclavicular or cervical) is frequently diagnostic.
  - Fiberoptic bronchoscopy can help visualisation of the major airways, brush of visible lesions or lung lavage (with cytological specimen evaluation), and assist various biopsy procedures, such as direct biopsy of endobronchial lesions, a transbronchial biopsy of peripheral nodules or of the lung parenchyma, and fine needle aspiration of mediastinal lymph nodes. Other biopsy techniques include percutaneous biopsy using image guidance and endobronchial ultrasound (EBUS) guided biopsy.

Key actions for prevention	Prevention measures in the occupational setting should reduce workers' exposure to coke oven emissions through technological improvements in the manufacturing processes. Valuable examples are enclosed sieves and conveyors for coke and coal handling and suppression of dust formation through sprinklers and plastic emulsions. Windbreaks should be provided when feasible. Drop distances should be reduced to a minimum, and materials should be stored in bunkers or warehouses. Personal protective equipment should be used when exposure is considered to be unavoidable. For several toxic emissions, exposure limits are recommended or enforced in most countries. Plant design should reduce emission of pollutants (black smoke, carbon dioxide, mercury, etc.) to the general environment, in compliance with local regulations.

3.1.12 Occupational cancer caused by coke oven emissions ICD Code C34 +T59.8 +Z57

Further reading

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2. Manolis Kogevinas, J Malcolm Harrington and Roel Vermeulen. Occupational cancer: epidemiology, biological mechanisms and biomarkers. Chapter 85 in Hunter's Diseases of Occupations. Editors Baxter PJ, Aw T-C, Cockcroft A, Durrington P, Harrington JM. Tenth Edition, London: Hodder Arnold, 2010, P 1086-8, 1092-3.
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▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
3.1.12	Other specified gases, fumes and vapours	T59.8	NE61
3.1.12	Lung cancer	C34	2C25.Z
	Occupational exposure to risk factors	Z57	QD84.Y

3.1.13 Cancer caused by nickel compounds	ICD Code C30.0, C31, C34 +T56.8 +Z57
General characteristics of the causal agent	There is sufficient evidence in humans for the carcinogenicity of mixtures containing nickel compounds and nickel metal, as these agents can cause cancers of the lung, nasal cavity and paranasal sinuses. Nickel compounds of industrial relevance that have been observed to be more frequently associated with increased cancer risks include nickel oxide, nickel hydroxide, nickel subsulphide, nickel sulphate, and nickel chloride. *Nickel oxide* [NiO (powder), CAS number 1313-99-1] is a green to black crystalline powder, mainly used as an intermediate in the production of nickel alloys. *Nickel hydroxide* [Ni $(OH)_2$, CAS number 12054-48-7] is an apple-green electroactive solid that finds widespread applications in rechargeable batteries. *Nickel subsulphide* [Ni_3S_2, CAS number 12035-72-2] appears as a pale yellowish bronze crystal with metallic lustre; it decomposes on heating to high temperatures producing sulphur oxides. *Nickel sulphate* [$NiSO_4$, CAS number 7786-81-4] is a green, yellow or blue coloured solid, mainly used in electroplating and as a chemical intermediate to produce other nickel compounds. *Nickel chloride* [$NiCl_2$, CAS number 7718-54-9] is a yellow or green coloured solid, mainly used in electroplating, in nickel catalysts, and to absorb ammonia in industrial "gas masks".
Occupational exposures	Exposure to airborne fumes, dusts and mists containing nickel and its compounds occurs for several million workers worldwide. Occupational exposure occurs both in nickel-producing industries e.g. mining, milling, smelting, and refining, and in nickel using industries and operations e.g. alloy and stainless steel manufacture; electroplating and electroextraction; welding, grinding and cutting. Exposure is possible in the manufacture of nickel cadmium batteries, coins, and kitchen utensils. Occupational exposure can occur in recycling operations since nickel-bearing materials especially from the steel industry, are commonly melted, refined and used to prepare alloys similar in composition to those that entered the recycling process. Increased cancer risk has been observed, especially among nickel refinery and nickel smelter workers.
Carcinogenic mechanisms, main health effects and diagnostic criteria	
Short profile of the carcinogenic mechanisms	Absorption of the metal from inhaled nickel containing particulate matter, such as from welding and metalworking fumes, depends on the solubility of the species in the alveolar fluid. Nickel from less soluble compounds, such as green nickel oxide, is removed by a macrophage-mediated mechanism and cleared only in faeces. On the contrary, nickel sub-sulphide is removed by dissolution absorption and excreted mostly in the urine. Soluble inorganic nickel (II) salts absorbed through the lungs are cleared in the urine within 36 hours. In general, metallic compounds are able to increase the mutagenicity and carcinogenicity of directly acting genotoxic agents by inhibiting the repair of damaged DNA. In addition, evidence suggests that nickel may stimulate cell proliferation by activating proto-oncogenes or interfering with tumour suppressor genes. The mutagenic properties of nickel may be attributed to its ability to cause chromosomal damage. Nickel compounds derive their carcinogenicity from their ability to increase the intracellular concentration of nickel ions. Intracellular nickel is able to bind DNA and nuclear proteins inducing damage and generating production of oxygen radicals, increasing cellular oxidative stress. Hence, the carcinogenic potential of nickel compounds may be directly related to their water solubility; water insoluble nickel compounds may be more potent carcinogens because of the greater ease with which they are able to phagocytose across the cell membrane. However, soluble nickel compounds may enter the cell via metal ion transporters and other channels and induce DNA damage. Nickel compounds of differing degrees of solubility have been demonstrated to mediate DNA strand breakage, DNA protein cross-linkage, and sister chromatid exchange. Oxidative stress is thought to play a significant role in nickel induced DNA damage. Oxygen radicals generated by nickel ions attack DNA resulting in alterations in transcription and transduction and errors in replication. In addition, epigenetic mechanisms may contribute to nickel-induced carcinogenesis as there is evidence that nickel alters patterns of histone acetylation, methylation, and phosphorylation. Mixtures that include nickel compounds and nickel metal have been found to cause cancers of the nasal cavity and paranasal sinuses, and of the lung.

3.1.13 Cancer caused by nickel compounds ICD Code C30.0, C31, C34 +T56.8 +Z57

Name of the diseases and ICD code: **Cancers of the nasal cavity (C30.0) and of the paranasal sinuses (C31) +T56.8 +Z57**

Short description of the disease

Sinonasal cancers i.e., cancers of the nasal cavity and of the paranasal sinuses, are rare in the general population and are often associated with specific chemical exposures or occupational settings; they are thus considered "sentinel" health events which may prompt investigation for a specific risk factor.

Delay in diagnosis is not uncommon as sinonasal tumours may be asymptomatic in around 10% of patients. Nonetheless, cancers of the nasal cavity are usually diagnosed earlier than those of the paranasal sinuses because of the earlier presentation of symptoms resembling nasal sinus inflammation, such as epistaxis and obstructive symptoms.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: nasal obstruction, nasal bleeding or discharge, headache and facial pain.
- Examinations:
  - Physical examination may reveal: proptosis, eye movement abnormalities due to extraocular muscle impairment; mass effect of the cheek, gingivobuccal or gingival sulcus, and loose dentition; trigeminal nerve abnormalities, such as numbness or hyperaesthesia in the territory of the infraorbital nerve of the maxillary branch.
  - Plain CT is helpful in assessing the extent of bone erosion, while the use of contrast can reveal tumour vascularity.
  - MRI can differentiate tumour borders from the surrounding soft tissue especially with gadolinium and demonstrate invasion of the surrounding anatomical structures.
  - An endoscopic biopsy allows histological characterisation of the lesion, with squamous cell carcinoma and adenocarcinoma being the two most common histological subtypes of this cancer.

Exposure assessment

- History of occupational exposure: evidence of prolonged or repeated exposure to nickel compounds, primarily via inhalation and, when available, workplace and biological monitoring.
- Minimum duration of exposure: six months.
- Maximum latent period: not applicable.

Name of the diseases and ICD code: **Lung cancer (C34) +T56.8 +Z57**

Short description of the disease

Elevated risk of lung cancer was reported among nickel refinery workers and nickel smelter workers. Evidence was documented specifically for some compounds, in particular: nickel chloride, nickel sulphate, nickel oxides, nickel sulphides, and for water soluble and insoluble nickel compounds in general. In the majority of affected subjects, the first clinical manifestations of the disease are related to local tumour growth (primary lesion), invasion or obstruction of adjacent lung structures, metastatic growth at distant sites, or paraneoplastic syndrome.

3.1.13 Cancer caused by nickel compounds — ICD Code C30.0, C31, C34 +T56.8 +Z57

Diagnostic criteria

Clinical manifestations

- Signs and symptoms:
  - Anorexia, asthenia, or weight loss.
  - New cough or change in chronic cough, sometimes with haemoptysis.
  - Nonspecific chest pain or pain from bone metastases to the ribs, vertebrae, or pelvis.
  - Local spread may cause obstruction of the bronchi with atelectasis and pneumonia, pleural effusion, superior vena cava syndrome (i.e., a plethora of symptoms following obstruction of blood flow through the superior vena cava, which include facial and arm swelling, nasal congestion, head fullness, headache and lightheadedness, nausea and dysphagia, distorted vision), change in voice (following the involvement of the recurrent laryngeal nerve), and Horner's syndrome (ipsilateral ptosis, miosis, anhidrosis, and enophthalmos following involvement of the inferior cervical ganglion and the paravertebral sympathetic chain).
  - Brain metastases may present with headache, seizures, altered mental status, nausea, and vomiting, while liver metastases might be associated with asthenia and weight loss.
  - Paraneoplastic syndromes include various symptoms related to immune-mediated or secretory effects of tumours, such as syndrome of inappropriate antidiuretic hormone secretion, hypercalcaemia, digital clubbing, increased adrenocorticotropin production, anaemia, hypercoagulability, peripheral neuropathy, and myasthenic syndromes.
- Examinations:
  - Chest X-ray: radiologic manifestations of lung cancer are diverse and include lung nodules and pulmonary, cavitated, or apical mass, with or without associated lymphadenopathy.
  - Chest CT provides information on the details of the neoplastic lesion, its relationship to other anatomical structures, the status of the pleural space, and the size of mediastinal lymph nodes.
  - Sputum cytology is highly specific, although not sensitive, with the maximum yield provided when there are lesions in the central airways.
  - Thoracentesis can be used to make diagnoses when malignant pleural effusions are present.
  - Fine needle aspiration of lymph nodes (supraclavicular or cervical) is frequently diagnostic.
  - Fiberoptic bronchoscopy can help visualisation of the major airways, brush of visible lesions or lung lavage with cytological specimen evaluation, and assist various biopsy procedures, such as direct biopsy of endobronchial lesions, a transbronchial biopsy of peripheral nodules or of the lung parenchyma, and fine needle aspiration of mediastinal lymph nodes. Other biopsy techniques include percutaneous biopsy using image guidance, and endobronchial ultrasound (EBUS) guided biopsy.

Exposure assessment

- History of occupational exposure: evidence of prolonged or repeated exposure to nickel compounds, primarily via inhalation and, when available, workplace and biological monitoring.
- Minimum duration of exposure: six months.
- Maximum latent period: not applicable.

Key actions for prevention	The metallurgical use of nickel for the preparation of steel and copper alloys is likely to continue as high-volume production. On the contrary, the use of nickel for electroplating and for the manufacturing of consumer goods is fading due to its sensitizing and carcinogenic properties. The prevention of exposure in the metallurgical industry is based on the enclosure of crucibles and ovens. In metal working, such as welding, cutting and machining, the enclosure of the sources of metal dusts and the use of personal protection devices by the workers is strongly advised. Pre-placement assessment of nickel exposed workers should identify preexisting medical conditions that may help in job placement and provide baseline data for subsequent functional, physiological or pathological changes. The assessment includes (i) detailed medical and occupational history, focusing on lung problems, exposures to lung toxins, past or present allergies particularly to nickel, asthma and personal habits e.g. smoking, (ii) complete physical examination, with attention to respiratory and skin problems and (iii) determination of the respiratory protective equipment that may be worn. Chest X-ray and pulmonary function tests may be included. If the organization conducts a biological monitoring programme for nickel exposed workers (see below), baseline nickel concentrations in urine or serum can be obtained during the pre-placement assessment, keeping in mind that urinary nickel levels mostly reflect recent exposures.

