Angiosarcoma of the liver

rare tumor

25 cases per year in the USA (~200,000,000 population)

=0.00125/100,000 person-yr

~50/100,000 person-yr in Goodrich Plant

~40,000 x of the background rate
In 1974, vinyl chloride (VC) was first reported in the open scientific literature to induce angiosarcoma of the liver both in humans and in animals.

Additional research has demonstrated the carcinogenicity of VC to other organs and at lower concentrations.

The target organs for VC now clearly include the liver, brain and the lung, and probably the lymphohematopoietic system.
The International Agency for Research on Cancer (IARC) is part of the World Health Organization.

IARC’s mission is to coordinate and conduct research on the causes of human cancer, the mechanisms of carcinogenesis, and to develop scientific strategies for cancer prevention and control. The Agency is involved in both epidemiological and laboratory research and disseminates scientific information through publications, meetings, courses, and fellowships.

**IARC News**

**IARC Postdoctoral Opportunities**

02/03/2012 - Call for applications for a postdoctoral opportunity in the Section of Nutrition and Metabolism/Nutritional Epidemiology Group. **Deadline: 23/03/2012**

Read more

**Industry group 'threatens' journals to delay publications of important study on diesel engine exhaust**

24/03/2012 - The Lancet Oncology reports today on an industry group 'threatening' journals to delay publications that may be relevant for the forthcoming IARC Monographs meeting on Diesel and gasoline engine exhausts and some nitroarenes (Vol. 105, 8-12 June, 2012).

Read more, The Lancet Oncology home page
### Incidences of Tumours in Mice Exposed to VCM for 30 Weeks and Dying Within 34 Weeks

<table>
<thead>
<tr>
<th>Concentrations of VCM (ppm) given 4 hrs/day on 5 days/week</th>
<th>Total no. of animals at start</th>
<th>Survivors at 34 weeks</th>
<th>Adenomas &amp; adenocarcinomas of the lungs</th>
<th>Mammary adenocarcinoma</th>
<th>Angiosarcoma of the liver</th>
<th>Others</th>
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<tbody>
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<td>10,000</td>
<td>60</td>
<td>26</td>
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<td>32</td>
<td>12</td>
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<td>6</td>
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<td>122</td>
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### Incidence of Tumours in Rats Exposed to VCM for 52 Weeks and Surviving Up to 130 Weeks

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<thead>
<tr>
<th>Concentration of VCM (ppm) given 4 hrs/day on 5 days/week</th>
<th>Total no. of animals at start</th>
<th>Survivors at 130 weeks</th>
<th>Zymbal gland tumour</th>
<th>Nephroblastoma</th>
<th>Angiosarcoma of the liver</th>
<th>Angiosarcoma at other sites</th>
<th>Others</th>
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<tr>
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<td>6</td>
<td>14</td>
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<td>0</td>
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</tr>
</tbody>
</table>

**Lung cancer**

**Angiosarcoma, liver & other sites**
US OSHA in 1974 proposed a 500-fold reduction in the occupational exposure standard for VCM gas—from 500 parts per million (ppm) in air to 1 ppm.

The plastic-manufacturing industry objected that such reduction was not possible and would drive VC polymerization industry overseas.

An industry-sponsored study estimated that the costs to comply with the proposed new standard would exceed $25 billion.
WITHIN THE YEAR, A MAJOR PLASTICS MANUFACTURER ANNOUNCED DEVELOPMENT OF A NOVEL CLOSED-LOOP POLYMERIZATION PROCESS THAT GREATLY REDUCED ATMOSPHERIC RELEASE OF VCM AND ALMOST COMPLETELY ELIMINATED WORKER EXPOSURE. THE MANUFACTURER PATENTED THIS SYSTEM AND SUBSEQUENTLY LICENSED IT TO OTHER MANUFACTURER AT SUBSTANTIAL PROFIT.
THE VCM STANDARD OF 1 PPM REMAINS IN FORCE TODAY AND IS READILY ACHIEVED IN THE WORKPLACE. NEW CASE OF HEPATIC ANGIOSARCOMA IN VINYL CHLORIDE POLYMERIZATION WORKERS HAVE BEEN VIRTUALLY ELIMINATED.

