Organic solvents and cancer.

Cancer Causes Control 1997 May;8(3):406-19 (ISSN: 0957-5243)

Lynge E; Anttila A; Hemminki K
Danish Cancer Society, Kobenhavn.

Epidemiologic evidence on the relationship between organic solvents and **cancer** is reviewed. In the 1980s, more than a million persons were potentially exposed to some specific solvents in the United States; in Canada, 40 percent of male **cancer** patients in Montreal had experienced exposure to solvents; in the Finnish population, one percent was regularly exposed. There is evidence for increased risks of **cancer** following exposure to: trichloroethylene (for the liver and biliary tract and for non-Hodgkin's lymphomas); tetrachloroethylene (for the esophagus and cervix--although confounding by smoking, alcohol, and sexual habits cannot be excluded--and non-Hodgkin's lymphoma); and carbon tetrachloride (lymphohematopoietic malignancies). An excess **risk** of liver and biliary tract **cancers** was suggested in the cohort with the high exposure to **methylene chloride,** but not found in the other cohorts where an excess **risk** of pancreatic **cancer** was suggested. 1,1,1-trichloroethane has been used widely, but only a few studies have been done suggesting a **risk** of multiple myeloma. **A causal** association between exposure to benzene and an increased **risk** of leukemia is well-established, as well as a suggested **risk** of lung and nasopharynx **cancer** in a Chinese cohort. Increased risks of various gastrointestinal **cancers** have been suggested following exposure to toluene. Two informative studies indicated an increased **risk** of lung **cancer,** not supported by other studies. Increased risks of lymphohematopoietic malignancies have been reported in some studies of persons exposed to toluene or xylene, but not in the two most informative studies on toluene. Occupation as a painter has consistently been associated with a 40 percent increased **risk** of lung **cancer.** (With the mixed exposures, however, it is not possible to identify the specific causative agent[s].) **A** large number of studies of workers exposed to styrene have evidenced no consistent excess **risk** of all lymphohematopoietic malignancies, although the most sensitive study suggested an excess **risk** of leukemia among workers with a high exposure.

Major Subject Heading(s)	Minor Subject Heading(s)	CAS Registry / EC Numbers
	• Alcohol Drinking [adverse effects] [epidemiology] • Benzene [adverse effects]	

Cancer Causes and Control, 1997, 8, pp. 406-419

Organic solvents and cancer

Elsebeth Lynge, Ahti Anttila, and Kari Hemminki

(Received 16 May 1996; accepted in revised form 25 July 1996)

Epidemiologic evidence on the relationship between organic solvents and cancer is reviewed. In the 1980s, more than a million persons were potentially exposed to some specific solvents in the United States; in Canada, 40 percent of male cancer patients in Montreal had experienced exposure to solvents; in the Finnish population, one percent was regularly exposed. There is evidence for increased risks of cancer following exposure to: ***trichloroethylene*** (for the liver and biliary tract and for non-Hodgkin's lymphomas); ***tetrachloroethylene*** (for the esophagus and cervix – although confounding by smoking, alcohol, and sexual habits cannot be excluded – and non-Hodgkin's lymphoma); and ***carbon tetrachloride*** (lymphohematopoietic malignancies). An excess risk of liver and biliary tract cancers was suggested in the cohort with the high exposure to ***methylene chloride,*** but not found in the other cohorts where an excess risk of pancreatic cancer was suggested. ***1,1,1-trichloroethane*** has been used widely, but only a few studies have been done suggesting a risk of multiple myeloma. A causal association between exposure to ***benzene*** and an increased risk of leukemia is well-established, as well as a suggested risk of lung and nasopharynx cancer in a Chinese cohort. Increased risks of various gastrointestinal cancers have been suggested following exposure to ***toluene.*** Two informative studies indicated an increased risk of lung cancer, not supported by other studies. Increased risks of lymphohematopoietic malignancies have been reported in some studies of persons exposed to ***toluene*** or ***xylene,*** but not in the two most informative studies on toluene. Occupation as a painter has consistently been associated with a 40 percent increased risk of lung cancer. (With the mixed exposures, however, it is not possible to identify the specific causative agent[s].) A large number of studies of workers exposed to ***styrene*** have evidenced no consistent excess risk of all lymphohematopoietic malignancies, although the most sensitive study suggested an excess risk of leukemia among workers with a high exposure. ***Cancer Causes and*** Control 1997, 8, 406-419

Key words: Malignant neoplasms, organic solvents.

Introduction

Solvents are used to dissolve or suspend material to make the application easier. Organic solvents denote those composed of carbon in their structure. Aliphatic solvents are composed of chained carbon structures while aromatic solvents contain carbon atoms arranged in rings. In some cases, such as styrene, reactive ingredients are also called solvents.

Organic solvents represent an important occupational health problem. Numbers of exposed persons are known from the National Occupational Exposure Survey in the United States in 1981-83,[1] from a multi-site case-control study of cancer patients in Montreal, Canada, in 1979-85,[2] and from surveys in Finland in 1989.[3] Forty percent of the men in Montreal had been exposed occupationally to at least one solvent: and 50,000 persons were exposed regularly in Finland[3] (Table 1). In Finland, levels of exposure estimated from the industrial hygiene surveys varied from 0.5 mg/m^3 for benzene to 100 mg/m^3 for styrene. As these solvents are well absorbed by inhalation, the uptake can be estimated by assuming a daily inhalation at work of 10 m^3.

Dr Lynge is with the Danish Cancer Society, København, Denmark. Dr Antilla is with the Finnish Institute of Occupational Health, Helsinki, Finland. Dr Hemminki is with the Center for Nutrition and Toxicology, Karolinska Institute, Huddinge, Sweden. Address correspondence to Dr Lynge, Danish Cancer Society, Strandboulevarden 49, DK-2100 København Ø, Denmark.

Table 1. Occupational exposures to solvents. Estimates of potentially exposed persons from United States, 1981-83, percent of exposed male cancer patients, Montreal, Canada, 1979-85, and regularly exposed persons in Finland, 1989

Compound	Use	United States 1981-83[a]	Montreal, Canada 1979-85[b]	Finland 1989[c]	
		Number of potentially exposed	Percent of exposed male cancer patients[d]	Number of regularly exposed[d]	Estimated concentration mg/m^3
Trichloroethylene	Degreasing	401,000	2%	1,000	1
Tetrachloroethylene	Dry cleaning, degreasing	566,000	1%	2,000	1
Carbon tetrachloride	Production of fluorocarbons, solvent	104,200	4%	NR	NR
Methylene chloride	Pharmaceuticals, paint removal	1,440,000	2%	2,000	10
1,1,1-Trichloroethane	Metal cleaning solvent	2,528,000	1%	NR	NR
Chloroform	Pharmaceuticals	96,000	0.7%	1,000	1
Benzene	Oil refining, gasoline distribution	272,000	17%	5,000	0.5
Toluene	Paint, printing, shoe industry	1,278,000	14%	10,000	40
Xylene	Paint	1,106,800	11%	10,000	10
Styrene	Lamination	333,000	1%	3,000	100
All solvents	Various	NR	40%	50,000	NR

[a] United States 1982: Total population 232 million.'
[b] Montreal, Canada, 1979-85: Total population 2.7 million.[2]
[c] Finland 1989: Total population 5 million.[3]
[d] Aged 35-70 years.

Few measurements are available from occupational exposures in prior decades. In general, the use of organic solvents has increased over time, but this does not necessarily correlate with exposure, as the selection of solvents may have changed for particular work tasks and industrial hygiene measures may have reduced the exposure level. In air measurements from Denmark, the exposure to styrene in 1955-70 was four times the level in 1981-88.[4] In biological-monitoring data from Finland, the exposure to trichloroethylene in 1965 was three times the level in 1987, whereas the exposure to tetrachloroethylene and styrene changed little from the mid-1970s to 1987.' Past exposures often are poorly recorded and also may have been to a number of solvents. It is difficult to assess the potential cancer risk following such exposures, and, therefore, we have focused on data related to specific solvents or to occupational groups heavily exposed to solvents.