3.1.13 Cancer caused by nickel compounds — ICD Code C30.0, C31, C34 +T56.8 +Z57

Key actions for prevention

Periodic assessment, typically performed annually, of nickel exposed workers should monitor the worker's general health and to address nickel associated concerns. The examination includes the history of recent illnesses, symptom review, physical examination and re-evaluation of the worker's ability to use the respiratory protective equipment required for particular tasks. Pulmonary symptoms might be assessed by means of standardized questionnaires. Chest X-ray may be legally required in some countries, while pulmonary function tests are generally left to the physician's discretion. In workers with high risk exposures in nickel refining, periodic procedures aimed to detect early neoplastic lesions e.g. rhinoscopy, nasal sinus X-rays, nasal mucosal biopsy, exfoliative cytology studies may be indicated.

Measurements of nickel concentrations in urine and serum samples should not be used as a surrogate for environmental exposure measurements since they do not furnish reliable measures of the total body nickel burden but just reflect the recent exposures of workers to metallic nickel and soluble nickel compounds. If a biological monitoring programme is implemented, it should be coupled with an environmental monitoring programme.

The manufacture and use of nickel carbonyl is a specialized activity, and very stringent safety measures need to be put into operation, including the use of supplied air respirators. Nickel carbonyl can under certain circumstances form in steel pipes that carry carbon monoxide in chemical plants. Apart from its toxicity, the generation of nickel and iron carbonyls can over time corrode pipes and other metalware especially at the margins of the metalwork such as pipe threads and give rise to corrosion leaks. Because of its flammability and tendency to explode, nickel carbonyl should be stored in tightly closed containers in a cool, well-ventilated area, away from heat and oxidizers such as nitric acid and chlorine. Flames and sources of ignition should be prohibited wherever nickel carbonyl is handled, used or stored. Nickel carbonyl should be transported in steel cylinders. Foam, dry chemical, or carbon dioxide fire extinguishers should be used to extinguish burning nickel carbonyl, rather than a stream of water, which might scatter and spread the fire.

In addition to the medical surveillance measures recommended for all nickel exposed workers, persons with occupational exposures to nickel carbonyl should have biological monitoring of nickel concentration in urine specimens on a regular basis, typically monthly. Persons who enter confined spaces where they might possibly be exposed to nickel carbonyl should have self-contained breathing apparatus and a suitable harness with a lifeline tended by another worker outside the space.

Several scientific bodies and regulatory agencies suggest or enforce exposure limits for the occupational exposure to nickel or its compounds. The group of experts considered that the following limits of exposure of workplace atmospheric concentrations have been observed to provide a reasonable level of protection for workers' health and to be used in a number of countries:

- Nickel (inhalable fraction): 1.5 mg/m^3 as 8hr TWA.
- Nickel subsulphide/sulphate/oxide/carbonate (inhalable fraction): 0.1 mg/m^3 as 8hr TWA.
- Nickel tetracarbonyl: 0.05 ppm as short-term exposure limit.

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3.1.13 Cancer caused by nickel compounds ICD Code C30.0, C31, C34 +T56.8 +Z57

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For the chemical entities listed below an entry exists in the collection of International Chemical Safety Cards (ICSC) hosted in the ILO website

Name	Synonyms	ICSC
Nickel (II) sulphate	Nickelous sulphate; Nickel(2+) sulfate	0063
Nickel (II) oxide	Nickel monoxide; Nickelous oxide	0926
Nickel sulfide	Heazlewoodite; Nickel subsulphide; Trinickel disulphide	0928

▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
3.1.13	Toxic effect of nickel compounds	T56.8	NE61&XM4E11
3.1.13	Cancer of the nasal cavity	C30.0	2C20.Z
3.1.13	Cancer of the paranasal sinuses	C31	2C22.Z
3.1.13	Lung cancer	C34	2C25.Z
	Occupational exposure to risk factors	Z57	QD84.Y

3.1.14 Cancer caused by wood dust	ICD Code C30.0, C31, C11 +Z57.2
General characteristics of the causal agent	Wood dust consists of the dust generated by the mechanical treatment of timber during the conversion of natural wood into technological products. Wood dust particles contain lignin (the rigid aromatic constituent of plant tissue), cellulose and other polysaccharide polyoses, as well as other substances of a lower molecular mass, such as fatty acids, rosin and triterpene acids and alcohols. Wood from different species of trees is classified based on density and technological properties as "hard" or "soft". Hardwood trees include oak, beech, lime ash, birch, elm; softwood trees include coniferous trees such as fir, spruce and pine. Hardwoods, especially oak and beech, are considered more carcinogenic compared to soft ones. Another source of wood dust is plywood and other forms of "reconstituted wood". This material is manufactured by glueing together wood chips, saw-wood, wood slices with synthetic (polymer resins) or natural (rosin resins) adhesives and subjecting the material to pressure and heat. This material finds use as a substitute to more expensive "natural" new wood in lower end applications and in some higher end technological applications, such as for naval building, bent furniture, "green" building architecture. Plywood and other reconstituted woods release dusts that contain adhesives and other chemicals used in their manufacture, such as inorganic and organic wood preservatives.
Occupational exposures	All tasks where wood is "*worked*" e.g. sawing, milling, planing, and sanding of wood, can release wood dusts that are likely to be inhaled by timber workers, carpenters, and cabinet-makers. The activities that show the highest levels of exposure are industrial furniture and cabinet making and the production of buildings fittings, such as window frames, doors, parquets, wall matchboards, especially where reconstituted rather than "*natural*" wood is used. Exposure to wood dust occurs in work where wood is machined on-site, such as in joinery, in wooden boat manufacture, in the installation and refinishing of wooden floors, in pattern and model making, in construction carpentry, and in logging.
Carcinogenic mechanisms, main health effects and diagnostic criteria	
Short profile of the carcinogenic mechanisms	The specific mechanisms responsible for the carcinogenicity of wood dust are not fully known. Among them, the most likely is the deposition of the dust particles in the sinonasal region, the consequent impairment of ciliary clearance and a direct genotoxic activity exerted by the dusts. Wood dust exerts an irritant effect on the upper respiratory system and may cause cellular changes in the mucous epithelium, evolving into squamous metaplasia and dysplasia. These changes very often precede the onset of neoplasia. Several agents may play a role in the carcinogenic process: they can originate from the endogenous products of wood, terpenes and terpene derived aromatic compounds, from industrial organic chemicals used to treat the wood or as adhesives and binders of reconstituted wood e.g. chlorophenols, phenolformaldehyde, melamine formaldehyde, polyacrylate resins. Additionally, wood preserving agents may be present: chromate copper-arsenate and copper azole, creosote, pentachlorophenol, didecyl dimethyl ammonium chloride, the Propiconazole Tebuconazole Imiadicloprid mixture. Their target organs are those of the respiratory tract, especially the upper airways. For this reason, airborne concentration and particle size are considered as the main determinants of occupational risk. The risk is higher in the activities bringing about the highest exposure levels, in particular to hard wood dusts and, among hardwood dusts, oak and beech.

Name of the diseases and ICD code: **Cancers of the nasal cavity (C30.0) and paranasal sinuses (C31), and of the nasopharynx (C11) +Z57.2**

Short description of the disease

Sinonasal cancers, i.e., cancers of the nasal cavity and the paranasal sinuses, are rare in the general population and are often associated with specific chemical exposures or occupational settings; thus, they are considered "sentinel" health events prompting investigation for a specific risk factor. Delay in diagnosis is not uncommon as sinonasal tumours may be asymptomatic in around 10% of patients. Nonetheless, cancers of the nasal cavity are usually diagnosed earlier than those of the paranasal sinuses because of the earlier presentation of symptoms resembling nasal sinus inflammation, such as epistaxis and obstructive symptoms.

Nasal, sinonasal and nasopharyngeal neoplasms are adenocarcinomas or squamous cell carcinomas. Among studies specifying histology, large excess risks were observed for sinonasal adenocarcinoma and wood dust exposure.

3.1.14 Cancer caused by wood dust — ICD Code C30.0, C31, C11 +Z57.2

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: nasal obstruction, nasal bleeding or discharge, headache and facial pain; nasopharyngeal cancer can manifest with cranial nerve palsies, usually associated with an extension of the tumour towards the base of the skull, and changes in hearing usually associated with blockage of the Eustachian tube; direct extension into the ear is possible.
- Examinations:
  - Physical examination may reveal: proptosis, eye movement abnormalities due to extraocular muscle impairment; mass effect of the cheek, gingivobuccal or gingival sulcus, and loose dentition; trigeminal nerve abnormalities, such as numbness or hyperaesthesia in the territory of the infraorbital nerve of the maxillary branch.
  - The most common physical finding for nasopharyngeal cancer is a neck mass consisting of painless firm lymph node enlargement; a mass arising in the nasopharynx is often visible on nasopharyngoscopy.
  - Plain CT is helpful in assessing the extent of bone erosion, while the use of contrast can reveal tumour vascularity.
  - MRI can differentiate tumour borders from the surrounding soft tissue especially with gadolinium, and demonstrate invasion of the surrounding anatomical structures.
  - An endoscopic biopsy allows the histological characterisation of the lesion.

Exposure assessment

- History of occupational exposure: evidence of prolonged occupational exposure to wood dust.
- Minimum duration of exposure: 10 years.
- Maximum latent period: not applicable.

Key actions for prevention	Prevention is based on the protection of the workers from inhalation of wood dusts. This is achieved primarily with environmental protection as well as with the provison of appropriate personal protective devices such as respiratory protection. Training and education are fundamental because, very often, workers are not aware of this risk. Different countries set different standards for occupational exposure to wood dust, in some cases distinguishing between hard and softwood. For example, an 8 hr (TWA) limit value of 1.0 mg/m^3 is reported by the American Conference of Governmental Industrial Hygienists (ACGIH), which also discriminates based on the type of wood with a different limit of 0.5 mg/m^3 TLV-TWA for red cedar, the latter being due to respiratory sensitization effects. The European Union fixed 5 mg/m^3 TLV-TWA as an occupational exposure limit for the inhalable fraction of hardwood dust.

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▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
3.1.14.	Cancer of the nasal cavity	C30.0	2C20
3.1.14	Cancer of the paranasal sinuses	C31	2C22
3.1.14	Cancer of the nasopharynx	C11	2B6B
	Occupational exposure to dust	Z57.2	QD84.0

3.1.15 Cancer caused by arsenic and its compounds	ICD Code C34, C44, C67 +T57.0 +Z57
General characteristics of the causal agent	Arsenic (As), CAS number 7440-38-2, is the chemical element with atomic number 33 in the periodic table of elements, has one stable isotope (^{75}As), and its mean atomic mass is 74.9 Da. Arsenic is classified in Group 15 (3-B, semi-metals) and features four different oxidation (valence) states: -3, 0, +3 (or III), and +5 (or V), the most important of which are: • inorganic arsenic (III) '*arsenite*' and arsenic (V) '*arsenate*' compounds; • organic arsenic compounds [both arsenic (V) and arsenic (III) oxidation state]; and • arsine gas and substituted arsines (-3 oxidation state: arsenic hydrides, arsenic alkyls). Elemental arsenic is an abundant, silver-grey, semi-metallic element, which sublimes into a vapour above 615°C rather than melting. Typical soil levels of arsenic are 1-10 ppm, while seawater has concentrations around 1.6 ppb. In nature, arsenopyrite (FeAsS) contained in sulphide ores is the most abundant form of arsenic. Other important minerals are sulphides, orpiment and realgar. Due to the natural presence of arsenic organic compounds in several organisms, there is a natural bio-geochemical arsenic cycle. Organic arsenic compounds are abundant in marine organisms and are usually characterized by very low toxicity and a low tendency to be biologically converted into toxic forms. Arsenic commonly occurs in the atmosphere, mainly in the particulate matter (ashes) released from the combustion of carbon reservoirs, such as coal and oil, of which it is a natural constituent at levels up to some tens of grams per ton (parts-per-million). Arsenic fumes [mainly consisting in arsenic (V) oxides] are also released from processing of mixed sulphides and arsenides in primary metallurgy. Arsine gas and alkyl-arsines (trimethyl-arsine, *Gosio gas*) are generated by moulds, which can naturally grow on arsenic-containing organic materials. Some benthonic seawater organisms are also able to incorporate arsenic into alkylarsenic fatty acids.
Occupational exposures	Humans have used arsenic since antiquity, as testified by manufactured bronze articles recovered at archaeological sites. Due to its toxicological hazard (see below), low-technology production and dispersion into the environment are decreasing, and the industrial use of arsenic has been restricted or banned in many countries. Nonetheless, current industrial uses and possible occupational exposures occur in several processes, which include: smelting of sulphide-arsenide ores in primary metallurgy, the preparation and manufacturing of alloys with other metals e.g. with lead, copper, zinc, and the residual manufacture and use of arsenic containing compounds. The latter include insecticides, herbicides, fungicides and wood preservatives (monosodium methyl arsenate, mainly historical), and arsenic containing pigments e.g. Paris green - cupric acetoarsenite; Scheele's green - cupric arsenite. Applications include the impregnation with chromate copper arsenate of wood timber as a biocide to protect the construction from rotting or from insect infestation. Arsenic-containing pesticides are banned as such in many countries, while in others, their use is still authorized. Some arsenic compounds are used in microelectronics (gallium arsenide), and in the glass-making and optical industry, where manufacturing is performed under strict conditions of insulation: occupational exposure in these contexts is thus usually very limited. The presence of natural and non-occupational exposures to arsenic should be considered in the differential aetiological diagnosis and when facing high concentrations of arsenic in biological samples. To this extent, consider that arsenic contained in traces in coal and released during coal burning is among the main sources of environmental contamination from anthropogenic sources. The natural presence of arsenic in groundwater in some countries and regions, such as coastal Bengal, India and Bangladesh, some regions in China, in the USA, in Andean South America as well as in Central Italy, can represent a source of environmental exposure for the general population. This may be a consequence of the intake of contaminated water as well as of arsenic tendency to be incorporated from water and soil into agricultural biomass, such as grains. Arsenic embedded in combustible biomass and that contained in treated timber can leach into the ground or be released in the atmosphere when such wood is burned.

