Vinyl Chloride: Still a Cause for Concern

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Vinyl chloride (VC) is both a known carcinogen and a regulated chemical, and its production capacity has almost doubled over the last 20 years, currently 27 million tons/year worldwide. According to recent reports it is still a cause for concern. VC has been found as a degradation product of chloroethylene solvents (perchloroethylene and trichloroethylene) and in landfill gas and groundwater at concentrations up to 200 mg/m^3 and 10 mg/L, respectively. Worldwide occupational exposure to VC still seems to be high in some countries (e.g., averages of approximately 1,300 mg/m^3 until 1987 in one factory), and exposure may also be high in others where VC is not regulated. By combining the most relevant epidemiologic studies from several countries, we observed a 5-fold excess of liver cancer, primarily because of a 45-fold excess risk from angiosarcoma of the liver (ASL). The number of ASL cases reported up to the end of 1998 was 197 worldwide. The average latency for ASL is 22 years. Some studies show a small excess risk for hepatocellular carcinoma, and others suggest a possible risk of brain tumors among highly exposed workers. Lung cancer, lymphomas, or leukemia do not seem to be related to VC exposure according to recent results. The mutation spectra observed in rat and human liver tumors (ASL and/or hepatocellular carcinoma) that are associated with exposure to VC are clearly distinct from those observed in sporadic liver tumors or hepatic tumors that are associated with other exposures. In rats, the substitution mutations found at A:T base pairs in the *ras* and *p53* genes are consistent with the promutagenic properties of the DNA adduct 1,N^6-ethenoadenine formed from VC metabolites. Risk assessments derived from animal studies seem to overestimate the actual risk of cancer when comparing estimated and reported cases of ASL. *Key words:* angiosarcoma of the liver (ASL), landfill leachate, liver cancer, occupational exposure, risk assessment, vinyl chloride. *Environ Health Perspect* 108:579–588 (2000). [Online 2 June 2000]
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Vinyl chloride (VC) is one of the best-studied chemicals. Because of evidence that VC was carcinogenic in both animal studies and in human case reports in the early 1970s, there were drastic changes in the production methods and in occupational hygiene in the VC/polyvinyl chloride (PVC) industry in the Western World, with the closure of some factories that were not able to conform to the strict regulations and occupational exposure limits. VC levels in PVC resins and products were also restricted. As a result of the strict occupational exposure limits, no cases of angiosarcoma of the liver (ASL), the rare tumor associated with VC exposure, have been reported in new workers exposed to VC in those factories since that time. It seemed that the VC problem had been solved and the story committed to the toxicologic history books. But recent epidemiologic, environmental, and biomechanistic findings have opened up new aspects of this chemical. VC has recently been evaluated by an international interdisciplinary task group; this paper highlights these recent developments, which are presented in more detail in the International Programme on Chemical Safety (IPCS) Environmental Health Criteria document on VC (*1*). VC remains a cause for concern because potential exposure to this chemical and new cases of ASL are still being reported.

Historical Background

VC was first used commercially in the 1920s, but it was not until the 1930s that techniques were devised to polymerize VC into stable forms of PVC. Polymerization is a batch process and takes place in a reactor (autoclave) under controlled conditions. Once the polymerization has ended, VC is emptied into degassing tanks. The reactor has to be cleaned periodically because a film of PVC forms on the inside wall of the reactor. Although this is now performed with solvents or automatic high-pressure jets, previously this task was a manual process requiring workers to use spatulas or hammers and chisels; the workers were exposed to high concentrations of VC up to 1,000 ppm (2,600 mg/m^3) and possibly even higher peaks of exposure. As a result, some of these workers suffered from a specific pathologic syndrome called "vinyl chloride disease," with symptoms including earache and headache, dizziness, unclear vision, fatigue and lack of appetite, nausea, sleeplessness, breathlessness, stomachache, pain in the liver/spleen area, pain and tingling sensation in the arms/legs, cold sensation at the extremities, loss of libido, and weight loss (*2*). Clinical findings included scleroderma-like changes in the fingers, with subsequent bony changes in the tips of the fingers described as acro-osteolysis; peripheral circulatory changes similar to Raynaud's phenomenon; and enlargement of the liver and spleen, with a specific histologic appearance and respiratory manifestations (*3–6*).