Animal carcinogenicity and genotoxicity

Organic solvents as single agents have been studied extensively for induction of cancer in experimental animals. By contrast, few studies are available on solvent mixtures. Among the aliphatic chlorinated compounds, there is sufficient evidence in experimental animals for the carcinogenicity of trichloroethylene, tetrachloroethylene, carbon tetrachloride, methylene chloride, and chloroform according to the International Agency for Research on Cancer (IARC)[5-6] (Table 2).

The liver has been a target site for all compounds; for trichloroethylene and chloroform, also the kidney; for trichloroethylene and methylene chloride, also the lung; and for trichloroethane, also the hematopoetic tissue. Studies on 1,1,1-trichloroethane have been negative, apart from one where leukemia was observed.'

Among the aromatic compounds, benzene has induced malignancies at many sites, including liver and mammary cancers and leukemias.[5] Styrene has increased the frequency of lung and other cancers in studies considered limited by IARC,[8] and studies on toluene and xylene were inadequate.'

None of the solvents discussed here are overtly genotoxic. With the exception of methylene chloride, none are mutagenic in bacteria. Yet, all the animal carcinogens, except tetrachloroethylene, have shown some genetic activity in yeast and fungi. Benzene has caused chromosomal aberrations in exposed humans, and styrene has induced adducts in hemoglobin and white blood-cell DNA of lamination workers.*Most of the solvents display organ toxicity which may be related to induction of cell proliferation and most are hepatotoxic; benzene is toxic to bone marrow; as are 1,1,1-trichloroethane, styrene, toluene, xylene, and benzene in high concentrations to the central nervous tissue. The occupational exposure levels often have been high enough to induce organ toxicity. Thus, cytotoxicity cannot be excluded as a possible mechanism of carcinogenicity for these solvents.

Table 2. Summary of the evidence on carcinogenicity of solvents as evaluated by the International Agency for Research on Cancer.

Compound	Genotoxicity			Animal carcinogenicity		Human carcinogenicity			
	Bacteria[a]	Eukaryotes[b]	Other	IARC evaluation[c]	Target organs	IARC evaluation[c]	Target organs	IARC group	Year of IARC evaluation
Trichloroethylene[6]	-	+	ND	S	Liver, kidney, lung	L	Liver, biliary tract, non-Hodgkin's lymphoma[e]	2A	1995
Tetrachloroethylene[6]			ND	S	Liver, bone marrow	L	Esophagus, cervix, non-Hodgkin's lymphoma[e]	2A	1995
Carbon tetrachloride[5]	-	+	ND	S	Liver	I		2B	1987
Methylene chloride[5]	+	+	ND	S	Liver, lung	I		2B	1987
1,1,1-Trichloroethane[5, 7]	-	-	ND	I		ND		3	1987
Chloroform[5]	-	+	ND	S	Liver, kidney	I		2B	1987
Benzene[5]	-	+	CA[d]	S	Liver, mammary, bone marrow, *etc.*	S	Leukemia[e]	1	1987
Toluene[9]	-	-	ND	I		I		3	1989
Xylene[9]	-	-	ND	I		I		3	1989
Styrene[8]	-	+	Adducts		Lung	I		2B	1994

[a] Mutagenicity in bacteria or
[b] In lower eukaryotes.
[c] Evaluation by the International Agency for Research on Cancer: S = sufficient L = limited, I = inadequate evidence, and ND = no data.
[d] Chromosomal aberrations in exposed workers.
[e] Cancer sites with sufficient or limited evidence in humans.

Trichloroethylene

The epidemiology on trichloroethylene and cancer has been reviewed recently.[6,10] Two cohort studies have been undertaken of workers biologically monitored for exposure to trichloroethylene. The first study" included 1,670 workers monitored in Sweden 1955-75. Seventy-eight percent of the person-years (PY) for men were accumulated in the category with mean concentration 0-49 mg/L, 14 percent with 50-99 mg/L, and eight percent with category > 100 mg/L. A total of 253 deaths were observed (standardized mortality ratio [SMR] = 1.0), and 129 incident cancer cases (SIR = 1.0).[11] The second cohort included 3,974 persons monitored in Finland 1965-83 for exposure to three halogenated hydrocarbons (trichloroethylene = 3,089; tetrachloroethylene = 849; and 1,1,1-trichloroethane = 271 with some persons monitored for exposure to more than one solvent). The median urinary concentration of trichloroacetic acid was 7.8 mg/L for men and 10.3 mg/L for women. There were 208 cancer cases among individuals monitored for trichloroethylene (SIR = 1.1).[12-13]

Three cohort studies investigated workers exposed to trichloroethylene in cleaning of metal parts in the aircraft industry. The most informative of these[14] included 14,457 civilians employed at an Air Force base in Utah (US) from 1952-56. In the early years, 1939-54, cold solvents were used to clean metal parts – primarily Stoddard solvent, but also carbon tetrachloride, trichloroethylene, and alcohols. In 1955, trichloroethylene replaced Stoddard solvent, and in 1968, 1,1,1-trichloroethane replaced trichloroethylene. Trichloroethylene was the primary solvent used in vapor drgreasing from 1939-79, when it was replaced by 1,1,1-trichloroethane. Of the 14,467 cohort members, 10,256 had been exposed to mixed solvents, 7,282 to trichloroethylene, 6,977 to Stoddard solvent, and 6,737 to carbon tetrachloride.[14] Combining data for men and women exposed to trichloroethylene, there were 1,694 deaths from all causes (SMR = 0.9), and 281 cancer deaths (SMR = 0.9).[15]

Of the less informative studies, one[16] included 20,535 employees from the Tucson, Arizona (US) facility of Hughes Aircraft Company. All employees were potentially exposed to trichloroethylene through the drinking water, but 4,733 also were potentially occupationally exposed. Among these employees, 484 cancer deaths occurred (SMR = 0.7). The last study[17] covered 14,067 persons who had worked in aircraft manufacturing in San Diego County, California (US), 1958-82. Data from a relatively small, nested case-control study indicated that 37 percent of the jobs held in the plant entailed exposure to trichloroethylene. A total of 1,804 deaths was observed (SMR = 0.8), and 453 deaths from cancer (SMR = 0.8).

A study of renal cancer and exposure to trichloroethylene" included 169 men employed for at least one year (during 1956-75) in a cardboard-manufacturing factory in Germany, and 190 unexposed workers. Assessment of cancer occurrence was based on abdominal sonography, various health records, and interviews with relatives. Four renal-cell carcinomas and one urothelial cancer of the renal pelvis were seen in the exposed group, and none in the controls. There are a number of, less informative studies on trichloroethylene which will not be reviewed here.[19-23]

The three most informative cohorts consistently indicated an excess relative risk (RR) for cancer of the liver and biliary tract with 23 observed (Obs) cases *cf* 12.9 expected (Exp) (Table 3). The risk for these cancers also was elevated in one of the two less informative studies. The results for liver cancer[24-26] were reported separately in the studies from Finland and the Utah Air Force base. Seven cases were observed *cf* 4.0 expected. Three case-control studies of primary liver cancer indicated elevated risks for people exposed to solvents, but only a few subjects in each study reported exposure to trichloroethylene.

The results for non-Hodgkin's lymphoma were consistent across the three most informative studies indicating a modest excess RR, with 27 Obs *cf* 18.9 Exp cases. The risk of non-Hodgkin's lymphoma was not increased in the two less informative studies. In a case-control study of malignant lymphomas,[27] an elevated odds ratio (OR) for exposure to trichloroethylene was indicated on the basis of seven exposed cases." The risk for non-Hodgkin's lymphoma was not increased among people exposed to trichloroethylene in the Canadian multi-site case-control study.'