3.1.15 Cancer caused by arsenic and its compounds ICD Code C34, C44, C67 +T57.0 +Z57

Carcinogenic mechanisms, main health effects and diagnostic criteria

Short profile of the carcinogenic mechanisms	Arsenic compounds are recognized as human carcinogens. Epidemiological investigations have shown that exposure to arsenic causes cancer of the lung both through inhalation and ingestion, skin and urinary bladder through ingestion of contaminated water. Associations between arsenic exposure in drinking water and other cancers, including liver, kidney, and prostate tumours, have been reported. However, several factors prevent firm conclusions: only limited information support an association with kidney cancer, it could be difficult to elucidate causes of liver cancer in groups at high risk for hepatitis B, and there is inconsistency in results from different countries as regard association between arsenic exposure and prostate cancer. The mechanism of arsenic carcinogenesis is not fully understood. Arsenic does not directly damage DNA; rather, it is thought to work through changes in gene expression, DNA methylation, inhibition of DNA repair, generation of oxidative stress, and altered signal transduction pathways. Animal studies indicate that arsenic compounds may act as tumour promoters or co-carcinogens, when combined with ultraviolet light. Arsenic co-carcinogenesis may involve inhibition of proteins involved in nucleotide excision repair. The IARC classifies arsenic and inorganic arsenic compounds as carcinogenic to humans (Group 1). Genetic analyses have demonstrated that populations native to certain regions with naturally high arsenic levels in water and soil show polymorphisms of the AS3MT gene, which provide increased resistance to arsenic related cancer. This may have arisen from evolutionary pressure on local populations over very long periods of time.

Name of the diseases and ICD code: **Lung cancer (C34) +T57.0 +Z57**

Short description of the disease

Evidence shows that occupational exposure to arsenic and its compounds, especially through inhalation, is associated with an increased risk of lung cancer. Epidemiological studies have established a positive association of arsenic exposure through drinking water and lung cancer risk. Genetic factors can modulate susceptibility to arsenic induced lung cancer. Carriers of CYP1A1*2A/GSTM1 homozygous deletion genotype show increased odds ratios for lung cancer, especially among smokers. On the contrary, less efficient genotypes of the AS3MT methylation gene present in specific populations, native and dwelling in areas with naturally high content of arsenic in drinking water, are linked to a lower susceptibility to arsenic induced cancers. In the majority of affected subjects, the first clinical manifestations of the disease are related to local tumour growth (primary lesion), invasion or obstruction of adjacent lung structures, metastatic growth at distant sites, or paraneoplastic syndrome.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms:
  - Anorexia, asthenia, or weight loss.
  - New cough or change in chronic cough, sometimes with haemoptysis.
  - Nonspecific chest pain or pain from bone metastases to the ribs, vertebrae, or pelvis.
  - Local spread may cause obstruction of the bronchi with atelectasis and pneumonia, pleural effusion, superior vena cava syndrome (i.e., a plethora of symptoms following obstruction of blood flow through the superior vena cava, which include facial and arm swelling, nasal congestion, head fullness, headache and lightheadedness, nausea and dysphagia, distorted vision), change in voice (following the involvement of the recurrent laryngeal nerve), and Horner's syndrome (ipsilateral ptosis, miosis, anhidrosis, and enophthalmos following involvement of the inferior cervical ganglion and the paravertebral sympathetic chain).
  - Brain metastases may present with headache, seizures, altered mental status, nausea, and vomiting, while liver metastases might be associated with asthenia and weight loss.
  - Paraneoplastic syndromes include various symptoms related to immune-mediated or secretory effects of tumours, such as: syndrome of inappropriate antidiuretic hormone secretion, hypercalcaemia, digital clubbing, increased adrenocorticotropin production, anaemia, hypercoagulability, peripheral neuropathy, and myasthenic syndromes.

3.1.15 Cancer caused by arsenic and its compounds ICD Code C34, C44, C67 +T57.0 +Z57

- Examinations:
  - Chest X-ray: radiologic manifestations of lung cancer are diverse and include lung nodules and pulmonary, cavitated, or apical mass, with or without associated lymphadenopathy.
  - Chest CT provides information on the details of the neoplastic lesion, its relationship to other anatomical structures, the status of the pleural space, and the size of mediastinal lymph nodes.
  - Sputum cytology is highly specific although not sensitive, with the maximum yield provided when there are lesions in the central airways.
  - Thoracentesis can be used to make a diagnosis when malignant pleural effusions are present.
  - Fine needle aspiration of lymph nodes (supraclavicular or cervical) is frequently diagnostic.
  - Fiberoptic bronchoscopy can help visualisation of the major airways, brush of visible lesions or lung lavage (with cytological specimen evaluation), and assist various biopsy procedures, such as: direct biopsy of endobronchial lesions, a transbronchial biopsy of peripheral nodules or of the lung parenchyma, and fine needle aspiration of mediastinal lymph nodes. Other biopsy techniques include percutaneous biopsy using image guidance, and endobronchial ultrasound (EBUS) guided biopsy

Exposure assessment

- History of occupational exposure: confirmed prolonged or repeated occupational exposure to arsenic dusts, fumes or vapour; measurements of arsenic and its compounds in blood, hair, and fingernails can document exposures that occurred in the past 6-12 months.
- Minimum duration of exposure: one year.
- Maximum latent period: not applicable.

Name of the diseases and ICD code: **Skin cancer (C44) +T57.0 +Z57**

Short description of the disease

Arsenic intake through ingestion of contaminated food and water i.e., mainly as environmental exposure, has been associated with increased risk of basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). The first evidences of arsenic as a carcinogen derived from investigations observing skin cancers after ingestion of medicines containing arsenicals and exposure to arsenic contaminated wine and drinking waters, as well as to arsenical pesticides. While arsenic is ubiquitous in the environment, its ambient concentration in both food and water may be higher near smelting, mining, coal burning units and in other contaminated areas. Aerosolized particulate matter produced from the combustion of arsenic rich coal and animal dung are other sources of environmental exposure.

BCC affects skin areas of head, neck or shoulders. The pearly, rolled, telangiectatic border with central ulceration is diagnostic of BCC. Despite being locally invasive, BCC does not metastasize. Crusting and bleeding in the centre of the tumour frequently develop. It is often mistaken for a sore that does not heal. This form of skin cancer only very seldom causes fatalities. Pigmented BCC characterized by the presence of melanin in the cells, may be wrongly diagnosed as melanoma.

SCC is a malignant neoplasm of the keratinized epidermal cells characterized by a quick growth and metastasizing capacity. The first manifestation is usually a painless, nonhealing, bleeding skin ulceration in the middle of a verrucous papule or plaque, often manifesting on sun damaged skin.

Diagnostic criteria

Clinical manifestations

- *Signs and symptoms of BCC:* it may present as pearly nodules i.e., nodular BCC or flat, brown or flesh-coloured lesions with a pearly border (superficial BCC).
- *Signs and symptoms of SCC:* it may present as firm, red nodules or flat lesions with scaly, crusted surfaces; all forms eventually evolve into ulcers, which are typically red with everted edges; skin around the ulcer is usually inflamed and hardened.
- Examinations:
  - Observation of the lesion, supported by dermoscopy, usually prompts the diagnosis.
  - Biopsy of the skin remains the most accurate way of assessing the histologic subtype of the tumour.

3.1.15 Cancer caused by arsenic and its compounds ICD Code C34, C44, C67 +T57.0 +Z57

Exposure assessment

- History of occupational exposure: confirmed chronic occupational exposure to arsenic dusts, fumes or vapour; measurements of arsenic and its compounds in blood, hair, and fingernails can document exposures that occurred in the past 6-12 months.
- Minimum duration of exposure: one year.
- Maximum latent period: not applicable.

Name of the diseases and ICD code: **Bladder cancer (C67) +T57.0 +Z57**

Short description of the disease

Populations exposed to arsenic through ingestion of contaminated drinking water i.e., mainly from environmental sources, have shown an increased risk of bladder cancer. High levels of arsenic exposure have also been found associated with an increased number of chromosomal gains and losses detected by comparative genomic hybridization (CGH) in bladder tumours.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: the affected subject may report blood or blood clots in the urine, dysuria, feeling the need to urinate many times during day and at night, feeling the need to urinate but being unable to do so, lower back pain on one side of the body. Other symptoms of advanced bladder cancer may include pain in the back or pelvis, unexplained appetite loss, and weight loss.
- Examinations: urinalysis is used to assess the presence of haematuria; urine cytology and cystoscopy help to reveal cancer cells and detect growths in the bladder that need biopsy or surgery. CT, MRI, PET and ultrasound help to stage cancer.

Exposure assessment

- History of occupational exposure: confirmed chronic occupational exposure to arsenic dusts, fumes or vapour; measurements of arsenic and its compounds in blood, hair, and fingernails can document exposures occurred in the past 6-12 months.
- Minimum duration of exposure: one year.
- Maximum latent period: not applicable.

Key actions for prevention	Most applications once involving arsenic have been superseded. In those where the use of the element, of its compounds and of arsenic-containing materials is required, strict insulation of the workers from the potential source of exposure should be enforced, and specific personal protective equipment should be provided. This is usually the case in high technology productions, such as semiconductors (gallium arsenide), where the production conditions themselves are in closed circuit plants. Where this is not the case, such as in energy generation from fossil fuels, tiered protection of workers through measures such as insulation of sources followed by personal protection of workers should be enacted. In addition to inhalation exposure, oral exposure via contaminated clothes, hands, tobacco and so on should be monitored, and biological monitoring of inorganic arsenic in urine may be useful for evaluation of absorbed doses. Workers should be supplied with suitable protective clothing, protective boots and, when there is a risk that the exposure limit for airborne arsenic will be exceeded, respiratory protective equipment. Lockers should be provided with separate compartments for work and personal clothes, and adjacent sanitary facilities of a high standard should be made available. Smoking, eating and drinking at the workplace should not be allowed. Pre-placement medical examinations should be carried out. Persons with pre-existing diabetes, cardiovascular diseases, anaemia, allergic or other skin diseases, neurologic, hepatic or renal lesions should be thoroughly assessed for appropriate job placement in arsenic related work. Periodic medical examinations of all arsenic exposed workers should be performed with special attention to possible arsenic related symptoms.