After the case series on hepatic angiosarcoma among workers exposed to vinyl chloride (*7*) was published in 1974, several further case series and small epidemiologic studies, primarily with emphasis on hepatic tumors, were published in the 1970s and 1980s (*8–28*). These reports showed that exposure to high levels of VC were associated with the incidence of ASL. Other (non-ASL) cancer sites and types that may be connected with VC exposure include tumors of the liver (e.g., non-angiosarcoma), particularly hepatocellular carcinoma; respiratory system; digestive system other than the liver; lymphopoietic and hematopoietic tissue; brain and other central nervous system; and malignant melanoma.

Parallel to human case reports, after the first reports of the carcinogenicity of VC in rats (*29,30*), extensive studies were carried out in the rat, mouse, and hamster on the effects of oral (*31–33*) and inhalation (*34–37*) exposure to VC. These studies have shown that VC is both genotoxic and carcinogenic, causing a wide spectrum of tumors in various

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animal species. Tumors that have been been found, at least in animal species, include ASL and other liver tumors, mammary gland carcinoma, neuroblastoma, nephroblastoma, forestomach and lung tumors, and Zymbal gland tumor. Non-neoplastic effects include reduced body weight and increased relative spleen weight, hepatocellular degeneration, proliferation of cells lining the liver sinusoids, degenerative alteration in the testis, tubular nephrosis, and focal degeneration of the myocardium in rats (*38,39*).

New Aspects of VC

Production

VC has a world capacity of about 27 million tons/year worldwide, almost double the production in 1980 (Table 1), and is produced in most industrial countries. Five percent of this VC goes into the production of chlorinated solvents, primarily 1,1,1-trichloroethane (10,000 tons/year). Most (95%) VC produced is further polymerized under varying conditions to produce PVC.

VC Environmental Contamination and Remediation

Reports from several countries (*43–59*) recently showed high levels of VC contamination in soil, groundwater, aquifers, and wells near landfill and industrial waste disposal sites that were not located near VC/PVC production facilities. VC concentrations were up to 12 mg/L in some groundwater samples and up to 230 mg/m^3 in landfill gas samples (Table 2). VC can be formed microbially, under anaerobic conditions, from the reductive dehalogenation of the more highly chlorinated chloroethenes: perchloroethylene (PCE), trichloroethene (TCE), and the dichloroethene isomers, *cis*-1,2-dichloroethene (*cis*-1,2-DCE), *trans*-1,2-DCE, and 1,1-DCE (Figure 1) (*59–62*). PCE and TCE are used as industrial solvents for degreasing and cleaning metal parts and electronic components and in dry cleaning. Careless handling, storage, and disposal, as well as the high chemical stability of these compounds, have made them, and consequently VC, some of the most frequently encountered groundwater contaminants. Although VC may be further degraded to less and nonchlorinated ethenes and possibly finally to carbon dioxide and ethane, this proceeds at a slow rate under highly reducing conditions (*63–65*); as a consequence, there can be a build-up of VC in landfills and surrounding areas.

Several field studies of PCE/TCE-contaminated landfill sites and aquifers (*61,66–70*) have shown that, under specific conditions, PCE and TCE can be intrinsically biodegraded anaerobically to ethene by indigeneous methanogenic, acetogenic, and sulphate-reducing bacteria. Also, under aerobic conditions there is a potential for direct or cometabolic oxidation of DCE and VC. Because each site has individual conditions (e.g., the presence of other solvents such as acetone and methanol), the degradation rates cannot be directly compared. In one study, half-lives of 1–2 years have been estimated for each stage in the reaction chain (e.g., DCE to VC; VC to ethene) (*49*). In general, except under specific conditions, there is little biodegradation of VC.

The awareness of this problem of VC formation has encouraged the development of *in situ* bioremediation of chlorinated solvents and VC using anaerobic or aerobic cometabolic processes (*72–74*).