Tetrachloroethylene and occupation as dry cleaner

The epidemiology of tetrachloroethylene and cancer has been recently reviewed.[6,28] As indicated earlier, the Finnish study' included 849 persons biologically monitored for exposure to tetrachloroethylene. The median level of tetrachloroethylene in the blood during 1974-83 was 116 µg/L in men and 66 µg/L in women. Thirty-one cancer cases were observed (SIR = 0.9).[12]

To date, we are aware of only two cohort studies of dry cleaning workers primarily exposed to tetrachloroethylene. The first study[29] included 1,701 workers in four labor unions from California, Illinois, Michigan, and New York (US), employed for at least one year before 1960 in a shop where tetrachloroethylene was the primary solvent used and where there was no known exposure to carbon tetrachloride. A survey in 1977-79 showed geometric mean, time-weighted average concentrations of tetrachloroethylene in the range of 20.3 to 149 mg/m^3. There were 769 deaths (SMR = 1.0), of which 209 were cancer deaths

Table 3. Retrospective cohort studies on the association between occupational exposure to trichloroethylene (TCE) and selected cancer sites (observed [Obs] and standardized mortality ratio [SMR])

Study (ref.) Year	Population and selection criteria	No. of subjects	All cancer		Liver and biliary tract		Liver only		Biliary tract only		Non-Hodgkin's lymphoma	
			Obs	SMR	Obs	SMR	Obs	SMR	Obs	SMR	Obs	SMR
Axelson *et al*[11] 1994	TCE, biological monitoring, Sweden, 1958-87, retrospective cohort, incidence	1,670	107	1.0	4	1.4	NR	—	NR	—	5	1.5
Anttila *et al*[12, 13] 1995a,b	TCE, biological monitoring, Finland, 1967-92, retrospective cohort, incidence	3,089	208	1.1	9	1.9	5	2.3	4	1.6	8	1.8
Spirtas *et al*[15] 1991	TCE in aircraft maintenance, USA, 1953-82, retrospective cohort, mortality	7,282	281	0.9	10	1.9	2	1.1	8	2.2	14	1.3
Wong & Morgan[16] 1990	TCE in aircraft manufacture, USA, 1958-87, retrospective cohort, mortality	4,733	484	0.7	5	1.8	NR	—	NR	—	3	1.1[a]
Garabrant *et al*[17] 1988	TCE in aircraft manufacture, USA, 1958-82, retrospective cohort, mortality	14,067	453	0.8	8	0.9	NR	—	NR	—	13	0.8[a]

[a] Including only ICD-9 code 200.

Table 4. Retrospective cohort studies on the association between occupational exposure to tetrachloroethylene (TeCE) and selected cancer sites (observed [Obs] and standardized mortality ratio [SMR])

Study (ref.) Year	Population and selection criteria	No. of subjects	All cancer		Esophagus		Pancreas		Cervix		Kidney		Non-Hodgkin's lymphoma	
			Obs	SMR	Obs	SMR	Obs	SMR	Obs	SMR	Obs	SMR	Obs	SMR
Exposure predominantly to TeCE														
Anttila *et al*[12,13] 1995a,b	TeCE biological monitoring, Finland, 1974-92, retrospective cohort, incidence	849	31	0.9	0	—	3	3.1	2	3.2	2	1.8	3	3.8
Ruder *et al*[29] 1994	TeCE in dry cleaning, USA, 1960-90, retrospective cohort, mortality	621	54	1.0	4	2.6	2	0.7	8	1.6[a]	1	1.2	NR[b,c]	—
Mixed exposure, including TeCE														
Ruder *et al*[29] 1994	TeCE and other solvents in dry cleaning, USA, 1948-78, retrospective cohort, mortality	1,080	155	1.3	6	1.9	13	2.1	12	1.2[a]	3	1.6	NR[b,c]	—
Blair *et al*[30] 1990	TeCE and other solvents in dry cleaning, USA, 1948-78, retrospective cohort, mortality	5,365	294	1.2	13	2.1	15	1.2	21	1.7	2	0.5	7	1.7[c]

[a] Female genital organs. [b] Total cohort, Obs = 2, SMR = 1.0. [c] including only ICD-9 code 200.

(SMR = 1.2, 95 percent confidence interval [CI] = 1.1-1.4). The cohort was divided into people employed in shops using only tetrachloroethylene, and other dry cleaners.

A union study of dry cleaning workers from Missouri (US)[30] included 5,365 identifiable members with membership for more than a year during 1945-78. There were 1,129 deaths (SMR = 0.9), of which 249 were cancer deaths (SMR = 1.2, CI = 1.0-1.3). The authors stated that the RRs were similar for workers first employed before 1960 and those employed after that date, when use of tetrachloroethylene became predominant.

A study was undertaken of 2,610 White men employed for one or more years, during 1956-80, in a chemical company in Louisiana (US),'' where tetrachloroethylene was one of many chemicals produced. There were 48 deaths (SMR = 0.6), of which 11 were cancer deaths (SMR = 0.8), including three deaths from leukemia and aleukemia (SMR = 4.9, CI = 1.01-1.4). Among civilians at the Utah Air Force base exposed to tetrachloroethylene,[15] there were two deaths from multiple myeloma (SMR = 17, CI = 2.1-61.6) and four deaths from non-Hodgkin's lymphoma (SMR = 3.2, CI = 1.2-7.1).[15]

Results for esophageal cancer were reported from the two subgroups of the four-state US study and the Missouri study, and elevated risks were found in all of them with a total of 23 observed cases *cf* 10.8 expected (Table 4). Results for cervical cancer were reported from these studies and from the cohort of biologically monitored women from Finland. Elevated risks were found in all studies with a total of 43 observed cases *cf* 28.4 expected. Although these associations appear unlikely to be due to chance, confounding by strong risk factors such as smoking, alcohol, and sexual habits cannot be excluded. Elevated risks for non-Hodgkin's lymphoma were observed both in the Finnish study, in the Missouri cohort, and among the civilians exposed to tetrachloroethylene at the Air Force base in Utah.

Carbon tetrachloride, methylene chloride, 1,1,1-trichloroethane, and chloroform

Two cohort studies, thus far, have assessed exposure to carbon tetrachloride.[15,32] A study from the 'lasting' and 'making' departments of boot and shoe manufacture listed use of carbon tetrachloride along with benzene and trichloroethylene.'' The cancer risk following exposure to carbon tetrachloride also has been assessed in the Canadian multi-site case-control study.' Some of these studies suggest an increased risk of lymphohematopoietic malignancies following exposure to carbon tetrachloride.

Three cohort studies have studied workers heavily exposed to methylene chloride.[34-36] In a study among employees in the production of cellulose triacetate fibers,[36] the median exposure level was 490 to 2,600 mg/m^3 in the main areas. The reported mean exposure in a study of film production workers was 91 mg/m^3.[35] The cohort with the highest exposure suggested an excess risk of liver and biliary tract cancers, not found in the two other cohorts (Table 5). The two latter studies suggested an excess risk of pancreatic cancer not found among the cellulose fiber workers. The Canadian multi-site case-control study' reported small increases in the risk of rectal and lung cancers following exposure to methylene chloride. Other studies, for which the use of methylene chloride has been documented, have not suggested consistent findings.[15,37-39]

Despite the common use of 1,1,1-trichloroethane as a metal cleaning solvent, there are only three studies on cancer risk[2,12,15] of which two[12,15] found increased risks of multiple myeloma based on small numbers.

To date, there is no study on cancer following occupational exposure to chloroform. Several studies''.'' have attempted to assess the potential carcinogenic effect of chlorination byproducts, including chloroform, in drinking water. Excess risks of rectal and bladder cancer have been suggested,[41] but it is not possible to evaluate the effect of chloroform alone.

Benzene

The association between occupational exposure to benzene and an increased risk of leukemia is well-documented.[42] The two largest cohort studies have been recently updated. They have provided further data on the risk of leukemia subtypes and improved the basis for assessment of the leukemia risk following low-dose exposure.