3.1.15 Cancer caused by arsenic and its compounds	ICD Code C34, C44, C67 +T57.0 +Z57
Key actions for prevention	Determination of the level of inorganic arsenic and its metabolites in urine allows estimation of the total dose of inorganic arsenic taken up by various exposure routes. This methodology is only useful when inorganic arsenic and its metabolites can be measured specifically. Total arsenic in urine may often give erroneous information about industrial exposure since even a single meal of fish or other marine organisms, which usually contain considerable amounts of nontoxic organic arsenic compounds, may cause greatly elevated urinary arsenic concentrations for several days. The group of experts considered that a limit of exposure of workplace atmospheric concentrations of 0.01 mg/m^3 (as 8hr TLV-TWA) for arsenic and its inorganic compounds has been observed to provide a reasonable level of protection for workers' health, and to be used in a number of countries.

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For the chemical entities listed below an entry exists in the collection of International Chemical Safety Cards (ICSC) hosted in the ILO website

Name	Synonyms	ICSC
Arsenic	Grey arsenic	0013
Arsenic trichloride	Arsenic (III) chloride; Arsenous chloride	0221
Arsine	Arsenic trihydride; Hydrogen arsenide; Arsenic hydride	0222
Disodium arsenate heptahydrate	Arsenic acid, disodium salt, heptahydrate; Sodium arsenate heptahydrate; Sodium arsenate, dibasic, heptahydrate	0326
Arsenic pentoxide	Arsenic (V) oxide; Arsenic acid anhydride; Arsenic anhydride; Diarsenic pentoxide	0377
Arsenic trioxide	Arsenic (III) oxide; Arsenous oxide anhydride; White arsenic; Arsenous acid anhydride; Diarsenic pentoxide	0378
Copper (II) orthoarsenate	Arsenic acid, copper salt; Copper arsenate	0648
Calcium arsenate	Tricalcium arsenate; Calcium ortho-arsenate	0765
Lead arsenate	Lead hydrogen arsenate; Arsenic acid, lead salt; Acid lead arsenate; Dibasic lead arsenate	0911
Diammonium hydrogen arsenate	Arsenic acid, diammonium salt; Ammonium arsenate	1207
Sodium arsenate dibasic	Arsenic acid disodium salt; Disodium arsenate; Disodium hydrogen arsenate	1208
Magnesium arsenate	Magnesium o-arsenat; Trimagnesium arsenate	1209
Potassium arsenate	Potassium dihydrogen arsenate; Potassium arsenate, monobasic; Potassium acid arsenate	1210
Copper (II) arsenite	Copper orthoarsenite; Acid copper arsenite; Arsenious acid, copper (II) salt; Cupric arsenite	1211
Lead (II) arsenite	Lead arsenite; Lead metaarsenite; Arsenious acid lead salt	1212
Potassium arsenite	Potassium metaarsenite; Arsenious acid, potassium salt; Potassium arsonate	1213
Iron (III)-o-arsenite, pentahydrate	Ferric arsenite	1241
Chlorodiphenylarsine	Diphenyl arsinous chloride; Diphenyl chloroarsine	
Sodium arsenite	Arsenious acid, sodium salt; Sodium meta-arsenite; Sodium dioxoarsenate	1526
Arsenic acid (80% in water)	Arsenic acid hemihydrate; ortho-Arsenic acid solution	1603

▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
3.1.15	Toxic effect of arsenic and its compounds	T57.0	NE61&XM2KQ2
3.1.15	Lung cancer	C34	2C25.Z
3.1.15	Skin cancer	C44	2C3Z
3.1.15	Bladder cancer	C67	2C94.Z
	Occupational exposure to risk factors	Z57	QD84.Z

3.1.16 Cancer caused by beryllium or its compounds — ICD Code C34 +T56.7 +Z57

General characteristics of the causal agent

Beryllium (Be), CAS number 7440-41-7, is the chemical element with atomic number 4 in the periodic table of the elements, has one stable isotope (^{9}Be), and its mean atomic mass is 9.01 Da. It is classified in Group 2 (2-A; Alkali earths) in the element families and features only the oxidation number II. Beryllium is the lowest density metal in the periodic table of the elements (1.85 g·cm^{-3}). Metallic beryllium is steel grey, mechanically strong (high tensile strength), lightweight, has one of the highest melting points of the light metals (1,287°C) and excellent thermal conductivity and is heat and corrosion resistant. It is primarily used as a hardening agent in alloys.

Beryllium oxide is the starting material to produce beryllium metal and is itself the bulk constituent of a ceramic material with electrical conducing properties. A surface layer of beryllium oxide protects the underlying metal from further oxidation in air and in water, but unprotected metal reacts with acids to yield soluble Be(II) tetra-hydrated and oligomeric oxygen bridged species, which in turn undergo extensive hydrolysis in water to yield acidic solutions. Soluble beryllium salts taste sweet, thence the previous alternative chemical name of the element, glucinium.

Beryllium occurs in the environment only in the form of its compounds. Its commonest ores are beryl (double silicate of aluminium and beryllium) and bertrandite (beryllium hydroxosilicate). Very pure gem quality beryls are known as blue-green aquamarine and green emerald.

Beryllium extraction from beryl and bertrandite ores is known to occur industrially only in the USA, China and Kazakhstan. These processes involve the use of corrosive chemicals and high temperatures, and the final product is beryllium hydroxide, from which the elemental metal is obtained by electrolysis or by thermal reduction with magnesium.

In the chemical industry, beryllium compounds are used in catalysts as Lewis acids, while the metal itself is no longer used in fluorescent lamps.

Beryllium-copper (up to 4% beryllium) is the most common beryllium containing alloy, prepared by fusing beryllium oxide with copper and characterized by high electrical conductivity and fatigue strength, wide temperature tolerance, high elasticity and corrosion resistance. For these reasons, the alloy is used in mechanical pieces subject to abnormal wear or extreme vibration, such as bearings, cams and gears, in corrosion-resistant springs, electrical contacts, switches, relays and connectors in automobiles, computers and radar, satellite, and telecommunications equipment.

As such, copper-beryllium alloys are thus used extensively:

- in high end industries and applications, such as in aerospace, electronics, civil and military nuclear appliances,
- in the telecommunications and computer manufacturing industry,
- in the manufacturing of:
  - high strength non-sparking tools,
  - casts for moulding metal, glass, and plastic items,
  - some alloys for dental use,
  - consumer goods such as sports equipment (golf clubs and bicycle frames),
  - ceramics installed in microwave ovens.

Beryllium-aluminium (<1-60% beryllium) is used in high technology applications, such as aircraft, scientific devices on spacecraft, defence avionics packaging, high resolution medical and industrial X-ray equipment.

Beryllium-nickel (0.275-7% beryllium) has high tensile strength and has age hardening characteristics. Among its uses are diamond drill bit matrices, watch balance wheels and aeroplane brakes.

3.1.16 Cancer caused by beryllium or its compounds	ICD Code C34 +T56.7 +Z57
Occupational exposures	Occupational exposure to beryllium dusts and fumes occurs in all phases of metal extraction and refining, in the preparation and machining of its alloys into usable goods processing by melting, grinding, welding, drilling, and in the decommissioning and recycling of items and waste materials. Recycling of end life manufactured goods for valuable constituents can be a source of strong exposure, especially in the informal sector, where precautions may not be taken. The now wide industrial use of beryllium has generated chances for exposure at higher than regarded as safe levels, which are estimated to involve 1% to 15% of exposed workers. Since beryllium is mostly used as an alloy metal with copper, aluminium and nickel, the importance of co-exposure to the other metals has to be kept in mind (for each of them, see the corresponding item).
Carcinogenic mechanisms, main health effects and diagnostic criteria	
Short profile of the carcinogenic mechanisms	The International Agency for Research on Cancer (IARC) recognizes beryllium and beryllium compounds as Group 1 carcinogens, because of their potential to cause cancer of the lung. Beryllium induces immunologic reactions in exposed and sensitized individuals by triggering an adaptive immune response to beryllium antigen in T lymphocytes. White blood cells accumulate around beryllium containing solid particles (beryllium oxide and alloys, the most important being beryllium-copper alloy) without being able to phagocytise them and clear them from the tissue. Lung mononuclear cell inflammation and granuloma formation are maintained by the accumulation in the lung of CD4 memory T cells specific for beryllium. The inflammatory processes associated with acute or chronic beryllium disease, such as increased rate of cell turnover, enhanced oxidative stress, and altered signalling pathways involved in cell replication, could plausibly contribute to the development of lung cancer. Like other carcinogenic metals, beryllium can produce oxidative stress, which can in turn lead to DNA damage, activation of proto-oncogenes, and apoptotic mechanisms. As such, beryllium induced carcinogenesis most likely involves several, possibly interrelated molecular mechanisms.

Name of the diseases and ICD code: **Lung cancer (C34) +T56.7 +Z57**

Short description of the disease

Beryllium exposed workers and workers suffering beryllium disease have an increased risk of lung cancer. Evidence of increased lung cancer mortality was primarily documented among workers of several beryllium processing plants.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms:
  - Anorexia, asthenia, or weight loss.
  - New cough or change in chronic cough, sometimes with haemoptysis.
  - Nonspecific chest pain or pain from bone metastases to the ribs, vertebrae, or pelvis.
  - Local spread may cause obstruction of the bronchi with atelectasis and pneumonia, pleural effusion, superior vena cava syndrome (i.e., a plethora of symptoms following obstruction of blood flow through the superior vena cava, which include facial and arm swelling, nasal congestion, head fullness, headache and lightheadedness, nausea and dysphagia, distorted vision), change in voice (following involvement of the recurrent laryngeal nerve), and Horner's syndrome (ipsilateral ptosis, miosis, anhidrosis, and enophthalmos following involvement of the inferior cervical ganglion and the paravertebral sympathetic chain).
  - Brain metastases may present with headache, seizures, altered mental status, nausea, and vomiting, while liver metastases might be associated with asthenia and weight loss.
  - Paraneoplastic syndromes include various symptoms related to immune mediated or secretory effects of tumours, such as: syndrome of inappropriate antidiuretic hormone secretion, hypercalcaemia, digital clubbing, increased adrenocorticotropin production, anaemia, hypercoagulability, peripheral neuropathy, and myasthenic syndromes.

3.1.16 Cancer caused by beryllium or its compounds ICD Code C34 +T56.7 +Z57

- Examinations:
  - Chest X-ray: radiologic manifestations of lung cancer are diverse and include lung nodules, and pulmonary, cavitated, or apical mass, with or without associated lymphadenopathy.
  - Chest CT provides information on the details of the neoplastic lesion, its relationship to other anatomical structures, the status of the pleural space, and the size of mediastinal lymph nodes.
  - Sputum cytology is highly specific, although not sensitive, with the maximum yield provided when there are lesions in the central airways.
  - Thoracentesis can be used to make a diagnosis when malignant pleural effusions are present.
  - Fine needle aspiration of lymph nodes (supraclavicular or cervical) is frequently diagnostic.
  - Fiberoptic bronchoscopy can help visualisation of the major airways, brush of visible lesions or lung lavage (with cytological specimen evaluation), and assist various biopsy procedures, such as: direct biopsy of endobronchial lesions, a transbronchial biopsy of peripheral nodules or of the lung parenchyma, and fine needle aspiration of mediastinal lymph nodes. Other biopsy techniques include percutaneous biopsy using image guidance, and endobronchial ultrasound (EBUS) guided biopsy.

Exposure assessment

- History of occupational exposure: confirmed occupational exposure to beryllium together with workplace monitoring data, if available.
- Minimum duration of exposure: one year.
- Maximum latent period: not applicable.

Key actions for prevention

The technological uses of beryllium are unlikely to be eliminated in the future and may expand in the production of high technology end products.

Due to the characteristics of persistence of beryllium in the body, the most effective prevention of beryllium-related disease is avoidance of exposure, by employing stringent precautions. In high technology industry, beryllium products are protected from contamination through the workers' use of full cover suits, facemasks and gloves, and worker protection is of a collateral benefit. In beryllium extraction, metallurgy, lower level manufacturing and recycling, higher exposures can occur and particular attention should be paid to risk assessment and mitigation.

"Take-home" contamination of work clothing can lead to exposure of family members and the wider community. To assess exposure to airborne beryllium dusts, measurement by air sampling of the personal breathing zone is preferred to area sampling. Various occupational exposure limits are suggested or enforced in some countries.

The group of experts considered that the following limits of exposure of workplace atmospheric concentrations have been observed to provide a reasonable level of protection for workers' health and to be used in a number of countries: 0.05 µg/m^3 as an 8hr TWA.