Several laboratories are now attempting to isolate strains of bacteria that can completely dehalogenate *cis*-DCE or VC to ethene. Although no known microorganism can aerobically destroy PCE, some anaerobic bacteria (e.g., *Dehalobacter restrictus*) use these chlorinated solvents as electron acceptors for energy conservation and growth (dehalorespiration), by breaking them down in the process to form *cis*-dichloroethene, although restricted diet and conditions are necessary (*75,76*). A coccoid bacterium has been isolated (provisionally named *Dehalococcoides ethenogenes* strain 195) that, together with extracts from mixed microbial cultures, can dechlorinate PCE to form *cis*-DCE and remove other chlorine atoms to form vinyl chloride and finally ethene (*77*). Meier (*78*) reported that quantitative mineralization of VC was possible with isolated aerobic cultures of *Mycobacterium aurum* under special conditions.

General Population Exposure

Exposure of the general population to VC is possible by several routes: inhalation of air polluted with VC, mainly in the vicinity of VC/PVC plants or waste disposal sites; intake of contaminated drinking water; ingestion of food, beverages, and medicaments packed in PVC; and absorption through skin from PVC-wrapped cosmetics. Normally, the general population is exposed, if at all, to only small amounts of VC. However, the exposure varies depending on the regulatory measures of each country, the occurrence of accidents, or the spread of precursor substances.

After an accident in Schönebeck, Germany, in June 1996, which involved the derailment of a train carrying VC and the subsequent fire, 325 persons were documented as having acute symptoms, but these correlated with exposure to the pyrolytic products (e.g., hydrochloric acid) and not to VC itself. Over 1,000 tons of VC were involved, of which approximately 250 tons burned and 350 tons were reclaimed after the fire. One hundred fifty tons of HCl were released (*79*). According to measurements first taken 14 hr after the fire, the maximum concentrations of VC were approximately 80 mg/m^3 near the train and 25 mg/m^3 at 200 m from the center of the fire (*80*). In a study of 29 individuals exposed as a result of this accident, there was a significant increase in chromosomal abberrations as compared to an unexposed control group (*81*).

With the improvement in industrial hygiene and stricter emission controls in many countries, the general population is not usually exposed to emissions from VC and PVC production facilities, but there are exceptions. For example, Zhao et al. (*82*) reported that, in China, workers and their families were exposed to VC because the dormitories were near or even on the campus of the PVC/VC plant. In 1988, maximum and mean daily concentrations of 12.7 and

Table 1. World PVC[a] production/capacity 1980–1998.

Region	Production/capacity in 1,000 tons/year				
	1980[b]	1985[b]	1990[b]	1995[c]	1998[d]
World capacity	16,000	17,000	20,700	26,400	~27,000
Production	11,750	14,200	18,300		
North America total	3,200	3,390	4,700	6,070	
Suspension and mass	2,810	2,990			
Vinyl acetate copolymer	200	210			
Emulsion	190	190			
Western Europe total	3,900	4,330	4,800	5,750	~ 5,600
Suspension and mass	33,350	3,700			
Vinyl acetate copolymer	130	130			
Emulsion	420	500			
Eastern Europe	925	1,100	1,200	2,700[e]	
Soviet Union	370	700	760		
Japan	1,400	1,550	2,070	8,200[f]	
Southeastern Asia	330	600	900		
People's Republic of China	150	400	790		
South America	400	540	780		
Rest of World	1,075	1,590	2,300	3,680	

[a]Approximate VC production/capacity. [b]Data from Allsopp and Vianello (*40*). [c]Data from Rehm and Werner (*41*). [d]Personal communication, European Council of Vinyl Manufacturers (*42*). [e]Including the former Soviet Union. [f]Total for Asia.

4.4 mg/m^3, respectively were measured in dormitories 50 m away from the plant (*82*).

Occupational Exposure Levels

Industrial environments associated with VC exposure include VC production plants, VC polymerization (PVC production) plants, and PVC processing factories. For example, the number of workers exposed to VC has been estimated to be approximately 80,000 in the United States (1981–1983) (*83*) and > 5,000 in Sweden (1975–1980) (*84*). Because VC was not recognized as a toxic compound at the beginning of VC/PVC production in the United States and Western Europe, no precautions were taken against contact and no regular workplace monitoring was performed. Therefore, only sporadic measurements or retrospective estimates of exposures are available for the period before 1975 (Table 3). Some VC workers, autoclave cleaners in particular, were estimated to be exposed to as much as 1,000 ppm (2,600 mg/m^3) in the 1950s and earlier (*85–89*). The exposure was reduced to one-tenth of this by the mid-1970s. After 1975, levels were usually < 1–5 ppm (< 2.6–13 mg/m^3) in many countries.