One cohort'' consisted of 1,212 white men employed from 1936-75 in the production of Pliofilm, a covering material made from rubber hydrochloride whose production involved the use of large volumes of benzene as a solvent. Various estimates have been made of the exposure levels in this cohort with the proportion of person-years accumulated by men exposed to less than 50 ppm-years varying from 78 percent to 56 percent. The latest follow-up showed 481 deaths (SMR = 1.0), 111 cancer deaths (SMR = 1.1), 14 leukemia deaths (SMR = 3.6, CI = 2.0-6.0)'' of which six were from acute myeloid leukemia (SMR = 5.0, CI = 1.8-11.0), and showing a strong association with cumulative exposure.''

A cohort of 74,828 workers were recruited from 1,427 benzene-exposed work units in 672 factories in 12 cities in China. There were 1,369 deaths which gave a low overall mortality compared with the general population (SMR = 0.5). However, a cohort of 35,805 unexposed workers had the same overall mortality (RR = 1.1). The exposed cohort had 42 incident leukemia cases (RR = 2.6 compared with unexposed, CI = 1.3-5.7). The largest group was acute myelogenous leukemia (Obs = 23, RR = 3.1, CI

Table 5. Retrospective cohort studies on the association between occupational exposure to methylene chloride (MEC) and selected cancer sites (observed [Obs] and standardized mortality ratio [SMR])

Study (ref.) Year	Population and selection criteria	No. of subjects	All cancer		Liver		Pancreas		Lung		Bladder		Kidney		Breast	
			Obs	SMR	Obs	SMR	Obs	SMR	Obs	SMR	Obs	SMR	Obs	SMR	Obs	SMR
Ott *et al*[34] 1985	MEC and other chlorinated solvents in chlorinated methanes area in chemicals manufacture, 1+ year, USA, factory files, men, retrospective cohort, mortality	2[illegible]	9	0.7	NR	—	3	3.3	[illegible][a]	0.7	NR	—	NR	—	NR	—
Shannon *et al*[37] 1988	MEC and trichloroethylene in wire drawing in lamp manufacture, Canada, factory files, women, retrospective cohort, incidence	203	19	1.6	NR	—	N	—	N[illegible]	—	NR	—	NR	—	8	2[illegible]
Hearne *et al*[35] 1990	MEC at roll film coating, USA, factory files, men, retrospective cohort, mortality	1,013	55	0.7	0	—	8	1.9	18	0.8	NR	—	NR	—	NR	—
Cragle *et al*[38] 1992	MEC and trichloroethylene in gas centrifuge process in a gaseous diffusion plant, Canada, factory files, retrospective cohort, incidence	[illegible]	N[illegible]	—	1	1[illegible]	NR	—	N[illegible]	—	[illegible]	7.8	1	N[illegible]	N[illegible]	—
Sinks *et al*[39] 1992	MEC, trichloroethylene, and formaldehyde among paperboard printing manufacture, USA, factory files, retrospective cohort, mortality	2,[illegible]0	16	0.6	NR	—	NR	—	5[a]	0.5	[illegible]	1.1[b]	6	3.7[b]	NR	—
Lanes *et al*[36] 1993	MEC among cellulose fiber production workers, USA, factory files, retrospective cohort, mortality	1,271	39	0.8	4	3.0	2	0.8	13	0.8	NR	—	NR	—	3	0.5
Siemiatycki[2] 1991	MEC, substantial, male lung cancer patients in Montreal, French Canada, case-control	592[c]	NR	—	N[illegible]	—	N[illegible]	—	7	3.8[c]	NR	–	NR	—	NR	—

[a] All respiratory cancer. [b] Incidence. [c] Case-control study, odds ratio.
NR = not reported.

Table 6. Retrospective cohort studies on the association between occupational exposure to toluene (TOL) or xylene (XYL) and selected cancer sites (observed [Obs] and relative risk [RR])

Study (ref.) Year	Population and selection criteria	No. of subjects	Stomach		Colon		Rectum		Lung		Cervix		Nervous system		Non-Hodgkin's lymphoma		Leukemia	
			Obs	RR	Obs	RR	Obs	RR	Obs	RR	Obs	RR	Obs	RR	Obs	RR	Obs	RR
Wilcosky *et al*[32] 1984	TOL in solvent mixture in rubber industry, USA, factory files, White men, nested case-control	NR	15	1.4	NR	—	NR		36[a]	1.0	NR	—	NR	—	6[b]	2.6	7	2.8
Svensson *et al*[68] 1990	TOL in rotogravure printing, Sweden, factory files, retrospective cohort, incidence	1,020	7	2.3	9	1.5[c]	[c]	[c]	16[a]	1.8	NR	—	NR	—	1	0.3	3	1.7
Siemiatycki[2] 1991	TOL, substantial, male cancer patients in Montreal, Canada, case-control	4,263	12	1.2	27	1.3	17	1.9	33	0.8	NR	—	NR	—	11	1.2	NR	—
Spirtas *et al*[15] 1991	TOL at an aircraft maintenance facility, USA, factory files, retrospective cohort, mortality	NR	NR	—	NR	—	NR	—	NR	—	NR	—	NR	—	5	2.1[d]	NR	—
Walker *et al*[69] 1993	TOL in shoe manufacturing, USA, factory files, retrospective cohort, mortality	7,814	NR[e]	—	46[f]	1.3	NR[e]	—	99	1.5	NR	—	NR	—	5g	0.8	15	1.1
Anttila *et al*[13] 1995b	TOL, files on biologic monitoring, Finland, retrospective cohort, incidence	1,856	1[h]	1.3	0[h]	—	1[h]	2.1	3h	1.6	0h	—	1h	1.7	0h	—	0h	—
Carpenter *et al*[70] 1988	TOL, XYL, or methyl ethyl ketone at nuclear facilities, USA; low level, factory files, nested case-control	89	NR	—	NR	—	NR	—	NR	—	NR	—	28	2.0	NR	—	NR	—
Berlin *et al*[71] 1995	White spirit, TOL,XYL in mixtures, Sweden, persons with suspected solvent-related disorders, retrospective cohort, incidence	5,653	5	1.0	7	1.0	6	1.3	15[a]	1.3	14	3.7	4	0.9	7	1.9	6	2.1
Wilcosky *et al*[32] 1984	XYL in rubber industry, USA, factory files, white men, nested case-control	NR	3	0.5	NR	—	NR	—	10[a]	0.6	NR	—	NR	—	4[b]	3.7	4	3.3
Siemiatycki[2] 1991	XYL, substantial, male cancer patients in Montreal, Canada, case-control	4,263	2	0.6	10	1.8	7	2.9	13	1.0	NR	—	NR	—	3	1.0	NR	—
Spirtas *et al*[15] 1991	XYL at an aircraft maintenance facility, USA, factory files, men, retrospective cohort, mortality	NR	NR	—	NR	—	NR	—	NR	—	NR	—	NR	14.4	0	—	NR	—
Anttila *et al*[13] 1995b	XYL, files on biologic monitoring, Finland, retrospective cohort, incidence	1,356	0[h]	—	0h	—	0h	—	2h	1.8	0[h]	—	1h	2.8	1h	4.7	1h	6.4

[a] All respiratory cancer. [b] Lymphosarcoma. [c] Colorectal cancer combined. [d] Both men and women. [e] 90 cases for all digestive system combined, RR = 0.9.
[f] Intestine except rectum (ICD-9 codes 152-153). [g] Lymphosarcoma and reticulosarcoma. [h] Latency 10+ yrs. NR = not reported.

= 1.2-10.7), but risk estimates of the same size were seen for chronic myelogenous leukemia (Obs = 2, RR = **2.6)** and acute lymphocytic leukemia (Obs = **5,** RR = **2.8).**[45]

Significantly elevated risks for other types of cancer were not found in the relatively small Pliofilm cohort. However, the large Chinese cohort had a borderline significant excess risk of lung cancer (RR = **1.4)** and an excess risk of nasopharynx cancer compared with the unexposed workers.