Further reading

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For the chemical entities listed below an entry exists in the collection of International Chemical Safety Cards (ICSC) hosted in the ILO website

Name	Synonyms	ICSC
Beryllium	Glucinium	0226
Beryllium oxide	Beryllia; Beryllium monoxide	1325
Beryllium sulfate		1351
Beryllium nitrate	Beryllium sulphate	1352
Beryllium carbonate	Beryllium basic carbonate; Beryllium carbonate hydroxide (3:2:2)	1353
Beryllium chloride		1354
Beryllium fluoride	Beryllium difluoride	1355

▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
3.1.16	Toxic effect of beryllium and its compounds	T56.7	NE61&XM4QG7
3.1.16	Lung cancer	C34	2C25.Z
	Occupational exposure to risk factors	Z57	QD84.Y

3.1.17 Occupational cancer caused by cadmium and its compounds ICD Code C34 +T56.3 +Z57	
General characteristics of the causal agent	Cadmium (Cd), CAS number 7440-43-9, is the chemical element with atomic number 48 in the periodic table of the elements. It has several stable isotopes between ^{106}Cd and ^{116}Cd, with ^{114}Cd and ^{112}Cd being the most abundant (24% and 29%, respectively). Its mean atomic mass is 112.4 Da. Cadmium belongs to Group 12 (2-B; Transition metals) in the element families and features only the oxidation number II. Cadmium is a silver-white, malleable metal, which has a low melting point (327°C) and is highly resistant to corrosion, although its standard reduction potential is at -0.40 V due to the protection afforded by the superficial oxide layer. Cadmium metal dissolves in mineral acids with the production of flammable hydrogen gas, and its dust reacts exothermically with oxidants, hydrogen azide, sulphur, selenium and tellurium. These reactions represent a fire and explosion hazard. Cadmium has many chemical and physical similarities to zinc and occurs together with zinc in several minerals. It is a byproduct of smelting zinc and some lead ores. The main cadmium compounds are cadmium acetate, cadmium sulphide, cadmium sulphoselenide, cadmium stearate, cadmium oxide, cadmium carbonate, cadmium sulphate, and cadmium chloride. Exposure of the general population has occurred through ingestion of contaminated rice and other food and possibly through drinking water. Cigarettes contain relatively high levels of cadmium, which derives naturally from the metal accumulated by the leaves and stems of tobacco grown in soil containing cadmium. This source contributes significantly to the non-occupational exposure of smokers.
Occupational exposures	About 80% of cadmium industrial usage is represented by the manufacturing of nickel-cadmium batteries. Other uses include electroplating mainly of iron and steel, paint pigmentation, and stearate heat stabilization in polyvinyl chloride (PVC) plastics. Cadmium can be found as an impurity in other metals (zinc, lead and copper), in fossil fuels (coal, oil, gas, peat and wood), in cement, and in phosphate fertilizers. This latter source may be as high as 300g per ton of extracted phosphate, and the use of such material for the production of fertilizers results in contamination of agricultural soils. Among the inorganic salts of cadmium, the most industrially important is cadmium stearate, followed by cadmium sulphide and cadmium sulphoselenide, which are used as yellow and red pigments in plastics and other materials. Cadmium sulphide is also used in photo- and solar cells. Cadmium chloride is the main chemical form of cadmium used in electroplating, and has a minor use as a fungicide, colorant for pyrotechnics, additive to tinning solution, and mordant in dyeing and printing textiles. Minor uses include the production of special photographic films and the manufacture of special mirrors and coatings for electronic vacuum tubes. Cadmium oxide is used in electroplating, in the preparation of PVC heat stabilizers, and as a component of silver alloys, phosphors, semiconductors, and glass ceramic glazes. Cadmium fumes are generated in potentially toxic concentrations in the production of cadmium alloys, in welding, and oxyacetylene cutting of cadmium coated steel and rivets, and in the smelting, melting, and refining of metals that contain cadmium. In summary workers may be exposed to cadmium, in occupational settings, through the inhalation of oxide fumes generated during heating or welding of cadmium containing materials or inhalation of particles of metal, oxide and pigment dust. Industries involving smelting and refining of metals, metal machining, batteries manufacturing, electroplating, plastics, ceramics, paint, and welding operations entail the highest occupational exposure to cadmium.
Carcinogenic mechanisms, main health effects and diagnostic criteria	
Short profile of the carcinogenic mechanisms	The carcinogenic potential of cadmium compounds, especially insoluble pigments (cadmium yellow) and cadmium based semiconductors (doped cadmium sulphide nanoparticles), probably depends on the degree to which the individual preparations release ionic cadmium in particular environments, e.g. when ingested and subject to the acidic environment of the stomach.

3.1.17 Occupational cancer caused by cadmium and its compounds ICD Code C34 +T56.3 +Z57

Short profile of the carcinogenic mechanisms

Toxicological studies on cultured mammalian cell lines indicate that cadmium causes several tiers of disruption to cellular biochemical mechanisms, some of which can be related to the initiation and progression of carcinogenesis. The detailed mechanisms involved are unclear. Lymphocytes of workers exposed to cadmium may show increased chromosomal aberrations.

Cadmium binds cellular glutathione and other biological thiols, such as serum albumin and red blood cell haemoglobin. It induces cell oxidative stress, alters signalling pathways, cell proliferation and cell transformation. It causes gene mutations, DNA strand breaks, and chromosomal damage; and disrupts DNA repair.

The sensitivity of individual cell lines to cadmium induced disturbance is probably related to their ability to produce metallothioneins (MT). These are a family of protective proteins that bind metals with affinity for sulphur, such as cadmium, mercury and lead, in turn releasing the physiologically bound zinc. Released zinc binds zinc-finger motifs in regulating protein effectors, which activate the MT gene. This enhances the production of metallothioneins and other genes that in turn induce the production of several other gene products. These include antioxidant and gene repair enzymes, which mitigate the biochemical and structural damage caused by cadmium, and hence its genotoxic effects.

The International Agency for Research on Cancer (IARC) classifies cadmium and cadmium compounds as Group 1 carcinogens, mainly because of their potential to cause cancer of the lung. In addition, positive associations have been observed between exposure to cadmium and cadmium compounds and cancer of the kidney and of the prostate.

Name of the diseases and ICD code: **Lung cancer (C34) +T56.3 +Z57**

Short description of the disease

Workers exposed to cadmium – such as in copper-cadmium alloy plants and cadmium processing plants have shown increased lung cancer risk.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms:
  - Anorexia, asthenia, or weight loss.
  - New cough or change in chronic cough, sometimes with haemoptysis.
  - Nonspecific chest pain or pain from bone metastases to the ribs, vertebrae, or pelvis.
  - Local spread may cause obstruction of the bronchi with atelectasis and pneumonia, pleural effusion, superior vena cava syndrome (i.e., a plethora of symptoms following obstruction of blood flow through the superior vena cava, which include facial and arm swelling, nasal congestion, head fullness, headache and lightheadedness, nausea and dysphagia, distorted vision), change in voice (following the involvement of the recurrent laryngeal nerve), and Horner's syndrome (ipsilateral ptosis, miosis, anhidrosis, and enophthalmos following involvement of the inferior cervical ganglion and the paravertebral sympathetic chain).
  - Brain metastases may present with headache, seizures, altered mental status, nausea, and vomiting, while liver metastases might be associated with asthenia and weight loss.
  - Paraneoplastic syndromes include various symptoms related to immune mediated or secretory effects of tumours, such as: syndrome of inappropriate antidiuretic hormone secretion, hypercalcaemia, digital clubbing, increased adrenocorticotropin production, anaemia, hypercoagulability, peripheral neuropathy, and myasthenic syndromes.
- Examinations:
  - Chest X-ray: radiologic manifestations of lung cancer are diverse and include lung nodules and pulmonary, cavitated, or apical mass, with or without associated lymphadenopathy.
  - Chest CT provides information on the details of the neoplastic lesion, its relationship to other anatomical structures, the status of the pleural space, and the size of mediastinal lymph nodes.
  - Sputum cytology is highly specific, although not sensitive, with the maximum yield provided when there are lesions in the central airways.
  - Thoracentesis can be used to make a diagnosis when malignant pleural effusions are present.
  - Fine needle aspiration of lymph nodes (supraclavicular or cervical) is frequently diagnostic.
  - Fiberoptic bronchoscopy can help visualisation of the major airways, brush of visible lesions or lung lavage with cytological specimen evaluation, and assist various biopsy procedures, such as: direct biopsy of endobronchial lesions, a transbronchial biopsy of peripheral nodules or of the lung parenchyma, and fine needle aspiration of mediastinal lymph nodes. Other biopsy techniques include percutaneous biopsy using image guidance, and endobronchial ultrasound (EBUS) guided biopsy.

3.1.17 Occupational cancer caused by cadmium and its compounds ICD Code C34 +T56.3 +Z57

Exposure assessment

- History of occupational exposure: evidence of prolonged exposure to cadmium and its compounds, in particular in working conditions bringing about a risk of exposure to cadmium fumes, such as foundry and battery production, supported by environmental and biological monitoring data, when available.
- Minimum duration of exposure: some years.
- Maximum latent period: not applicable.

Key actions for prevention

Due to its recognized carcinogenic activity, cadmium is progressively being eliminated from the industrial and manufacturing uses for which substitutes have been found; especially for electrical batteries, PVC plasticizers and red/yellow pigments in consumer goods.

Cadmium electro-finishing of iron and steel parts in car manufacturing, e.g. bumpers and other aesthetic finishes, is being replaced or eliminated by changes in car design. However, its use continues for specialised applications such as hydraulic actuators. The electroplating industry can process items in enclosed tanks from which little or no worker exposure is expected, and compliance with stringent environmental regulations has resulted in lower cadmium concentrations in the wastewater. In activities where exposure to cadmium can occur, the use of personal protective equipment may be necessary (e.g. respiratory protective equipment to prevent inhalation, as well as gloves and coveralls to prevent splashes and skin contact with corrosive electroplating solutions).

Worker exposure in the manufacture of nickel cadmium batteries is decreasing, with improvements in occupational hygiene, and as these batteries are superseded by more environmentally friendly forms of electric power storage. However, workers involved in waste recovery from electric and electronic appliances, as well as in cadmium smelting and recovery from iron and steel scrap, should adopt adequate prevention measures to avoid or minimize exposure. This is of particular importance for commercial activities in the informal sector.

Several international or national agencies and institutional databases report limits of exposure of cadmium concentrations that have been observed to provide a reasonable level of protection for workers' health. We report some of them as examples:

- ILO International Chemical Safety Cards (ICSC) database:
  - Cadmium: 0.01 mg/m^3 as 8hr TLV-TWA.
  - Cadmium chloride: 0.002 mg/m^3 as 8hr TLV-TWA.
  - Cadmium oxide: 0.002 mg/m^3 as 8hr TLV-TWA.
- ACGIH:
  - An 8hr TLV-TWA of 0.01 mg/m^3 for "total" particulate, and of 0.002 mg/m^3 for the respirable particulate fraction are recommended for occupational exposure to cadmium and its compounds. The 0.01 mg/m^3 "total" particulate TLV is intended to minimize the potential for development of early kidney dysfunction. The respirable particulate TLV is intended to minimize the potential for lower respirable tract accumulation of a cadmium burden that could induce lung cancer. The TLVs should significantly reduce the potential for metal fume fever in cadmium exposed workers.
- SCOEL:
  - The Scientific Committee on Occupational Exposure Limits of the European Commission proposed an occupational exposure limit (8hr TWA) of 1 µg/m^3 (i.e., 0.001 mg/m^3) for the inhalable fraction of cadmium.