In many countries, factories that could not reduce the emissions of VC to satisfy the rigorous laws in the early 1970s were forced to close. In other countries, this was not possible for socioeconomic reasons; thus, large factories with old-fashioned technologies continued the manufacturing process (*90*) and workers continued to be exposed to high levels of VC (Table 4).

Recent data from Croatia may reflect the actual conditions still prevalent in some countries. A retrospective investigation of the exposure to VC has been performed in 37 autoclave workers in Split, Croatia, who were maximally exposed to the emission of VC by the nature of their job (emptying and cleaning) in a suspension polymerization plant. The investigation covered the period from 1969 to 1987, after which the factory was closed due to the high emission of VC. Data show that the 37 workers were exposed over this period to average VC concentrations of approximately 500 ppm (1,300 mg/m^3) (*90,92*). As a consequence of this high exposure to VC, a disproportionately large number of ASL mortalities have been reported in Croatia (Table 5).

Angiosarcoma of the Liver

ASL, also known as hemangioendothelial sarcoma, is an extremely rare liver tumor and is difficult to diagnose. ASL constitutes only 2% of all primary tumors of the liver in the general population; for example, from 1975–1987 figures in England and Wales, there was an annual incidence of 1.4 cases/10 million people (*101*). ASL has been associated only with exposure to VC, Thorotrast (a

Table 2. Vinyl chloride found in landfill/waste disposal sites as a gas, in leachate, and in groundwater formed probably from degradation of higher chloroethenes.

Sample	Place of sampling	Measure	Concentrations	Reference
Landfill gas	United States: 2 landfills	Maximum Average	230 mg/m^3 34 mg/m^3	(*43*)
Landfill gas	United Kingdom: landfill Plume, 100 m from boundary due to subsurface migration (1991)	Maximum concentration	11 mg/m^3 40 mg/m^3	(*44*)
Landfill gas	Braunschweig, Germany: landfill	Mean	9 mg/m^3	(*45*)
Gas effluents	Berlin, Germany: garbage dump		0.27 mg/m^3	(*46*)
Gas	Germany Industrial landfill; Municipal landfill	Average	 41 mg/m^3; 10 mg/m^3	(*47*)
Gas	Germany, landfill	Range	0.03–0.3 mg/m^3	(*48*)
Landfill gas	United Kingdom, 7 waste disposal sites	Range	< 0.1–87 mg/m^3	(*49*)
Soil air	Germany, solvent waste sites	3 Highest samples of 200	128 mg/m^3; 47 mg/m^3; 5 mg/m^3	(*50*)
Leachate	Wisconsin: municipal solid waste site (1982)	Range	61 µg/L	(*51*)
Leachate	U.S. sites established before 1980 (6 chosen sites)	Range	8–61 µg/L	(*52*)
Groundwater	Germany, contaminated water	Range Range	< 5–460 µg/L 15–1,000 µg/L	(*53*)
Groundwater (wells)	Germany, solvent waste site	3 Highest samples of 200	1,000 µg/L 500 µg/L 200 µg/L	(*50*)
Groundwater	Germany	Maximum	120 µg/L	(*54*)
Groundwater	Santa Clara Valley, California (near plants manufacturing electronic equipment, which use significant amounts of chlorinated solvents)	Range	50–500 µg/L	(*55*)
Groundwater	Germany: 136 samples from down-gradient wells of 100 waste disposal sites	Maximum Mean	12,000 µg/L 1,694 µg/L	(*56*)
Groundwater	Michigan: sand aquifer near industrial site; concentration increased with depth consistent with methane	Maximum	> 5 µg/L at 10m 56,400 µg/L at 23m	(*57*)
Outwash aquifer	Canada: Gloucester landfill (1988)	Range	< 1–40 µg/L	(*58*)

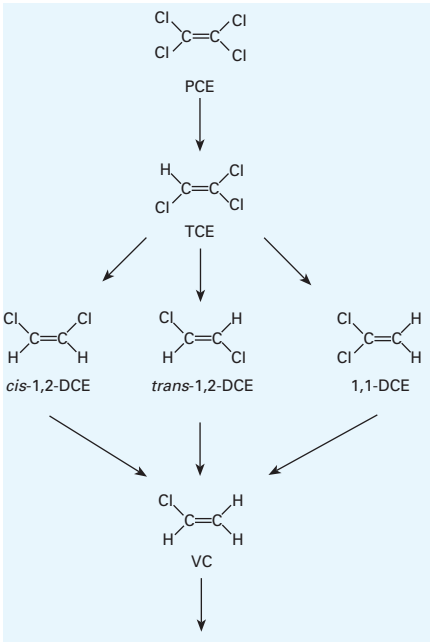

Figure 1. Microbial degradation of chlorinated ethenes to form vinyl chloride.