**Successful case of cluster investigation and sentinel event identification**
A slow process in identifying occupational risk of VC

1927, introduced into American commerce
1947, cause cardiac arrhythmia in experimental animals
1949, hepatic abnormalities in workers in a Russian plastic factory
1957, toxic angioneuropathy among workers exposed to VC below the then Russian maximum allowable concentration of 390 ppm
1960, a severe neurologic disorder in Minamata, Japan
1961, centrilobular granular degeneration of the liver at concentrations down to 200 ppm
1966, induce acro-osteolysis in workers cleaning reactor vessels

• 1971, inhalation to 30,000 ppm of VC induced tumors of the skin, lung and bone in rats

(Adopted from Wagoner, EHP 1983)
The evidence for a carcinogenic risk has been extended to jobs associated with poly(vinyl chloride) exposure.

Cases of liver angiosarcoma have been reported among individuals employed in PVC fabrication facilities and an epidemiological study has demonstrated a significant association between exposure to PVC dust and the risk of lung cancer mortality.

Cases of angiosarcoma of the liver also have been reported among individuals living in near proximity to vinyl chloride-poly(vinyl chloride) plants.
Another disease cluster: Samsung apologizes for workers' leukemia

Samsung offered its "sincerest apology" for the sickness and deaths of some of its workers, vowing to compensate those affected and their families.

"Some of Samsung’s former employees have passed away after contracting leukemia or are coping with difficult-to-treat diseases after having worked at our manufacturing facility," the company said in an emailed statement on Wednesday.

"It is truly sad and heart-breaking for us," the company said, adding that it could have been more diligent in addressing the hardship and sorrow of former employees and the families of the deceased. "We feel regret that a solution for this delicate matter has not been found in a timely manner, and we would like to seize this opportunity to express our sincerest apology to the affected people."

Samsung said it wants to resolve the issue with the concerned parties with "utmost sincerity," adding that will compensate former employees battling illness and the families of the deceased.

Samsung’s apology came in response to a proposal by families and the Supporters for the Health And Rights of People in the Semiconductor Industry (SHARPS) group.

So far there have been 26 victims of blood cancers (leukemia and lymphoma) reported to SHARPS, who worked in Samsung’s Gi-Heung and On-Yang semiconductor plants. Ten have died, the group said on its site.

Other alleged workplace-related illnesses reported to SHARPS include miscarriages, infertility, irregular menstruation, loss of hair, blood disorders, kidney troubles and liver disease.

Working in Samsung’s semiconductor plants is hazardous, SHARPS said.

Thousands of chemicals that are used for the manufacturing of chips aren’t disclosed to the workers, leanrooms in the factories don’t filter toxic gases and are designed to protect the wafers rather than the workers, according to the organization. Workers are also often forced to turn off recently installed protective devices to keep up with the production rate, it said.

The parties will now discuss setting up an impartial independent mediating group that will determine the criteria and eligibility for compensation, Samsung said, adding that it will fully comply with any guideline or compensation set by that mediator.

Moreover, an independent professional organization will conduct a thorough examination of health and safety conditions in Samsung’s semiconductor facilities. Measures to prevent recurrences of health issues will be established based on the findings, the company said.

Samsung will also withdraw as a party of interest from lawsuits filed by Samsung employees and their families against the Korea Workers’ Compensation & Welfare Service, it said.

"We hope this issue can soon be resolved amicably and help relieve the pains of our concerned employees and their families," Samsung said.
Objective: To investigate whether workplace exposures to recognized lymphohematopoietic carcinogens were possibly related to cancers in six semiconductor-manufacturing workers.