3.1.17 Occupational cancer caused by cadmium and its compounds ICD Code C34 +T56.3 +Z57

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For the chemical entities listed below an entry exists in the collection of International Chemical Safety Cards (ICSC) hosted in the ILO website

Name	Synonyms	ICSC
Cadmium		0020
Cadmium chloride	Cadmium dichloride	0116
Cadmium oxide	Cadmium monoxide	0117
Cadmium sulfide	Cadmium monosulphide; Cadmium sulphide; Cadmium monosulfide	0404
Cadmium acetate	Acetic acid, cadmium salt; Bis(acetoxy) cadmium	1075
Cadmium sulfate	Cadmium sulphate	1318

▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
3.1.17	Toxic effect of cadmium and its compounds	T56.3	NE61&XM0V73
3.1.17	Lung cancer	C34	2C25.Z
	Occupational exposure to risk factors	Z57	QD84.Y

3.1.18 Occupational cancer caused by erionite	ICD Code C45 + Z57.2, T57.8
General characteristics of the causal agent	Erionite is a crystalline fibrous mineral that belongs to a group of alumino-silicates called zeolites. Zeolites are found in the cavities of volcanic rocks and structurally feature a hexagonal, cage like structure composed of a framework of linked tetrahedral units of silicate and aluminate. Due to the presence of an inorganic backbone and of large cavities, zeolites have good thermal stability and a large adsorption capacity towards water vapour and small organic molecules, with good reversible kinetics. For this reason, zeolites have gas absorption, ion exchange, and catalytic properties that are highly selective and depend on the molecular size of the absorbed compounds. Based on the most dominant metal ion present, the forms of erionite can be differentiated into erionite-Na, erionite-K, and erionite-Ca. Erionite forms brittle, wool-like fibrous masses in the hollows of rock formations that consist of white prismatic crystals in radiating groups of crystal fibres. Erionite is able to absorb up to 20% of its weight in water and has an internal molecular structure similar to chabazite. In the USA, deposits of fibrous erionite are located in Arizona, Nevada, Oregon, and Utah, in the Tertiary Arikaree Formation in southeast Montana and northwest South Dakota. These zeolite beds may be up to 15 feet (≈ 4.5 meters) thick and may lie in surface outcroppings. Other large deposits of erionite are found in Turkey, where this material is held responsible for the high local incidence of mesothelioma in some villages of Cappadocia (see below).
Occupational exposures	Although erionite is a comparatively rare zeolite, it has found some use in the past as a natural sorption material in liquid filtration, in sweetening of 'hard' water by ion exchange, and in crude oil refining during extraction. Due to its paucity, the use of this material has been largely abandoned. In the past, exposure occurred during the mining, processing, and formulation of derived materials. Nowadays, occupational exposure to erionite may occur during mining and processing of other commercial zeolites where it is contained as a minor component. During agricultural work in areas where soils and water naturally contain erionite, human environmental exposure may occur from drinking water. In several rural villages in Turkey, erionite is utilized in domestic construction as a component of stucco plaster. Therefore, there is a potential for occupational exposure in mason workers and of non-occupational indoor exposure when dry plaster slowly degrades.
Carcinogenic mechanisms, main health effects and diagnostic criteria	
Short profile of the carcinogenic mechanisms	An epidemic of mesothelioma, both pleural and peritoneal, of non-occupational origin occurred in two small villages in Turkey (Karain and Tuzkoy), which are located close to the city of Nevsehir in Cappadocia, a region of central Anatolia. The entire area contains narrow valleys cut into the thick layer of volcanic tuff with flat uplands in between. A more than 20 year prospective study found that, in the two villages, mesothelioma caused almost 50% of all deaths. Mesothelioma cases have been reported in other villages of the area, with an incidence varying from zero to over 50%. Many of the fatal cases occurred in middle aged subjects, although the youngest reported cases were seen among adolescents. The causal agent was identified as erionite present in the volcanic tuff that is quarried and used for building. Since the population of the villages has a very well identified kinship pattern and a large degree of intra-familiar breeding, there might be a genetically determined susceptibility to mesothelioma. A frankly increased incidence of mesothelioma was observed in a cohort of migrants from one of the exposed villages. The available evidence suggests that the potency of erionite to induce mesothelioma is much higher than for any type of asbestos. Erionite has been classified as a Group 1 human carcinogen by the IARC.
Name of the diseases and ICD code: **Malignant mesothelioma (C45) + Z57.2, T57.8**	
Short description of the disease Pleural and peritoneal mesotheliomas are rare malignancies occurring in the mesothelial cells that line these cavities (i.e., serous membranes). The most common site of mesothelioma is the pleura. However, mesothelioma of the peritoneum has also been observed in subjects exposed to erionite. The prognosis of malignant mesothelioma is generally very poor, and the survival from the diagnosis is usually less than 1.5 years, estimated median survival time varies from 4 to 12 months.	

3.1.18 Occupational cancer caused by erionite — ICD Code C45 + Z57.2, T57.8

Diagnostic criteria

Clinical manifestations of pleural mesothelioma

- Signs and symptoms:
  - Disease onset is often insidious, with chest pain and dyspnoea being very common presenting symptoms. Other accompanying symptoms may include fever, sweats, weight loss, and fatigue.
  - Findings of pleural effusion are usually noted upon percussion and auscultation on physical examination.
- Examinations:
  - Chest X-ray may show a unilateral pleural effusion, in some cases associated with a pleural based mass or masses. After clinical assessment and chest X-ray or CT imaging, thoracentesis with an aspiration of pleural effusion fluid is generally conducted.
  - Surgical tissue biopsy e.g. video-assisted thoracoscopic surgery-VATS, could represent the primary investigation for diagnosis, but in those with poor physical condition, minimally invasive procedures (e.g. thoracentesis and fine needle aspiration) can be conducted.
  - Cytological features and histology are needed to confirm a diagnosis of mesothelioma. The confirmation can be reached only through immunocytochemistry, which is currently the standard ancillary procedure for distinguishing this malignancy from other types of cancer. This technique relies on the detection of various mesothelial and carcinoma related antigens in cytology cell block sections or in biopsy tissue; a panel of markers expected to be positive [e.g. calretinin, cytokeratins 5/6 (CK 5/6), Wilms tumour-1 (WT-1) and podoplanin/D2-40] and negative (e.g. TTF1, CEA, Ber-EP4) should be performed to guide the differential diagnosis. Histological subtype (epithelioid, sarcomatoid or biphasic) should be described as well due to its prognostic value, along with age, sex, tumour stage, and Karnofsky score (a method to assess the functional status of a patient).
  - None of the available blood markers to be looked for seems sufficiently reliable to be used currently in the early diagnosis of mesothelioma.

Clinical manifestations of peritoneal mesothelioma

- Signs and symptoms: affected subjects most frequently report abdominal pain and distension. Other symptoms include abdominal mass, anorexia, weight loss, and abdominal wall hernia.
- Examinations:
  - Areas of bowel structures with fixity and loss of peristaltic activity are shown through radiographic studies with barium administration, whilst CT shows tumour mass and related ascites.
  - Laparoscopy can be used to assess the volume and distribution of the disease.
  - Diagnosis is confirmed through histopathological analysis of tissue biopsies obtained either percutaneously or surgically.
  - Mesothelioma typically stains positive for D2-40, CK 5/6, calretinin, and WT-1 and negative for BerEP4 antibody and thyroid transcription factor 1 (TTF1).

Exposure assessment

- History of occupational exposure: evidence of occupational exposure to erionite through inhalation.
- Minimum duration of exposure: unknown.
- Maximum latent period: not applicable.

Key actions for prevention	Since the large scale use of erionite is almost or totally discontinued, prevention is mostly aimed at avoiding occupational exposure in activities that involve the repair and removal of items and materials that may contain erionite. When the presence of this material is suspected, it is necessary to activate the same precautions suggested for work that involve other carcinogenic mineral fibres (e.g. asbestos), such as training workers about the risk and awareness regarding the presence at the workplace of erionite containing materials; adopting wet methods to reduce dust generation; establishing decontamination protocols also with appropriate cleaning/disposal of personal protective equipment; ensuring work clothing is not washed at home and limiting bystander exposure by preventing visitors and co-workers from standing in work areas where airborne erionite presence may be anticipated.

3.1.18 Occupational cancer caused by erionite ICD Code C45 + Z57.2, T57.8

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▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
3.1.18	Malignant mesothelioma	C45	XH0XV0
	Occupational exposure to dust	Z57.2	QD84.0
	Other specified inorganic substances	T57.8	XM3M65

3.1.19 Cancer caused by ethylene oxide	ICD Code C82-85, C90, C91.1, C50 + Z57.5
General characteristics of the causal agent	Ethylene oxide (CAS number 75-21-8) is the simplest oxirane (three-membered ring, oxygen-containing heterocyclic organic compound). At ambient conditions, it is a colourless, heavier than air gas with an ethereal odour that can be detected above an airborne concentration of approximately 260 ppm or 468 mg/m^3. Vapours of ethylene oxide (EtO) are flammable and potentially explosive at concentrations as low as 3% and decompose or polymerize in the absence of air on heating above 560°C. The gas can condense to a liquid below 10°C and is miscible with water. EtO is a very reactive chemical that can polymerize under a variety of conditions, especially under acid or basic catalysis and in the presence of metal surfaces or metal salts.
Occupational exposures	EtO is a bulk chemical product manufactured at more than 26 million metric tons per year as of 2018 and is expected to expand to 36 million metric tons in 2023. It is employed in the chemical synthesis of several bulk and speciality chemical products. The main bulk industrial uses of EtO are in the textile sector (35%), detergents (25%), oilfield chemicals and personal care products (each 10%), pharmaceuticals (8%), and agrochemicals (7%). EtO is mostly synthesized by direct oxidation of ethylene of petrochemical origin on a silver catalyst. Since most produced EtO is directly converted into other chemical products, producing units are mostly integrated into large chemical plants, although liquefied EtO can be transported in refrigerated tanks. Of the EtO that is converted into other chemical products, approximately 65% is directly hydrated to prepare ethylene glycol (see item 1.1.15), 13% is converted into ethoxylated alcohols and phenols (detergents), while lower proportions are converted into diethylene and triethylene glycols (7%), ethanolamines (6%), glycol-ethers, polyols, and polymers (e.g. polyethylene glycols). In large chemical plants, exposure is usually limited to workers that perform maintenance or repair work or are dedicated to cleaning reactors. Among non-manufacturing uses of EtO are that as a sterilizing gas, especially for surgical equipment and textiles, and as a fumigant preservative for food products, such as packaged cereals, bagged rice, and spices. In these uses, and especially in the sterilization of surgical equipment, there is a higher chance of exposure than in chemical plants where fire and explosion risks are much higher, given the very large amounts used, and precautions are thus more likely to be very strict.
Carcinogenic mechanisms, main health effects and diagnostic criteria	
Short profile of the carcinogenic mechanisms	Ethylene oxide is quickly absorbed by inhalation and reacts with proteins and with DNA in all tissues and cells. The reaction can impair key cell functions and lead to cell death and to cancer. It is known to act as an alkylating agent in biological systems, binding to the genetic material and other electron donating sites, such as haemoglobin, and causing mutations and other functional damage. EtO has also been linked to chromosomal damage. The IARC has classified EtO as a Group 1 human carcinogen capable of causing cancer in humans. The biotransformation of EtO mainly occurs through reaction with glutathione, and hydroxyethyl mercapturic acid is the main product excreted in the urine, although its specificity as a biomarker of exposure to EtO is sometimes poor, especially at contemporary low levels in the chemical industry. EtO reacts with blood proteins, and the products formed with human serum albumin and with haemoglobin ("*adducts*") are promising biomarkers of month long exposure, although the cost and difficulty of determinations still preclude their utility.

Name of the diseases and ICD code: **Chronic lymphocytic leukaemia (CLL) (C91.1), Non-Hodgkin lymphoma (NHL) (C82-C85), Multiple myeloma (MM) (C90), Breast cancer (C50) + Z57.5**

Short description of the disease

Studies on workers chronically exposed to ethylene oxide have shown an increased risk of lymphoid tumours (i.e., non-Hodgkin's lymphoma, chronic lymphocytic leukaemia, and multiple myeloma), especially after allowance for a latency of more than 20 years. Increased relative risks for breast cancer were found when considering the highest levels of cumulative exposure to EtO (15 years lag), with a significant exposure response relationship.

3.1.19 Cancer caused by ethylene oxide ICD Code C82-85, C90, C91.1, C50 + Z57.5

Diagnostic criteria

Clinical manifestations of non-Hodgkin lymphoma

- Signs and symptoms: may vary depending on the location of the neoplastic process, the rate of tumour growth, and the function of the organ being compromised/displaced by the tumour. In the case of low grade lymphomas, peripheral adenopathy is usually slowly progressive and painless; fatigue may be common in advanced stage diseases. In intermediate and high grade lymphomas, adenopathy occurs in most affected subjects, together with fever, sweating and chills, and weight loss.
- Examinations: peripheral adenopathy, accompanied by splenomegaly and hepatomegaly. Full blood count may be normal at early stages and show anaemia later on, together with lymphocytosis, thrombocytosis, and either thrombocytopaenia, leukopaenia or pancytopaenia. Liver function tests may show alterations. Chest X-ray may show lymph node enlargement, eventually confirmed by ultrasound evaluation, CT, MRI or PET, also focused on other sites suspected to be affected by the disease. The diagnosis relies on pathologic confirmation following adequate tissue biopsy.