Table 3. Retrospective estimates of daily occupational exposures to vinyl chloride before 1975.

Country/period	VC exposure (mg/m^3)	References
Germany		
"First years"	> 2,600	(*85*)
Before 1971	1,300	
1971	260	
1974	5.2–7.8	
United Kingdom		
1945–1955	2,600	(*86–88*)
1955–1960	1,040–1,300	
1960–1970	780–1,040	
Mid-1973	390	
1975	13	
United States		
1945–1955	2,600	(*89*)
1955–1970	780–1,300	
1970–1974	260–520	
1975	< 2.6–13	

Exposure levels during autoclave cleaning may have been as high as 7,800 mg/m^3 (*86*).

contrast medium used in X-ray radiography in the 1930s–1950s), and arsenic (*7,102*). There are only a few instances where the diagnosis of a rare tumor enables the identification of a risk without having to rely on large epidemiologic studies. Furthermore, cases of ASL in VC workers could be directly attributable to exposure to VC. Regular international surveillance of cases of ASL from VC exposure shows that 118 cases were registered in 1985 (*103*), 173 in 1993 (*104*) and 197 up to the end of 1999 (*105*) (Table 5). The average latent period between starting work in an occupation involving VC exposure and the ASL diagnosis or death for 99 cases was 22 years (*87,106*). Because of this long latency, tumors are still detected although the exposure has ceased or has been considerably reduced. ASL seems to be associated only with high exposure to VC.

Abdominal pain, weakness, fatigue, and weight loss are the most prominent clinical symptoms, and hepatosplenomegaly, ascites, and jaundice are the most common clinical signs. Remarkably, except for the final stages, there seems to be little impairment of hepatic function in ASL patients (*106*). Any treatment is generally unsuccessful, and survival after diagnosis usually averages < 12 months. Hepatic failure and intra-abdominal hemorrhage are the usual terminal effects (*104,107*). Liver transplantation might be the only chance of survival (*108*). Surgical resection and adjuvant chemotherapy have been suggested if ASL is detected early enough (*109–111*).

Epidemiologic Studies on VC/PVC Workers

From the data on health surveillance and mortality records of VC workers and the easy correlation of ASL with VC exposure, there have been numerous case reports, cohort studies, and epidemiologic studies on VC/PVC workers from many countries. But because there are only estimates of levels of VC exposure before the mid-1970s, there are not enough data in many cases to estimate an exposure–response relationship.

Two larger studies combined earlier studies from the United States (*112*) and Europe (*113*) and updated the mortality follow-up. These studies have been or are currently being updated again (*114,115*).

Wong et al. (*112*) updated earlier U.S. studies (*8,9*) and subsumed others (*10–15*). The cohort included 10,173 men who had worked for at least 1 year in jobs involving VC exposure in 37 plants in the United States before January 1973. The observation covered 1942–1982, and the authors compared the observed mortality to the expected rates, based on U.S. national rates for white males, standardized for age, and calendar time. In an attempt to characterize historical exposures, Wong et al. (*112*) graded individual jobs and job locations by each company as "high," "medium," or "low"; this approach failed because of differences of interpretation of the terms into parts-per-million levels. The actual levels of exposure are not known.

The second large cohort study, by Simonato et al. (*113*), updated several earlier European cohorts (*16–22,96*), and comprised a total of 14,351 subjects from 19 factories. After exclusion of short-term employees (< 1 year), females, deaths outside the observation period, and members of more than one cohort, 12,706 subjects remained for the analysis. The follow-up was 97.7% complete, and the average length of follow-up was 17 years, giving a total number of 222,746 person-years. National rates of mortality, specific for age and 5-year calendar periods were used

Table 4. Occupational exposure: reported levels of vinyl chloride in workplace air samples in VC/PVC production plants.