Low level exposure to benzene is widespread as gasoline contains benzene in up to five percent concentration.[46] Based on data from the Pliofilm cohort, it has been estimated that a worker occupationally exposed to benzene at an average exposure level of 1 ppm for **40** years would have an increased risk of death from leukemia of 1.7.[47] Estimates based on the updated cohort data show a lifetime leukemia risk following **45** years of exposure to **1** ppm to vary between **0.3** and **1.3** per 1,000.[48] In order to overcome the uncertainty inherent in extrapolation of results from high exposures to low exposures, studies also have been undertaken of the cancer risk among gasoline distribution workers.

Toluene, xylene, and solvents in mixtures

Use of toluene, xylene, Stoddard solvent, white spirits, and other solvents in mixtures have prevailed in industries considered to entail carcinogenic risks, such as furniture and cabinet making, paint manufacture and painting, boot and shoe manufacture, graphics industry, petrochemical and other chemical industries.[2,6,9,49-57] Due to exposure to concurrent agents, no evaluation of solvent-specific risks can be made from these studies.

A meta-analysis of **55** cohort studies of mortality among workers exposed to organic solvents showed a significantly elevated mortality from leukemia (SMR = 1.1, CI = 1.0-1.5) and from cancer of the liver and biliary tract (SMR = 1.2, CI = **1.0-1.4).** No other cause of death was significantly elevated.[58] Several,[27,59-63] but not all,[2,64] case-control studies have reported a risk of non-Hodgkin's lymphoma following occupational exposure to organic solvents.[65] Four case-control studies[27,61,63,66] have indicated a risk of Hodgkin's disease following solvent exposure, and one study[67] indicated a risk of acute myeloid leukemia. Only one small study of Hodgkin's disease[65] had a detailed description of the solvents; all exposed cases had handled several solvents/mixtures, including xylene and toluene.

Of two cohort studies of workers heavily exposed to toluene, one[68] followed-up 1,020 rotogravure printers employed **1925-85** and exposed to average air levels of toluene from **110** to **1690** mg/m^3. Benzene also may have been used in the earlier years, and contact with carcinogenic dyestuffs was common. The cohort had **129** deaths (SMR = 1.0), and **68** incident cancers **(SIR = 1.3).** The other study[69] included **7,814** workers from two shoe-manufacturing plants with toluene levels from **83** to 188 mg/m^3, where exposure to hexane and some other solvents was also documented. There were **1,540** deaths (SMR = 1.0), and **353** cancer deaths (SMR = **1.0).**

In addition, there are four minor studies reporting risks for toluene.[13,15,32,70] In a study of **5,653** persons with suspected solvent-related disorders from Sweden,[71] exposure information was obtained only for a subsample of the cohort, showing that most of the workers were exposed to mixtures of solvents including white spirits, xylene, and toluene. There were 182 deaths (SMR = 0.9), and **118** incident cancer cases (SIR = **1.2).**

Five of the cohort-based studies on toluene have indicated some elevated risks for cancers of digestive organs such as stomach, intestine, or rectum (Table **6).** Among Swedish rotogravure printers: the risk of gastrointestinal cancers was slightly higher for a longer duration of exposure (five or more years, latency of more than 10 years). The risks of rectal cancer were elevated among persons with substantial exposure to toluene and xylene in the Canadian multi-site case-control study.'

Both of the most informative cohort studies on toluene have shown an increased risk of lung cancer,[68-69] although this finding was not repeated in the less informative studies. Increased risks of lymphohematopoietic malignancies have been reported in many studies of persons exposed to toluene or xylene, but the results from the two most informative cohorts on toluene do not support this finding. Two studies have suggested an association between exposure to toluene or xylene and brain tumors.[15,70] A significantly elevated risk of cervical cancer was found in the cohort of solvent-exposed workers."

Occupation as a painter, Stoddard solvent, white spirits

Occupation as a painter was evaluated for carcinogenicity by IARC in **1989.**[9] A consistent increase was found of about 20 percent in the risk of overall cancer and of about 40 percent in the risk of lung cancer.' The risks of cancers of the esophagus, stomach, rectum, liver, pancreas, buccal cavity, larynx, prostate, bladder, and lymphomas and leukemias were raised in some studies. As painters in general have been exposed to a multitude of carcinogens – such as asbestos, metals, pigments, solvents, gasoline, and polycyclic aromatic hydrocarbons (PAH), there is no firm evidence concerning specific causative agents.

Seven studies have been published on the carcinogenic risk of painters after 1989,[2,72-77] in which the risks of cancers of the lung and urinary organs have been consistently elevated. The studies provide further evidence that there may be increased risks of cancer in the liver,[73,75-76]

Table 7. Retrospective cohort studies on the association between occupational exposure to styrene and malignant neoplasms of the lymphohematopoietic tissue (observed [Obs] and standardized mortality ratio [SMR])

Study (ref.) Year	Population and selection criteria	No. of subjects	All lympho-hematopoietic		Non-Hodgkin's lymphoma		Hodgkin's disease		Multiple myeloma		Leukemia	
			Obs	SMR	Obs	SMR	Obs	SMR	Obs	SMR	Obs	SMR
Styrene-butadiene rubber plants												
Meinhardt *et al*[80] 1982	USA, 1943/50-76, factory files, retrospective cohort, mortality	2,756	11	1.3	4	1.7[a]	1	0.7	NR	—	6	1.7
Matanoski *et al*[81] 1990	USA, 1942/43-76, factory files, retrospective cohort, mortality	12,160	55	1.0	7	0.6[a]	8	1.2	—	—	22	1.0
Styrene monomer and polymonomer plants												
Bond *et al*[82] 1992	USA, 1937-70, factory files, retrospective cohort, mortality	2,904	28	1.4	7	1.2	5	2.2	7	1.8	9	1.2
Nicholson *et al*[83] 1978	USA, 1960, union records, retrospective cohort mortality	560	NR	—	1	0.8	NR	—	NR	—	1	1.3
Hodgson & Jones[84] 1985	UK, 1945-74, factory files, retrospective cohort mortality	662	NR	—	3	5.4	NR	—	NR	—	0	—
Okun *et al*[85] 1985	Boat building, US, 1959-78, factory files, retrospective cohort, mortality	5,201	0	—	0	—	0	—	0	—	0	—
Coggon *et al*[86] 1987	Boat building, UK, 1947-84, factory files, retrospective cohort, mortality	8,354	5	0.4	0	—	1	0.5	1	0.5	3	0.5
Wong *et al*[87] 1994	Reinforced plastics plants USA, 1948-77, factory files, retrospective cohort, mortality	15,826	31	0.8	4	0.7[a]	4	0.9	NR	—	11	0.7
Kogevinas *et al*[88] 1994	Reinforced plastics plants international, various periods, factory files and pension scheme data, retrospective cohort, mortality	35,443	50	1.0	12	0.8	7	1.1	8	1.0	23	1.0
Kolstad *et al*[89] 1994	Reinforced plastics plants, Denmark, 1964-88, pension scheme data, retrospective cohort, incidence	36,525	112	1.2	42	1.3	16	1.1	12	1.0	42	1.2
Pooled estimate Kolstad[91] 1995			270	1.1	76	1.1	40	1.2	22	1.0	101	1.0

[a] Only lymphosarcoma and reticulosarcoma

gallbladder,[73-74] colorectum,[2,72] pancreas,[76] mouth and pharynx," prostate: testis,[73] lymphomas,[77] myeloma,[74] and leukemias.[72] There is also a consistent but marginal increased risk of brain tumors.

Good data on the cancer risk following exposure to Stoddard solvent or white spirits are not yet available. The study by Siemiatycki *et al*[2] showed small increased risks of pancreatic, lung, and prostatic cancers. In Swedish case-control studies, exposure to white spirit and thinners has been suggested to be associated with an increased risk of malignant lymphomas,[61,63] primary liver cancer,[26] and acute leukemia."