Clinical manifestations of chronic lymphocytic leukaemia

- Signs and symptoms: a relevant proportion of affected subjects (25-50%) may be asymptomatic at the time of presentation; symptoms may vary and include enlarged lymph nodes, liver or spleen, weakness, tiredness, weight loss, fever, night sweats, recurrent infections, loss of appetite or early satiety.
- Examinations: full blood count shows lymphocytosis, accompanied by reduction of red blood cells and platelets, with the presence of smudge cells. Flow cytometry confirms the diagnosis, showing the presence of leukaemia cells. Bone marrow biopsy may be necessary in selected cases to establish the diagnosis.

Clinical manifestations of multiple myeloma

- Signs and symptoms: specific symptoms may be absent at early stages; bone pain or even fractures may occur later on, together with fatigue and increased vulnerability to infections. In some cases, hypercalcaemia can be found, which may manifest with confusion, somnolence, constipation, nausea, and thirst.
- Examinations: electrophoresis of plasma proteins shows the typical monoclonal peak; bone X-rays may show enlargement due to compression and fractures; full blood count may show anaemia and reduced number of red blood cells; renal failure may occur as a complication in about 25% of cases.

Clinical manifestations of breast cancer

Breast cancer is often detected as an abnormality at a mammogram. In other cases, the affected subject notices a lump, which may be associated with changes in breast size or shape, skin dimpling, inversion or other alterations of the nipple, such as ulceration, retraction, and discharge (even bloodstained). The recommended approach for a definite diagnosis is core biopsy with image guidance.

Exposure assessment

- History of occupational exposure: evidence of prolonged/repeated exposure to ethylene oxide.
- Minimum duration of exposure: six months.
- Maximum latent period: not applicable.

Key actions for prevention	The use of ethylene oxide as an industrial starting material is likely to continue and possibly to increase in the future. It is not likely that other less hazardous reagents can substitute the use of EtO in chemical syntheses. Due to the inherent hazard of the production and further chemical reaction of this very reactive product, catastrophic accidents can occur in large plants and therefore, stringent safety measures to avoid runaway reactions, fires and explosions are actually enforced. In particular, tanks, gas lines and reactors are purged with inert gas, such as nitrogen, before opening to the air and allowing access to maintenance and repair workers. The displaced EtO cannot be released into the atmosphere but is destroyed on-site by combustion or scrubbed by a chemical reaction with a strong alkali. Workers that need to intervene on EtO plants must be equipped with suitable protection that includes suits for hazardous materials and items, and respirators and exposure should be monitored with passive devices that are commercially available.

3.1.19 Cancer caused by ethylene oxide	ICD Code C82-85, C90, C91.1, C50 + Z57.5
Key actions for prevention	Proper emergency procedures and protective equipment should be available to deal with spills or leaks of ethylene oxide. Ethylene oxide should not be allowed to enter a confined space such as a sewer. Workers should not enter confined spaces where ethylene oxide has been stored without following proper operating procedures designed to ensure that toxic or explosive concentrations are not present. Whenever possible, ethylene oxide should be stored and used in closed systems or with adequate local exhaust ventilation. As for all substances having carcinogenic properties, ethylene oxide must be handled with extreme care to avoid contact with the workers' skin or being inhaled during both production and use. Prevention of contact is promoted by designing the work premises and process plant so as to preclude any leakage of the product, application of slight negative pressure, hermetically sealed process, etc. The group of experts considered that a limit of exposure of 2 ppm for EtO as an 8hr TLV-TWA of workplace atmospheric concentration has been observed to provide a reasonable level of protection for workers' health and used in a number of countries.

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For the chemical entities listed below an entry exists in the collection of International Chemical Safety Cards (ICSC) hosted in the ILO website

Name	Synonyms	ICSC
Ethylene oxide	1,2-Epoxyethane; Oxirane; Dimethylene oxide	0155

▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
3.1.19	Non-Hodgkin lymphoma (NHL)	C82-C85	XH3FE9, XH3400, XH2216
3.1.19	Chronic lymphocytic leukaemia (CLL)	C91.1	2A82.0
3.1.19	Multiple myeloma (MM)	C90	2A83.1
3.1.19	Breast cancer	C50	2C6Z
	Occupational exposure to toxic agents in other industries-solids, liquids, gases or vapours	Z57.5	QD84.2

3.1.20 Cancer caused by hepatitis B virus (HBV) and hepatitis C virus (HCV) ICD Code (C22.0, C85.9) + Z57, Y40-Y84	
General characteristics of the causal agent	Hepatitis B virus (HBV) and hepatitis C virus (HCV) are hepatotropic members of the hepadnavirus and flavivirus family, respectively. HBV infection is transmitted through contact with infected human blood and body fluids and can give rise to acute and chronic outcomes. In both instances, high levels of infectious HBV particles (i.e., virions) circulate in the bloodstream. Virions are thought to pass through fenestrations of the liver sinusoidal endothelial cells and reach the surface of hepatocytes. The combination of the viral replication level and the host's immune response determines the degree of liver inflammation. The incubation period ranges from 4 to 24 weeks. Approximately 95% of those acutely infected develop antibodies against hepatitis B surface antigen (HBsAg), clear HBsAg and HBV virions, and fully recover. The remaining persons develop chronic infection. Persistent HBV infection is associated with different degrees of chronic liver disease, but it often evolves into cirrhosis and, eventually, hepatocellular carcinoma (HCC). HCV transmission route is analogous to HBV; infection with HCV has an incubation period of 2 to 26 weeks. Approximately 15-45% of subjects acutely infected with HCV lose virologic markers for HCV. Thus, about 55-85% remain viraemic and may develop chronic liver disease and HCC. There is a high prevalence of B cell non-Hodgkin's lymphoma (NHL) in subjects chronically infected with HCV, and studies showing lymphoma regression after successful antiviral therapy and clearance of HCV support a causative role for HCV in this malignant proliferative disorder. The association between HBV and lymphomas is weaker. Positive associations have also been observed between HBV/HCV infections and cholangiocarcinoma.
Occupational exposures	Since hepatitis B and C are transmitted through contact with infected human blood and body fluids, health workers, police and ambulance crews, and workers employed in rescue services may be exposed. Sharp injuries, as needle stick accidents, are the most frequent exposure event. In the non-working environment, hepatitis B and C can be transmitted from carrier individuals mainly by personal relationships (sexual intercourse, mother-to-child transmission, sharing of personal items, such as shaving razors, scissors, toothbrushes, and needles). Workers in clinical laboratories may handle biological specimens from infected individuals or directly handle the virus.
Carcinogenic mechanisms, main health effects and diagnostic criteria	
Short profile of the carcinogenic mechanisms	At a molecular level, the genesis of HBV induced HCC is a complex and multistep process mainly characterized by a series of genetic/epigenetic changes in the genes that govern cell proliferation and cell death. Knowledge regarding the precise role of the virus and the molecular mechanisms involved in hepatocarcinogenesis remains still incomplete. However, the available evidence supports the notion that tumour development results from a combination of host responses to the presence of the virus and molecular mechanisms either directly or indirectly induced by the virus itself. The hepatic inflammation and injury that occur in acute and chronic HBV induced hepatitis and cirrhosis are attributed to the immune responses of the host to the presence of the virus. A large proportion of HBV induced HCCs occurs in association with cirrhosis or, less often, chronic hepatitis: this suggests that the underlying necro-inflammatory hepatic disease can provide an environment in which virus induced genetic changes can lead to hepatocarcinogenesis. HBV may play a direct role in HCC: the integration and mutation of the viral genome into the host cellular DNA may result in the altered expression of important cellular genes. Secondly, the expression of HBV proteins may have a direct effect on cellular functions and in the promotion of malignant transformation. In addition, epigenetic mechanisms have been invoked in the carcinogenesis of HCC, with a number of tumour suppressor genes being affected by epigenetic silencing. Dual infection with HBV and HCV is common and is associated with a more severe chronic hepatic parenchymal disease, an increased frequency and a younger age of development of HCC than with either virus alone.

3.1.20 Cancer caused by hepatitis B virus (HBV) and hepatitis C virus (HCV) ICD Code (C22.0, C85.9) + Z57, Y40-Y84

Short profile of the carcinogenic mechanisms	Although chronic HCV infection is one major risk factor for HCC, the mechanisms involved in HCC development remain uncertain. Chronic endoplasmic reticulum stress and inflammatory responses, together with the associated oxidative stress and altered intracellular redox state, lead to the accumulation of genomic damage, thus likely predisposing infected cells to hepatocarcinogenesis. In addition, direct interactions of various HCV proteins with host factors correlate with alterations in cellular signalling cascades that are involved in the regulation of cell metabolism and division. Pro-carcinogenic cofactors in chronic HCV infection are steatosis, oxidative stress and insulin resistance. A complex interplay between these factors can, in turn, lead to chronic liver inflammation, apoptosis and fibrogenesis, which are thought to form the prelude to liver cirrhosis and cancer. The mechanisms by which lymphoma is induced by HCV remain uncertain. Several hypotheses have been suggested, among which 1) antigen-driven proliferation induced by continuous activation of B cells; and 2) a direct role of HCV replication and expression in infected B cells. Regarding the role of HBV in the development of lymphoma and of HBV and HCV in the development of cholangiocarcinoma, the evidence is currently lacking.

Name of the diseases and ICD code: **Hepatocellular carcinoma (C22.0) + Z57, Y40-Y84**

Short description of the disease

Hepatocellular cancer may follow chronic HBV or HCV infection and is typically associated with the development of cirrhosis. In the case of HBV infection, delta hepatitis superinfection augments the risk of HCC, and increased levels of HBeAg and HBV DNA have both been associated with the development of HCC. In the case of HCV infection, radiation exposure and infection with human T-lymphotropic virus type 1 (HTLV-1) are cofactors for developing HCC, as is HBV co-infection (see above).

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: symptoms may be absent until the presentation of abdominal pain, weakness, and weight loss, typically in a patient with liver cirrhosis. In addition, ascites may appear, suggesting portal or hepatic vein thrombosis by tumour or bleeding from a necrotic tumour. The liver may be found enlarged and tender at physical examination.
- Examinations: leucocytosis may be present, together with anaemia. The sudden elevation of the serum alkaline phosphatase is common. High to a mild elevation of alpha-fetoprotein is frequent. As regards serology of hepatitis:
  - *Hepatitis B:* serological testing and persistence of hepatitis B surface antigen (HBsAg) in the serum for more than six months after the exposure event, together with liver inflammation, confirm the diagnosis of underlying chronic hepatitis B. However, it is possible to have an "occult" HBV infection with HBV DNA detectable in the absence of HBsAg. When necessary, evidence of HBV DNA can be used to quantify viraemia. The pattern of chronic hepatitis B serologic markers are summarised in the table at the end of the item.
  - *Hepatitis C:* presence and persistence of HCV RNA for more than six months after an occupational exposure confirm the diagnosis of underlying chronic hepatitis C. Anti-HCV antibodies will usually be present with HCV RNA but may be absent in those who are immunosuppressed.
  - *Delta hepatitis:* present with HBV infection and confirmed by serology for anti-HD antibodies; HDV RNA is present.
  - For all types of hepatitis, liver function tests (e.g. transaminases, albumin); liver ultrasound, contrast enhanced triple phase CT scan, MR scan, and liver biopsy can be used to confirm the diagnosis, exclude other possible diagnoses and indicate the extent of liver dysfunction and involvement.

Exposure assessment

- History of occupational exposure: confirmed occupational exposure to HBV/HCV infected blood or body fluids.
- Minimum duration of exposure: a single exposure can cause the disease. In some cases, this episode cannot be reported.
- Maximum latent period: not applicable.

3.1.20 Cancer caused by hepatitis B virus (HBV) and hepatitis C virus (HCV) ICD Code (C22.0, C85.9) + Z57, Y40-Y84

Name of the diseases and ICD code: **Non-Hodgkin lymphoma (C85.9) + Z57, Y40-Y84**

Short description of the disease

Chronic HCV infection is associated with at least a doubling of the risk of non-Hodgkin lymphoma, with the effect being more strongly seen for B-cell tumours. There is evidence of a role for HBV in B-cell lymphoma, although weaker.