Country	Workplace	Year	Concentrations reported[a] (mg/m^3)	Reference
China	PVC production plant	Not specified	30–210	(*91*)
Croatia	Plastic industry	Not specified	Mean = 13, occasional peak = 5,200	92
Croatia	VC/PVC plant	1949–1987	Mean = 543, occasional peak =1,300	(*90,93*)
Egypt	VC/PVC plant	Not specified	8-hr TWA = 0.05–18	(*94*)
Finland	PVC production plant,	1981–1985	< 0.3–57	(*95*)
	breathing zone	1986–1989	< 0.3–46	
	concentrations (TWA)	1993	< 0.3–26	
Italy	VC/PVC plants	1950–1985	< 13 – ≥ 1300	(*96*)
Poland	VC/PVC plants	1974	Geometric mean = 990	(*97*)
	(autoclave cleaners)	1982	9–180	
Poland	Breathing zone of VC	1986	21.3	(*98*)
	synthesis mechanic	1987	66.9	
		1988	43.7	
		1989	0.7	
		1990	0.2	
Russia	VC/PVC plant			(*99*)
	16 Probes (whole plant)	1990–1993	Range of annual means = 1–9	
	Under the reactor	1990–1993	Range of annual means = ≤ 200	
	In compressor room	1990–1993	Range of annual means = ≤400	
Taiwan	PVC plants (n = 5)	Not specified		(*100*)
	15 Operation units		Range = 0.13 (ND)–1,009 (n = 114)	
	Area measurements (e.g.,		Range = 6–1,009; mean = 296;	
	outside reaction tank)		median = 86 (n = 4)	
	Personal measurements		Range = (n = 85): ND–3,680	
	(TWA): 15 job titles			
	Tank supplier		Range = 5.7–3,680	
			(mean = 660; median = 24)	
	Tank cleaner		Range = 0.36–342 (n = 14)	

Abbreviations: ND, not determined; TWA, time-weighted average.
[a]1 ppm = 2.6 mg/m^3.

Table 5. Number of vinyl chloride-associated ASL cases reported per country.

Country	Cases to 1985[a]	Cases to 1993[b]	Cases to 1999 (changes since 1993)[c]
United States	35	44	50 (+6)
Germany	26 (West)	41	40 (-1)
France	18	28	31 (+3)
United Kingdom	9	20	21 (+1)
Canada	10	13	13
Croatia	4	4	12 (+8)
Slovakia	2	2	6 (+4)
Italy	4	8	8
Sweden	5	5	5
Japan	2	3	4 (+1)
Belgium	2	2	2
Norway	1	1	1
Spain		1	1
Australia		1	1
Brazil			1 (+1)
Israel			1 (+1)
Total[d]	118	173	197

[a]From Forman et al. (*103*). [b]From Lee et al. (*104*). [c]Association of Plastics Manufacturers in Europe (*105*). [d]There is no information regarding ASL cases from several countries known to be producers of PVC, and some plants have contributed disproportionately to the total.

for the comparison. The observation period was different for different factories. In most cases, the observation period began in 1955 and extended to 1986. Calendar period-specific job exposure matrices were developed for 13 of the 19 factories. These job exposure matrices were developed using the job title as basic unit in which exposure was assessed. Estimates of exposure were assigned *a priori* by a group of industrial hygienists on the basis of the historical information available from the companies.

Four smaller prospective studies on VC exposure workers have been conducted in Canada (*23*), Germany (*24,25*), France (*26,27*) and the former Soviet Union (*28*).

IPCS Task Group Findings

The IPCS Task Group (*1*) reported that "there is a 5-fold excess risk for liver cancer observed among workers exposed to VC"; this occurs primarily in PVC polymerization factories, where the highest exposures to VC occur (Table 6). Much of the excess risk can be attributed to the excess risk for ASL. In the European study, Simonato et al. (*113*) found a 45-fold excess risk for ASL in workers exposed to VC > 10,000 ppm-years as compared to workers exposed to < 2,000 ppm-years (Table 7). In the European study, there was histopathologic confirmation of type of liver cancer for 17 out of 24 liver cancers; of those confirmed, 16 were ASL. In the U.S. study, Wong et al. (*112*) registered 21 out of 37 liver cancer deaths as ASL. In the Canadian study, Thériault and Allard (*23*) reported that all 8 of the liver cancer deaths were ASL; this was also the case for the 3 liver cancer deaths reported in the French study by Laplanche et al. (*27*). There is no information about whether liver cancers were ASL in the German study by Weber et al. (*24*), and in the Russian study, Smulevich (*28*) reported no diagnosed liver cancers. Some ASL cases in VC-exposed workers have probably remained undiagnosed; the causes of these deaths may have been recorded on death certificates as unspecified liver cancers or other liver-associated disease.