- Methods: A job-exposure matrix was developed for chemical and physical process agents and anticipated by-products. Potential cumulative occupational exposures of the six cases were reconstructed. The role of workplace exposures in cancer was evaluated through quantitative risk assessment and by comparison with epidemiological literature.

- Results: Two workers were potentially exposed to agents capable of causing their diagnosed cancers. Reconstructed exposures were similar to levels in outdoor environments and lower than exposures associated with increased risks in epidemiological studies. Cancer risks were estimated to be less than 1 in 10,000 persons.

- Conclusions: The development of cancer among the six workers was unlikely to be explained by occupational exposures to recognized lymphohematopoietic carcinogens.
From ENVIRON International Corporation (Dr Jones, Ms Simmons, and Ms Boelter) and School of Public Health, University of Illinois at Chicago (Dr Jones); ENVIRON International Corporation (Ms Dell), Amherst, MA; ENVIRON International Corporation (Mr Torres), Atlanta, GA; ENVIRON International Corporation (Dr Poole), Tampa, FL; and ENVIRON International Corporation (Mr Harper), Phoenix, AZ. Ms Simmons is currently employed by Simmons Environmental and Occupational Health Solutions. Mr Torres is currently employed by Gates Rubber.

This research work, but not the writing of the manuscript, was funded by Samsung Electronics Co., Ltd. Participation by Samsung Electronics Co., Ltd. was limited to the provision of the information described. The opinions expressed are solely those of the authors and do not reflect those of the Scientific Advisory Panel members nor of Samsung Electronics Co., Ltd. The authors have no conflicts of interest to declare.

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Address correspondence to: Paul Harper, MBA, 1702 E Highland Ave, Ste 412, Phoenix AZ 85016 (pharper@environcorp.com).
Time at litigation
Too few chemicals studied
Too few measurements and environmental investigations
Poor re-establishment of previous work conditions

“... We have no idea why JOEM decided this was a legitimate report to publish.”
Rachael Jones, the first author of the Environ paper

Associate Professor, Environmental and Occupational Health Sciences, School of Public Health, University of Illinois at Chicago
Objectives: Seven cases of malignant lymphohematopoietic (LHP) disorder were claimed to have developed from occupational exposure at two plants of a semiconductor company from 2007 to 2010. This study evaluated the possibility of exposure to carcinogenic agents for the cases.

Methods: Clinical courses were reviewed with assessing possible exposure to carcinogenic agents related to LHP cancers. Chemicals used at six major semiconductor companies in Korea were reviewed. Airborne monitoring for chemicals, including benzene, was conducted and the ionizing radiation dose was measured from 2008 to 2010.

Results: The latency of seven cases (five leukaemias, a Non-Hodgkin’s lymphoma, and an aplastic anemia) ranged from 16 months to 15 years and 5 months. Most chemical measurements were at levels of less than 10% of the Korean Occupational Exposure Limit value. No carcinogens related to LHP cancers were used or detected. Complete-shielded radiation-generating devices were used, but the ionizing radiation doses were 0.20-0.22 μSv/hr (background level: 0.21 μSv/hr). Airborne benzene was detected at 0.31 ppb when the detection limit was lowered as low as possible. Ethylene oxide and formaldehyde were not found in the cases' processes, while these two were determined to be among the 263 chemicals in the list that was used at the six semiconductor companies at levels lower than 0.1%. Exposures occurring before 2002 could not be assessed because of the lack of information.

Conclusion: Considering the possibility of exposure to carcinogenic agents, we could not find any convincing evidence for occupational exposure in all investigated cases. However, further study is needed because the semiconductor industry is a newly developing one.
“Causality” means?

Different levels:

• ...  
• Without the exposure, such disease would not have occurred  
• If having this disease, 50% or more was induced by the exposure  
• Increased risk by <100%  
• Slight increase in risk  
• ...
SMRs for All Cancer Mortality by Exposure to Chemical A
Aims: To evaluate cancer incidence among workers at two facilities in the USA that made semiconductors and electronic storage devices.