Styrene

Studies in the rubber industry raised suspicion about a risk of lymphohematopoietic malignancies among workers employed in manufacture of styrene-butadiene rubber." This suspicion was confirmed in the first study which focused on this industry." Further studies in both the styrene-butadiene rubber industry and in the manufacture of styrene monomers and polymonomers showed inconsistent results.[81-84]

Exposure to styrene has been high in the reinforced plastics industry where boats and similar products have been produced, and exposures to known carcinogens are limited. In a study from two reinforced-plastics boat-building facilities in the US,[85] no case of lymphatic or hematopoietic malignancies was found. A study from eight British facilities[11b] included 7,949 persons employed during 1947-84. Exposure for hand laminators was estimated to 170-426 mg/m^3. There were 693 deaths (SMR = 0.8), and 181 cancer deaths (SMR = 0.8). A cohort of 15,826 persons from 30 reinforced plastics plants in the US[87] who had worked from 1948-77 showed 1,628 deaths (SMR = 1.1), of which 425 were cancer deaths (SMR = 1.2, CI = 1.0-1.3).

An international cohort study[88] included 35,443 workers from 660 plants of the reinforced plastics industry from Denmark, Finland, Italy, Norway, Sweden, and the United Kingdom. Exposure to styrene was reconstructed from job and production records, environmental measurements, and, in Italy, biological monitoring. An exposure database was based on 16,500 personal air samples and 18,500 measurements of styrene metabolites in urine. Styrene exposure levels decreased considerably during the study period. Data from Denmark, considered to be representative of all six countries, showed exposures of about 852 mg/m^3 in the 1950s and 85 mg/m^3 in the 1980s. The cohort had 2,196 deaths (SMR = 1.0) and 550 cancer deaths (SMR = 0.9).

A cancer incidence study from Denmark[89] included 36,525 men employed 1964-89 in 386 facilities having produced reinforced plastics. Of these men, 12,800 also were included in the international cancer mortality study." Exposures were assessed from national air samples going back to 1955. The cohort had 3,031 deaths (SMR = 1.1) and 1,246 incident cancer cases (SIR = 1.0).[89-90]

The data on lymphohematopoietic malignancies are summarized in Table 7, together with a 'pooled estimate' where account is taken of the overlap among studies." Overall, there is no excess risk of all lymphohematopoietic malignancies, nor of any of the diagnostic subgroups. An increasing risk by average exposure was suggested for all lymphohematopoietic malignancies and for lymphomas in the international study, but not for leukemia.[88] In the Danish cancer-incidence study? which is the most sensitive, an excess risk of leukemia (Obs = 30, SMR = 1.5, CI = 1.0-2.2) was found among persons employed in the early production phase, 1964-70, where an average exposure level of 767 mg/m^3 was measured. A risk of pancreas cancer was suggested in the high exposure group.

Conclusion

Organic solvents are widely used. Several of these solvents are carcinogenic in experimental animals, and it is therefore important to assess thoroughly their carcinogenicity in humans.

Trichloroethylene is used as a degreasing agent. There is some evidence for increased risks of cancer of the liver and biliary tract and for non-Hodgkin's lymphomas following exposure. Tetrachloroethylene is used for dry cleaning and degreasing. There is some evidence for increased risks of cancer of the esophagus and cervix following exposure, but confounding by smoking, alcohol, and sexual habits cannot be excluded. There is also some evidence for an increased risk of non-Hodgkin's lymphomas.

Carbon tetrachloride is used in the production of fluorocarbons, *etc.* Some excess risk of lymphohematopoietic malignancies has been suggested following exposure. Methylene chloride is used widely in paint removal and pharmaceuticals. An excess risk of liver and biliary tract cancers was suggested in the cohort with the highest exposure, but not found in the other cohorts where a risk of pancreatic cancer was suggested. 1,1,1-trichloroethane has been used widely as a metal cleaning solvent, but only a few epidemiologic studies have been made suggesting a risk of multiple myeloma.

Benzene previously was used widely as a solvent in glues, *etc.* Low level exposure to benzene is widespread as gasoline contains benzene in up to a five percent concentration. There is convincing evidence that exposure to benzene is associated with an increased risk of leukemia. A study of a large Chinese cohort also suggested a risk of lung and nasopharynx cancer.

Toluene is used widely in paint, printing, and in shoe

manufacture. Increased risks of various gastrointestinal cancers have been suggested following exposure. Both of the most informative cohort-studies showed an increased risk of lung cancer, not supported by the other studies. Increased risks of some lymphohematopoietic malignancies have been found for persons exposed to toluene or xylene, but not in the two most informative studies on toluene.

Occupation as a painter has been shown consistently to be associated with a 40 percent increased risk of lung cancer. With the mixed occupational exposures, however, it is not possible to identify the specific causative agent(s).

Styrene is used widely in lamination of reinforced plastics. Based on a large number of cohort studies of workers exposed to styrene, there is no consistent excess risk of lymphohematopoietic malignancies. A large incidence study from Denmark suggested an excess risk of leukemia among workers employed in the 1960s when the exposure level was high.

Apart from the association between exposure to benzene and the risk of leukemia, the available data on exposure to organic solvents and the risks of cancer are not conclusive. However, for several of the solvents, there is sufficient evidence for carcinogenicity in experimental animals and there are some indications of a possible cancer risk in humans. Given the widespread use, further epidemiologic studies on the specific solvents are needed, including, for styrene, a further follow-up of the existing cohorts.