The risk for hepatocellular carcinoma (HCC) was examined in several studies. Simonato et al. (113), Thériault and Allard (*23*), and Laplanche et al. (*27*) did not observe an excess risk of HCC, whereas data from Wong et al. (*112*) in the United States and from updates of the Italian component of the European cohort (*116,117*) seem to indicate that there is an excess risk for HCC. The risk for HCC is not as great as the risk for ASL. It is difficult to interpret the results of these studies for HCC because of the possible inaccuracies of diagnoses of angiosarcoma and HCC based on death certificate information and because of the lack of histopathologic confirmation of liver cancer diagnoses. The IPCS Task Group (*1*) has determined that "although the results are not fully consistent between studies, the data suggest that there may be a small excess risk for HCC."

The IPCS Task Group (*1*) also reported that

> Four out of five studies reporting results for brain tumours identified a moderate excess risk with [a standard mortality ratio] of 1.42 for the combined data from 5 studies (43 observed, 95% CI [confidence interval], 1.03–1.91).

The risk for brain tumors tended to increase with duration of exposure and employment in the European (*113*) and U.S. (*112*) studies. Furthermore, in the U.S. study, Wong et al. (*112*) reported that the highest risk occurred in the two factories where the most ASL cases had been diagnosed; these were the factories where the highest VC exposure was presumed to have occurred. In the European

Table 6. Summary of findings on selected neoplasms for the epidemiologic studies on workers in PVC polymerization plants.

Cause of mortality	European study (*113*)	U.S. study (*112*)	German study (*24*)	Russian study (*28*)	Canadian study (*23*)	French study (*27*)	All studies[a]
All causes							
Obs/Exp	1,438/1,636.4	1,536/1,705.27	414/434.7		59/71.07	40/43[b]	
SMR	0.88	0.9	0.95		0.83	1.0	
CI	(0.83–0.93)	(0.86–0.95)				(0.6–1.5)	
All malignant neoplasms							
Obs/Exp	445/427.8	359/341.7	79/82.9	63/58.88	20/16.37		966/927.65
SMR	1.04	1.05	1.03[c]	1.07	1.22	1.3	1.04
CI	(0.95–1.14)	(0.94–1.16)				(0.7–2.3)	(0.98–1.11)
Liver cancer including ASL							
Obs/Exp	24/8.4	37/5.77	12/0.9	0/n.a	8/0.14	3	81/19.21
SMR	2.86	6.41	15.23		57.14	3 ASL	5.33
CI	(1.83–4.25)[d]	(4.5–8.84)[e]			8 ASL[f]		(4.23–6.62)
Brain							
Obs/Exp	14/13.1	23/12.76	2/1.3	4/2.61	0/0.6		43/30.37
SMR	1.07	1.81	1.62	1.53	0		1.42
CI	(0.59–1.80)	(1.14–2.71)					(1.03–1.91)
Lung							
Obs/Exp	144/148.3	111/115.87	24/26.6	1/1.2	2/5.78[g]		282/297.75
SMR	0.97	0.96	0.96	0.83	0.34		0.95
CI	(0.82–1.14)	(0.79–1.16)					(0.84–1.06)
Lymphatic and hematopoietic							
Obs/Exp	29/32.7	37/36.28	15/7.7	10/2.2	1/1.67		92/80.55
SMR	0.89	1.02	2.14	4.54	0.60		1.14
CI		(0.72–1.41)					(0.92–1.40)
Lymphomas							
Obs/Exp	18/19.3[h]	24/21.8[h]		5/1.2			
SMR	0.93	1.1		4.17			
Stomach							
Obs/Exp	49/45.1	10/16.01	18/14.4	21/24.7			98/100.21
SMR	1.09	0.63	1.38	0.85			0.98
CI	(0.8–1.44)	(0.3–1.15)					(0.79–1.19)