Methods: 89,054 men and women employed by International Business Machines (IBM) were included in the study. We compared employees' incidence rates with general population rates and examined incidence patterns by facility, duration of employment, time since first employment, manufacturing era, potential for exposure to workplace environments other than offices and work activity.

Results: For employees at the semiconductor manufacturing facility, the standardised incidence ratio (SIR) for all cancers combined was 81 (1,541 observed cases, 95% confidence interval (CI) 77 to 85) and for those at the storage device manufacturing facility the SIR was 87 (1,319 observed cases, 95% CI 82 to 92). The subgroups of employees with >15 years since hiring and >5 years worked had 6–16% fewer total incidents than expected. SIRs were increased for several cancers in certain employee subgroups, but analyses of incidence patterns by potential exposure and by years spent and time since starting in specific work activities did not clearly indicate that the excesses were due to occupational exposure.

Conclusions: This study did not provide strong or consistent evidence of causal associations with employment factors. Data on employees with long potential induction time and many years worked were limited. Further follow-up will allow a more informative analysis of cancer incidence that might be plausibly related to workplace exposures in the cohort.
Objectives: The purpose of this study was to evaluate cancer risks in the Korean semiconductor industry.

Methods: A retrospective cohort study was performed in eight semiconductor factories between 1998 and 2008. The number of subjects was 113,443 for mortality and 108,443 for incidence. Standardized mortality ratios (SMR) and standardized incidence ratios (SIR) were calculated.

Results: The SMR of leukemia was 0.39 (95% Confidence Interval 0.08-1.14) in males (2 cases) and 1.37 (0.55-2.81) in females (7 cases). The SMR of non-Hodgkin’s lymphoma (NHL) was 1.33 (0.43-3.09, 5 cases) in males and 2.5 (0.68-6.40, 4 cases) in females. The SIR of leukemia was 0.69 (0.30-1.37, 8 cases) in males and 1.28 (0.61-2.36, 10 cases) in females. The SIR of NHL in females was 2.31 (1.23-3.95, 13 cases) and that of thyroid cancer in males was 2.11 (1.49-2.89, 38 cases). The excess incidence of NHL was significant in female assembly operators [SIR=3.15 (1.02-7.36, 5 cases)], but not significant in fabrication workers. The SIR of NHL in the group working for 1-5 years was higher than the SIR of NHL for those working for more than five years. The excess incidence of male thyroid cancer was observed in both office and manufacturing workers.

Conclusion: There was no significant increase of leukemia in the Korean semiconductor industry. However, the incidence of NHL in females and thyroid cancer in males were significantly increased even though there was no definite association between work and those diseases in subgroup analysis according to work duration. This result should be interpreted cautiously, because the majority of the cohort was young and the number of cases was small.
### Editorial

**New concept for occupational health development: 3 phases**

<table>
<thead>
<tr>
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<th>Related event</th>
<th>Core problem</th>
<th>Solution</th>
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<td><strong>External Environment</strong></td>
<td>CS2 and other chemicals</td>
<td>Poor work environment OD diagnosis</td>
<td>OD control Work environment control</td>
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<tr>
<td><strong>Personal Environment</strong></td>
<td>Cerebro-cardiovascular dis</td>
<td>Life-style dis Work ability</td>
<td>Occupational health service (OHS) Person-job fit</td>
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<td>Leukemia in a semiconductor factory</td>
<td>Uncertainty of cause Income loss by ill health retirement</td>
<td>Risk communication Sick-leave benefits</td>
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SK Kang, KOSHA Med Director
ICOH vice President
# Editorial

New concept for occupational health development: 3 phases

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</tbody>
</table>
Real cluster or unreal…

Lung cancer occurs in Taiwan at a rate of 6/100,000 per year

In an industry of 100,000 employees, the chance of having > 3 persons with lung cancer is 0.65 per year; the chance of having > 6 persons with lung cancer is 0.35 per year

A perceived cluster forms when these three cases of lung cancer occur in vicinity, in similar departments, or exposed to similar procedures
Real cluster or unreal…

2 lung cancer, and 1 thyroid cancer → NOT a cluster of 3 cancers

Early identification through screening → may NOT be a part of a cluster

Comparison the occurrence rate with background rate

Do not forget the possibilities of new agents, like in VCM case

Attention span should cover IARC group 1 and 2A, etc.