References

1. United States National Institute for Occupational Safety and Health. *National Occupational Exposure Survey 1981-83.* Cincinnati, OH (USA): NIOSH, 1994.
2. Siemiatycki J, ed. *Risk Factors for Cancer in the Workplace.* Boca Raton, FL (USA): CRC Press, 1991: 1-325.
3. Anttila A, Sallmén M, Hemminki K. Carcinogenic chemicals in the occupational environment. *Pharmacol Toxicol* 1993; 72: 69-76.
4. Jensen AA, Breum N, Backer J, Lynge E. Occupational exposure to styrene in Denmark 1955-88. *Am J Ind Med* 1990; 17: 593-606.
5. International Agency for Research on Cancer. *Overall Evaluations of Carcinogenicity: An Updating of IARC* Monographs Volumes 1-42. Lyon, France: IARC, 1987; *IARC Monogr Eval Carcinog Risks Humans,* Suppl. No. 7.
6. International Agency for Research on Cancer. *Dry Cleaning, Some Chlorinated Solvents and Other Industrial Chemicals.* Lyon, France: IARC, 1995; *IARC Monogr Eval Carcinog Risk Humans,* Vol. 63.
7. International Programme on Chemical Safety. Environmental Health Criteria. 136 *1,1,1-Trichloroethane.* Geneva, Switzerland: World Health Organization, 1992.
8. International Agency for Research on Cancer. *Some Industrial Chemicals.* Lyon, France: IARC, 1994; *IARC Monogr Eval Carcinog Risk Humans,* Vol. 60.
9. International Agency for Research on Cancer. *Some Organic Solvents, Resin Monomers and Related Compounds, Pigments and Occupational Exposures in Paint Manufacture and Painting.* Lyon, France: IARC, 1989; *IARC Monogr Eval Carcinog Risks Humans,* Vol. 47.
10. Weiss N. Cancer in relation to occupational exposure to trichloroethylene. *Occup Environ Med* 1996; 53: 1-5.
11. Axelson O, Seldén A, Andersson K, Hogstedt C. Updated and expanded Swedish cohort study on trichloroethylene and cancer risk. *J Occup Med* 1994; **36:** 556-62.
12. Anttila A, Pukkala E, Sallmén M, Hernberg S, Hemminki K. Cancer incidence among Finnish workers exposed to halogenated hydrocarbons./ *Occup Environ Med* 1995; 37: 797-806. (1995a)
13. Anttila A, Riala R, Pukkala E, Sallmén M, Hernberg S, Hemminki K. *Occupational Exposure to Solvents and Cancer Incidence.* Helsinki, Finland: Finnish Institute of Occupational Health, 1995: 1-74 (in Finnish). [Työntekijoiden liuotinaltistuminen ja syöpäsairaudet. Työterveyslaitos, Helsinki 1995: 1-74.] (1995b)
14. Steward PA, Lee JS, Marano DE, Spirtas R, Forbes CD, Blair A. Retrospective cohort mortality study of workers at an aircraft maintenance facility. II. Exposures and their assessment. *Br J Ind Med* 1991; 48: 531-7.
15. Spirtas R, Stewart PA, Lee JS, *et al.* Retrospective cohort mortality study of workers at an aircraft maintenance facility. I. Epidemiological results. *Br J Ind Med* 1991; **48:** 515-30.
16. Wong O, Morgan R. *Final Report: Historical Prospective Mortality Study of Hughes Aircraft Employees at Air Force Plant No 44.* Alameda, CA (USA): ENSR Health Sciences, 1990.
17. Garabrant DH, Held J, Langholz B, Bernstein L. Mortality of aircraft manufacturing workers in southern California. *Am J Ind Med* 1988; 13: 683-93.
18. Henschler D, Vamvakas S, Lammert M, *et al.* Increased incidence of renal cell tumors in a cohort of cardboard workers exposed to trichloroethene. *Arch Toxicol* 1995; **69:** 291-9.
19. Novotná E, David A, Málek B. An epidemiological study on hepatic tumour incidence in subjects working with trichloroethylene [in Czech]. *Prac Lék* 1979; 31: 121-3.
20. Blair A, Mason TJ. Cancer mortality in United States counties with metal electroplating industries. *Arch Environ Health* 1980; 35: 92-4.
21. Paddle GM. Incidence of liver cancer and trichloroethylene manufacture: joint study by industry and a cancer registry. *Br Med J* 1983; **286:** 846.
22. Shindell S, Ulrich S. A cohort study of employees of a manufacturing plant using trichloroethylene. *J Occup Med* 1985; 27 577-9.
23. Dubrow R, Gute DM. Cause-specific mortality among Rhode Island jewelry workers. *Am J Ind Med* 1987; 12: 579-93.
24. Hernberg S, Korkala ML, Asikainen U, Riala R. Primary liver cancer and exposure to solvents. *Int Arch Occup Environ Health* 1984; 54: 147-53.
25. Hernberg S, Kauppinen T, Riala R, Korkala ML, Asikainen U. Increased risk for primary liver cancer among women exposed to solvents. *Scand J Work Environ Health* 1988; 14: 356-65.
26. Hardell L, Bengtsson NO, Jonsson U, Eriksson S, Larsson LG, Aetiological aspects on primary liver cancer with special regard to alcohol, organic solvents and acute intermittent porphyria – an epidemiological investigation. *Br J*

Cancer 1984; 50: 389-97.
27. Hardell L, Eriksson M, Lenner P, Lundgren E. Malignant lymphoma and exposure to chemicals, especially organic solvents, chlorophenols and phenoxy acids: a case-control study. *Br J Cancer* 1981; **43:** 169-76.
28. Weiss N. Cancer in relation to occupational exposure to perchloroethylene. *Cancer Causes Control* 1995; **6:** 257-66.
29. Ruder AM, Ward EM, Brown DP. Cancer mortality in female and male dry-cleaning workers. *J Occup Med* 1994; **36:** 867-74.
30. Blair A, Stewart PA, Tolbert PE, *et al.* Cancer and other causes of death among a cohort of dry cleaners. *Br J Ind Med* 1990; **47**: 162-8.
31. Olsen GW, Hearn S, Cook RR, Currier MF, Allen S. Mortality experience of a cohort of Louisiana chemical workers. *J Occup Med* 1989; **31:** 32-4.
32. Wilcosky TC, Checkoway H, Marshall EG, Tyroler HA. Cancer mortality and solvent exposures in the rubber industry. *Am Ind Hyg Assoc J* 1984; **45:** 809-11.
33. Pippard EC, Acheson ED. The mortality of boot and shoe makers, with special reference to cancer. *Scand J Work Enwiron Health* 1985; **11:** 249-55.
34. Ott MG, Carlo GL, Steinberg S, Bond GG. Mortality among employees engaged in chemical manufacturing and related activities. *Am J Epidemiol* 1985; 122: 311-22.
35. Hearne FT, Pifer JW, Grose F. Absence of adverse mortality effects in workers exposed to methylene chloride: an update. *J Occup Med* 1990; **32:** 234-40.
36. Lanes SF, Rothman KJ, Dreyer NA, Soden KJ. Mortality update of cellulose fiber production workers. *Scand J Work Environ Health* 1993; **19:** 426-8.
37. Shannon HS, Haines T, Bernholz C, *et al.* Cancer morbidity in lamp manufacturing workers. *Am J Ind Med* 1988; **14:** 281-90.
38. Cragle DL, Wells SM, Tankersley WG. An occupational morbidity study of a population potentially exposed to epoxy resins, hardeners, and solvents. *Appl Occup Environ Hyg* 1992; 7: 826-34.
39. Sinks T, Lushniak B, Haussler BJ, *et al.* Renal cell cancer among paperboard printing workers. *Epidemiology* 1992; **3**: 483-9.
40. International Agency for Research on Cancer. *Chlorinated Drinking Water, Chlorination By-products, Some Other Halogenated Compounds, Cobalt and Cobalt Compounds.* Lyon, France: IARC, 1991; *IARC Monogr Eval Carcinog Risks Humans,* Vol. 52.
41. Morris RD, Audet A-M, Angelillo IF, Chalmers TC, Mosteller F. Chlorination, chlorination by-products, and cancer: A meta-analysis. *Am J Public Health* 1992; **82:** 955-63.
42. International Agency for Research on Cancer. *Some Industrial Chemicals and Dyestuffs.* Lyon, France: IARC, 1982; *IARC Monogr Eval Carcinog Risks Humans,* Vol. 29.
43. Paxton MB, Chinchilli VM, Brett SM, Rodricks JV. Leukemia risk associated with benzene exposure in the Pliofilm cohort: I. Mortality update and exposure distribution. *Risk Analysis* 1994; **14:** 147-54.
44. Wong O. Risk of acute myeloid leukaemia and multiple myeloma in workers exposed to benzene. *Occup Environ Med* 1995; 52: 380-4.
45. Yin SN, Hayes RB, Linet MS, Li GL, *et al.* A cohort study of cancer among benzene exposed workers in China: Overall results. *Am J Ind Med* 1996; 29: 227-35.
46. European Union. *Council Directive* 85/210/EEC of 20 March 1985 on the harmonization of legislation on lead content in gasoline.
47. Rinsky RA, Smith AB, Hornung R, *et al.* Benzene and leukemia. An epidemiologic risk assessment. N *Engl J Med* 1987; **316:** 1044-50.
48. Paxton MB, Chinchilli VM, Brett SM, Rodricks JV. Leukemia risk associated with benzene exposure in the Pliofilm cohort. II. Risk estimates. *Risk Anal* 1994; **14:** 155-61.
49. International Agency for Research on Cancer. *Wood, Leather and Some Associated Industries.* Lyon, France: IARC, 1981; *IARC Monogr Eval Carcinog Risks Humans,* Vol. 25.
50. McMichael AJ, Spirtas R, Kupper LL, Gamble JF. Solvent exposure and leukemia among rubber workers: an epidemiologic study. *J Occup Med* 1975; **17:** 234-9.
51. Greene MH, Hoover RN, Eck RL, Fraumeni JF Jr. Cancer mortality among printing plant workers. *Environ Res* 1979; **20:** 66-73.
52. Thomas TL, Waxweiler RJ. Brain tumors and occupational risk factors. *Scand J Work Environ Health* 1986; **12:** 1-15.
53. Wong O. A cohort mortality study of employees exposed to chlorinated chemicals. *Am J Ind Med* 1988; 14: 417-31.
54. Partanen T, Heikkila P, Hernberg S, Kauppinen T, Moneta G, Ojajärvi A. Renal cell cancer and occupational exposure to chemical agents. *Scand J Work Environ Health* 1991; **17:** 231-9.
55. Lagorio S, Forastiere F, Iavarone I, Vanacore N, Fuselli S, Carere A. Exposure assessment in a historical cohort of filling station attendants. *Int J Epidemiol* 1993; **22(Suppl 2)**: S51-6.
56. Miller BA, Blair A, Reed EJ. Extended mortality follow-up among men and women in a U.S. furniture workers union. *Am J Ind Med* 1994; **25:** 537-49.
57. Kauppinen T, Partanen T, Degerth R, Ojajärvi A. Pancreatic cancer and occupational exposures. *Epidemiology* 1995; **6:** 498-502.
58. Chen R, Seaton A. A meta-analysis of mortality among workers exposed to organic solvents. *Occup Med* 1996; **46:** 337-44.
59. Woods JS, Polissar L, Severson RK, Heuser LS, Kulander BG. Soft tissue sarcoma and non-Hodgkin's lymphoma in relation to phenoxyherbicide and chlorinated phenol exposure in Western Washington. *JNCI* 1987; **78:** 899-910.
60. Olsson H, Brandt L. Risk of non-Hodgkin's lymphoma among men occupationally exposed to organic solvents. *Scand J Work Environ Health* 1988; **14:** 246-51.
61. Persson B, Dahlander AM, Fredriksson M, Noorlind Brage H, Ohlson CG, Axelson O. Malignant lymphomas and occupational exposures. *Br J Ind Med* 1989; **46:** 516-20.
62. Scherr PA, Hutchison GB, Neiman RS. Non-Hodgkin's lymphoma and occupational exposure. *Cancer Res* 1992; **52(Suppl)**: 5503s-9s.
63. Persson B, Fredriksson M, Olsen K, Boeryd B, Axelson O. Some occupational exposure as risk factors for malignant lymphomes. *Cancer* 1993; **72:** 1773-8.
64. La Vecchia C, Negri E, D'Avenzo B, Franceschi S. Occupation and lymphoid neoplasms. *Br J Cancer* 1989; **60:** 385-8.
65. D'Amore F, Hasle H, Hansen KS. Occupational exposures and non-Hodgkin's lymphoma. *Hematol Rev* 1992; **6:** 183-99.
66. Olsson H, Brandt L. Occupational exposure to organic