Diagnostic criteria

Clinical manifestations

- Signs and symptoms: painless lymphadenopathy, fever, weight loss, night sweats; at physical examination, splenomegaly and hepatomegaly may be found.
- Examinations:
  - Signs of bone marrow involvement might be observed, such as anaemia, increased susceptibility to infections, and bleeding.
  - Nodal biopsy should confirm the diagnosis of malignancy.
  - Whole body PET/CT scan, a bone marrow biopsy, and a lumbar puncture in selected cases, contribute in staging the disease.
  - Viral serology as described above should document the viral infection, especially from HCV.

Exposure assessment

- History of occupational exposure: confirmed occupational exposure to HBV/HCV infected blood and body fluids.
- Minimum duration of exposure: a single exposure can cause the disease (in some cases, this episode cannot be reported).
- Maximum latent period: not applicable.

Key actions for prevention	The presence of hepatitis viruses in several job environments is endemic and unavoidable, and the activities that can expose the workers to the infectious agents are mostly essential, such as patient care. Exposures to infected biological materials should be avoided by implementing the hierarchy of controls as appropriate to the work circumstances: for instance, feasible measures in a clinical/research laboratory will differ from those of a clinical treatment area. Engineering controls in the clinical area may include using sharp free or safety engineered safer sharp systems. Sharp injuries, as needle stick accidents, certainly represent the most frequent exposure event for blood-borne infections. As such, many countries, as well as national and supranational institutions, have developed guidelines aimed at preventing them. Some key elements are summarized below. Risk assessment should be conducted, and include an exposure determination, and cover all situations where there is injury, blood or other potentially infectious material. Risk assessments should take into account technology, organisation of work, working conditions, and the influence of factors related to the working environment. Where the results of the risk assessment reveal a risk of injuries with a sharp and infection, workers' exposure must be eliminated by specifying and implementing safe procedures for using and disposing of sharp medical instruments and contaminated waste. Unnecessary use of sharps should be eliminated, providing medical devices incorporating proven safety engineered protection mechanisms. Finally, the practice of recapping needles should be banned. The risk of exposure must be reduced to as low a level as practicable in order to adequately protect the safety and health of the workers concerned. Effective disposal procedures and clearly marked and technically safe containers for the handling of disposable sharps and injection equipment should be placed as close as possible to the assessed areas where sharps are being used or to be found.

3.1.20 Cancer caused by hepatitis B virus (HBV) and hepatitis C virus (HCV)
ICD Code (C22.0, C85.9) + Z57, Y40-Y84

Key actions for prevention

Other preventive measures include:

- point of care alcohol based hand rub (ABHR);
- point of use sharps containers;
- appropriately functioning and accessible dispensers for hand hygiene products (ABHR, soap, lotion, paper towels);
- designated handwashing sinks for health worker use;
- appropriate supply and accessibility of personal protective equipment for routine practices, such as:
  - gloves;
  - gowns;
  - masks (surgical or procedure masks used by a health worker and infectious source); and
  - facial protection (masks and eye protection, or face shields, or masks with visor attachment);
- appropriate occupational health and safety policies, including sharps safety and prevention of exposure to bloodborne pathogens and immunization programs;
- education of health workers; and
- policies, procedures and resources to support the application of:
  - point of care risk assessment; and
  - routine practices as the standard of care for all patients in all healthcare settings.

Hepatitis B and D are preventable through vaccines. Hepatitis B immune globulin is effective in preventing infection in non immune individuals significantly exposed to HBV. Screening of close contacts of infected persons should be considered and followed by vaccination as appropriate.

In subjects who have been infected, reducing or avoiding cofactors such as drinking alcohol can be effective in reducing the risk of complications of chronic infections.

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▶ Common serologic patterns in chronic hepatitis B virus infection and their interpretation

HBsAg	Anti-HBs	Anti-HBc	HBeAg**	Anti-HBe	Interpretation
+	-	IgG*	+	-	Chronic hepatitis B with active viral replication
+	-	IgG	-	+	Chronic hepatitis B generally with low viral replication
+	+	IgG	+ or -	+ or -	Chronic hepatitis B with heterotypic anti-HBs (about 10% of cases)

* IgM antibodies may also be detected at low levels. ** The presence of HBV DNA in serum generally parallels the presence of HBeAg; however, HBV DNA is more sensitive in detecting viral replication and infectivity.

▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
3.1.20	Liver cancer (hepatocellular carcinoma)	C22.0	2C12.02
3.1.20	Non-Hodgkin lymphoma (unspecified)	C85.9	2B33.5
	Occupational exposure to risk factors	Z57	QD84.Y
	Needle stick associated with injury or harm in therapeutic use	Y40-Y84	PK81.F

4. Other diseases

4.1.1 Miners' nystagmus	ICD Code H55 +Z57
Short profile of the aetio-pathogenesis	This disease is characterized by attacks of nystagmus accompanied by other symptoms related to an impairment of equilibrium. It was very frequent in the past and affected miners returning to an open environment after a work shift in the mine. Miners' nystagmus was suggested to be caused by the poor quality of the safety lamps used in the coal mines in the early 20th century. Awkward posture maintained by miners for long periods in the darkness, with deprivation of spatial points of reference, might also have played a relevant role.
Occupational exposures	Mining in improperly illuminated small tunnels, working under very low light levels over long periods, and inadequate ergonomic conditions, the affected miners often had to lie on their sides when working, may all contribute to the disease.

Main health effects and diagnostic criteria

Name of the diseases and ICD code: **Miners' nystagmus (H55) +Z57**

Short description of the disease

Coal miners' nystagmus ranks among the first occupational illnesses ever recognized for compensation. The prognosis is generally favourable unless the disease is not properly diagnosed and the occupational exposure is not avoided. In such cases, the disorder may become severe, resulting in total disability. The onset is usually between 40 and 60 years of age.

Diagnostic criteria

Clinical manifestations

The disease consists of attacks of pendular or rotating nystagmus, a rhythmic, involuntary, oscillatory motion of the eyeballs, often horizontal and in some cases accompanied by dizziness, headache, tremor, excessive sensitivity to glare (photophobia), and loss of night vision. It is suggested that the deafferentation of light receptors occurs due to prolonged low light exposure resulting in changes in the visual pathways and nystagmus. Because of these oscillations, there may be apparent movement of objects and defective visual acuity. Psychoneurotic symptoms e.g. anxiety and depression, may accompany the later stages of the disease. In the beginning, the symptoms are very mild, and the disease could be ignored by the affected subject and highlighted only through a periodical medical examination. The severity of symptoms increases over time if exposure is not eliminated. Complete neurological examination and radiological exams (e.g. CT) may be conducted to rule out other non-occupational causes of nystagmus e.g. central nervous system disorders, intoxications, vestibular disorders.

Exposure assessment

- History of occupational exposure: evidence of occupational exposure to very low light levels, largely below the proposed standards for comfort, over long periods of time, especially if work is performed in incongruous postures and in very small underground holes for most of the shift.
- Minimum duration of exposure: years.
- Maximum latent period: unknown.

Key actions for prevention	With the introduction of the electric cap lamp in mines, miner's nystagmus as such has virtually disappeared. However, while the condition has historically been related to miners, similar scenarios might also be present in other job activities characterized by very dim light and the absence of physical references. The disease may arise in these situations but could be prevented by proper ergonomic designs of the workplace and adequate illumination.

4.1.1 Miners' nystagmus ICD Code H55 +Z57

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▶ Table of diseases and risk factors with ICD-10 and ICD-11 codes

ILO	Disease name	ICD-10	ICD-11
4.1.1	Miners' nystagmus	H55	9C84.5Y
	Occupational exposure to risk factors	Z57	QD84.Z

Annex:
Use of ICD-10 and ICD-11 codes

Throughout the document ICD-10 codes are provided relating to the title of the ILO item and for each of the individual disease manifestations associated with the exposures to agents and work activities. For convenience of reference, these ICD-10 codes are also compiled in a table at the end of each item together with the corresponding ICD-11 codes. The use of disease coding systems is helpful in monitoring trends of occupational diseases at a national, jurisdictional, or enterprise level. These codes may also be useful to researchers in the field of occupational health.

The exposures to the agents and workplace activities causing occupational diseases are self-evidently due to occupational exposure to risk factors. The representation of this association should be denoted by the addition of the ICD-10 code Z57 (Occupational exposure to risk factors) or one of its subdivisions when increased specificity is possible.

ICD-10	
Z57	Occupational exposure to risk factors
Z57.0	Occupational exposure to noise
Z57.1	Occupational exposure to radiation
Z57.2	Occupational exposure to dust
Z57.3	Occupational exposure to other air contaminants
Z57.4	Occupational exposure to toxic agents in agriculture - Solids, liquids, gases or vapours
Z57.5	Occupational exposure to toxic agents in other industries - Solids, liquids, gases or vapours
Z57.6	Occupational exposure to extreme temperature
Z57.7	Occupational exposure to vibration
Z57.8	Occupational exposure to other risk factors
Z57.9	Occupational exposure to unspecified risk factor

There is a similar representation within ICD-11 so that a medical condition can be attributed to a workplace exposure with varying levels of specificity.

ICD-11	
QD84	Occupational exposure to risk factors
QD84.0	Occupational exposure to dust
QD84.1	Occupational exposure to toxic agents in agriculture
QD84.2	Occupational exposure to toxic agents in industries other than agriculture
QD84.3	Occupational exposure to vibration
QD84.4	Occupational exposure to ergonomic risk
QD84.Y	Other specified occupational exposure to risk factors
QD84.Z	Occupational exposure to risk factors, unspecified

▶ Site of musculoskeletal involvement

ICD-10 allows the indication of an anatomical site, which may be particularly useful for musculoskeletal codes. Where used, it is suggested that the supplementary site subclassification (see table) be placed in an identifiably separate position (e.g. in an additional box). Different sub-classifications for use with derangement of knee, dorsopathies, and biomechanical lesions not elsewhere classified are given within ICD-10 at codes M23, before M40 and at M99 respectively.

0	**Multiple sites**
1	**Shoulder region** clavicle scapula • acromioclavicular • glenohumeral • sternoclavicular joints
2	**Upper arm** humerus elbow joint
3	**Forearm** radius ulna wrist joint
4	**Hand** carpus fingers metacarpus joints between these bones
5	**Pelvic region and thigh** buttock femur pelvis hip (joint) sacroiliac joint
6	**Lower leg** fibula knee joint tibia
7	**Ankle and foot** metatarsus tarsus toes ankle joint other joints in foot
8	**Other** head neck ribs skull trunk vertebral column
9	**Site unspecified**

ICD-11 allows the significance of occupational causation to be indicated with the following extension codes:

Occupational relevance

XB17 Occupation as primary factor

XB5G Occupation as cofactor

XB80 Not occupation-related

For exposures to harmful substances there are several codes that specify substances themselves which can be used in combination with one of the subcodes in “Harmful effects of substances”. For instance, the code NE61 “Harmful effects of or exposure to noxious substances, chiefly nonmedicinal as to source, not elsewhere classified” can be combined with XM0QY7 “Benzene” as NE61&XM0QY7. More information is available including training videos on the WHO ICD-11 website: https://icd.who.int/en.

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Diseases caused by work have to be recognised so that measures can be taken to prevent the occurrence of similar diseases among fellow workers and victims of the diseases be properly compensated. Thus, the identification of occupational diseases has an impact not only on provisions of the employment injury benefits, but also on national and on enterprise level preventive programmes.

The causal relationship between work and disease is established on the basis of clinical and pathological data, occupational background and job analysis, identification and evaluation of occupational risk factors and of the role of other risk factors. The relationship between occupational exposure and the resulting severity of impairment among workers, and the number of workers exposed, are important criteria for the determination of occupational diseases.

This publication is intended to assist the Member States in the application of the ILO List of Occupational Diseases (revised 2010) and in the recognition of the diseases specified in the ILO List at the national level as occupational in origin for the purpose of their prevention, recording, notification and, if applicable, compensation.

This publication includes guidance notes for each type or group of the disease items specified in the ILO List of Occupational Diseases (revised 2010) and provides information and criteria to be considered in the diagnosis and prevention of these diseases. It is intended for the use of competent authorities, social security institutions, workers' compensation funds, occupational safety and health professionals, physicians, employers and workers, and persons in charge of recording, notification, prevention, and compensation programmes for occupational diseases.

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