Try to understand the cases as early as possible
Other health effects of concern

Reproductive
  ◦ Reproductive organs in directly exposed
  ◦ The second generation
Long-term exposure to chemicals used in the production of chips for Samsung significantly contributed to one of their factory workers developing terminal cancer, a South Korean court said in a first-of-a-kind ruling.

Lee Eun-joo struggled with the disease for more than a decade and died after working for the company for six years.

On Friday, the Seoul Administrative Court found a “significant causal relationship” between the sickness and the chemicals found at Samsung’s chip factories. The court ruled that it did not matter that the concentration of the harmful chemicals was low, as Lee Eun-joo had been exposed to them for a long time.
Background: Despite concerns over the harmful health effects of semiconductor production, epidemiological studies have shown mixed results.

Objectives: We aim to critically appraise epidemiologic studies to date, and to suggest future research and actions to protect workers in semiconductor industry.

Methods: Epidemiologic studies were identified through electronic database searches, review of reference lists of relevant published works, and expert consultations, and were narratively reviewed.

Results: Most evidence suggests reproductive risks from fabrication jobs, including spontaneous abortion (SAB), congenital malformation, and reduced fertility. Although chemicals have been suspected as causal agents, knowledge of the likely contribution(s) from specific exposures is still limited. Evidence of cancer risk seems to be equivocal. However, the available studies had serious limitations including healthy worker effects (HWEs), information bias, and insufficient power, all of which are associated with underestimation. Nevertheless, excess risks for non-Hodgkin’s lymphoma (NHL), leukemia, brain tumor, and breast cancer were observed.

Conclusions: Monitoring and innovative research based on international collaboration with a focus on sentinel events are required.
Some conclusions

Toxicological data from animal studies are important

Potential new health effects: reproductive (directly exposed and 2\textsuperscript{nd} generation)

Responsibility of evidence: at least partially shifted from workers to the industry

Some attention needs to be paid to the surrounding environments

→ Proactive
Toxicology studies 2016-7

Pro-Inflammatory and Pro-Fibrogenic Effects of Ionic and Particulate Arsenide and Indium-Containing Semiconductor Materials in the Murine Lung

Toxicity of indium arsenide, gallium arsenide, and aluminium gallium arsenide

Toxicological Assessment of CoO and La2O3 Metal Oxide Nanoparticles in Human Small Airway Epithelial Cells

Susceptibility to quantum dot induced lung inflammation differs widely among the Collaborative Cross founder mouse strains

Comparative analysis of redox and inflammatory properties of pristine nanomaterials and commonly used semiconductor manufacturing nano-abrasives

...
Human studies 2016-7

Has dry/cold weather an impact on the skin condition of cleanroom workers?

Exposure Potential and Health Impacts of Indium and Gallium, Metals Critical to Emerging Electronics and Energy Technologies

NIOSH field studies team assessment: Worker exposure to aerosolized metal oxide nanoparticles in a semiconductor fabrication facility

Occupational exposure to airborne nanomaterials: An assessment of worker exposure to aerosolized metal oxide nanoparticles in a semiconductor fab and subfab
如何早期發現同仁生理或心理不佳之訊號，或如何有效收集同仁抱怨？

當員工身體不舒服影響工作表現時，主管該怎麼關心員工？

當員工覺得工作過負荷時但仍執著於工作績效時，如何強化勞資雙方之良好溝通機制？

如何關懷職災員工，以提早復工

如何強化職業病之風險溝通機制(抱怨篩選、溝通與紀錄)