solvents and Hodgkin's disease in men. *Scand J Work Environ Health* 1980; 6: 302-5.
67. Flodin U, Andersson L, Anjou CG, Palm UB, Vikrot O, Axelson O. A case-referent study on acute myeloid leukemia, background radiation and exposure to solvents and other agents. *Scand J Work Environ Health* 1981; 7: 169-78.
68. Svensson BG, Nise G, Englander V, Attewell R, Skerfving S, Möller T. Deaths and tumours among rotogravure printers exposed to toluene. *Br J Ind Med* 1990; 47: 372-9.
69. Walker JT, Bloom TF, Stern F, Okun AH, Fingerhut MA, Halperin WE. Mortality of workers employed in shoe manufacturing. *Scand J Work Environ Health* 1993; 19: 89-95.
70. Carpenter AV, Flanders WD, Frome EL, Tankersley WG, Fry SA. Chemical exposures and central nervous system cancers: A case-control study among workers at two nuclear facilities. *Am J Ind Med* 1988; 13: 351-62.
71. Berlin K, Edling C, Persson B, *et al*. Cancer incidence and mortality of patients with suspected solvent-related disorders. *Scand J Work Enwiron Health* 1995; 21: 362-7.
72. Miller BA, Silverman DT, Hoover RN, Blair A. Cancer risk among artistic painters. *Am J Ind Med* 1986; 9: 281-7.
73. Gubéran E, Usel M, Raymond L, Tissot R, Sweetnam PM. Disability, mortality, and incidence of cancer among Geneva painters and electricians: a historical prospective study. *Br J Ind Med* 1989; 46: 16-23.
74. Bethwaite PB, Pearce N, Fraser J. Cancer risks in painters: study based on the New Zealand Cancer Registry. *Br J Ind Med* 1990; 47: 742-6.
75. Skov T, Weiner J, Pukkala E, Malker H, Andersen A, Lynge E. Risk for cancer of the pharynx and oral cavity among male painters in the Nordic countries. *Arch Enwiron Health* 1993; 48: 176-80.
76. Pukkala E. *Cancer Risk by Social Class and Occupation. A Survey of 109,000 Cancer Cases among Finns of Working Age. Contributions to Epidemiology and Biostatistics*. Basel, Switzerland: Karger, 1995: Vol. 7.
77. Terstegge CW, Swaen GM, Slangen JJ, van Vliet C. Mortality patterns among commercial painters in the Netherlands. *Occup Environ Health* 1995; 1: 303-10.
78. Lindquist R, Nilsson B, Eklund G, Gahrton G. Increased risk of developing acute leukemia after employment as a painter. *Cancer* 1987; 60: 1378-84.
79. McMichael AJ, Spirtas R, Gamble JF, Tousey PM. Mortality among rubber workers: relationship to specific jobs. *J Occup Med* 1976; 18: 178-85.
80. Meinhardt TJ, Lemen RA, Crandall MS, Young RJ. Environmental epidemiologic investigation of the styrene-butadiene rubber industry. *Scand J Work Enwiron Health* 1982; 8: 250-9.
81. Matanoski GM, Santos-Burgoa C, Schwartz L. Mortality of a cohort of workers in the styrene-butadiene polymer manufacturing industry (1943-1982). *Enwiron Health Perspect* 1990; 86: 107-17.
82. Bond GG, Bodner KM, Olsen GW, Cook RR. Mortality among workers engaged in the development or manufacture of styrene-based products – an update. *Scand J Work Enwiron Health* 1992; 18: 145-54.
83. Nicholson WJ, Selikoff IJ, Seidman H. Mortality experience of styrene-polystyrene polymerization workers. *Scand J Work Enwiron Health* 1978; 4(Suppl 2): 247-52.
84. Hodgson JT, Jones RD. Mortality of styrene production, polymerization and processing workers at a site in northwest England. *Scand J Work Environ Health* 1985, 11: 347-52.
85. Okun AH, Beaumont JJ, Meinhardt TJ, Crandall MS. Mortality patterns among styrene-exposed boatbuilders. *Am J Ind Med* 1985; 8: 193-205.
86. Coggon D, Osmond C, Pannett B, Simmonds S, Winter PD, Acheson ED. Mortality of workers exposed to styrene in the manufacture of glass-reinforced plastics. *Scand J Work Environ Health* 1987; 13: 94-9.
87. Wong O, Trent LS, Whorton MD. An updated cohort mortality study of workers exposed to styrene in the reinforced plastics and composites industry. *Occup Environ Med* 1994; 51: 386-96.
88. Kogevinas M, Ferro G, Andersen AA, *et al*. Cancer mortality in a historical cohort study of workers exposed to styrene. *Scand J Work Enwiron Health* 1994; 20: 251-61.
89. Kolstad HA, Lynge E, Olsen J, Breum N. Incidence of lymphohematopoietic malignancies among styrene-exposed workers of the reinforced plastics industry. *Scand J Work Environ Health* 1994; 20: 272-8.
90. Kolstad HA, Juel K, Olsen J, Lynge E. Exposure to styrene and chronic health effects: mortality and incidence of solid cancers in the Danish reinforced plastics industry. *Occup Environ Med* 1995; 52: 320-7.
91. Kolstad HA. *Styrene and Chronic Diseases* [in Danish]. Arhus, Denmark: Institut for Epidemiologi og Socialmedicin, Kræftens Bekæmpelse, 1995; Rapport nr. 13.