Abbreviations: CI, 95% confidence interval; Obs/Exp, observed/expected; SMR, standard mortality ratio.
[a]Calculated by the IPCS Task Group (*1*); includes all studies except Laplanche et al. (*27*), who do not provide Obs/Exp values. [b]Values shown are exposed/nonexposed, relative risk, and CI. [c]Reported in the original paper. [d]Of 17 liver cancer deaths confirmed by histopathology, 16 were ASL. [e]There were 15 ASL cases recorded on death certificates and 21 ASL cases recorded in an international register. [f]Plus 2 undiagnosed ASL cases. [g]All respiratory neoplasms. [h]Lymphoma and malignant myeloma.

study in which the dose–response relationship was examined, Simonato et al. (*113*) observed no association of brain tumors with cumulative exposure to VC. The overall epidemiologic evidence suggests a possible risk for brain tumors among VC workers.

An increase in lung cancer among VC workers had been reported in some early studies (*10*). However, there was no excess risk indicated in the two largest studies—the European (*113*) and U.S. (*112*) studies—or in the other four smaller studies (*23,24, 27,28*). No associations were found for either the duration of exposure/employment in the U.S. (*112*) or European (*113*) studies, or for cumulative exposure to VC in the European study (*113*).

An excess risk for malignant lymphomas was reported in some early studies (*10,14, 25,28*), but no excess risk was observed in the two largest cohorts [the U.S. (*112*) and European studies (*113*)] or in the Canadian cohort (*23*). In both the Russian (*28*) and German (*24*) studies, an excess risk for leukemia and lymphoma combined was observed.It should be noted that different methods of disease classification were used and sometimes lymphomas were grouped with malignant myelomas. The overall results of these studies do not show any significant increased risk for lymphomas or leukemia.

Since the IPCS Task Group meeting in January 1999 in Hanover, Germany, the update of the study by Wong et al. (*112*) has been completed (*114*). Specific cancers that showed meaningful excesses both through 1982 and through 1995 included cancers of the liver and the biliary tract (mostly due to a large excess of deaths due to ASL), the brain, and the connective and soft tissues. Of several causes of death previously believed to be related to VC exposure, no excesses were observed; these include lung cancer, cancers of lymphatic and hematopoietic tissue, emphysema and pneumoconioses, and other lung diseases, including chronic obstructive pulmonary disease.

VC Initiation of Hepatocarcinogenesis

Carcinogenesis is a multistep process. In the last few years, progress has been made in the understanding of a possible mechanism of initiation of hepatocarcinogenesis by VC. Recent studies (*1,118–121*) indicate that VC acts as a genotoxic carcinogen. After metabolic activation of VC into chloroethylene oxide (CEO) by cytochrome P450 isozyme 2E1 (CYP2E1), it exerts various genotoxic effects (including gene mutations and chromosomal aberrations) in different organisms, including bacteria, yeasts, mammalian cells in culture, Drosophila, rodents, and humans [reviewed by Giri (*122*) and updated by the IPCS (*1*)]. Among the mutagenic events induced by VC, base pair substitutions appear to be the most frequent (*118*).

In vitro studies have demonstrated that CEO and chloroacetaldehyde can alkylate nucleic acid bases (Figure 2) (*1,118,119,123*). 7-(2′-Oxoethyl)guanine, the major DNA adduct formed by VC and CEO, does not exhibit promutagenic properties. In contrast, four minor adducts, 1,N^6-ethenoadenine (εA), 3,N^4-ethenocytosine (εC), N^2,3-ethenoguanine (N^2,3-εG), and 1,N^2-ethenoguanine (1,N^2-εG), show promutagenic properties, inducing mainly base pair substitutions and a low level of frameshift mutations (*124*). Site-specific mutagenesis studies in *Escherichia coli* and in mammalian cell lines have shown that both εG and εC can induce G:C → A:T transitions; εC can also lead to C:G → A:T transversions (*125,126*). εA can induce misincorporation of G, C, or A during replication, thus inducing the base-pair substititions A:T → C:G, A:T → G:C, or A:T → T:A (*127,128*).

7-(2′-Oxoethyl)guanine and three etheno adducts (εA; εC; and N^2,3-εG; Figure 2) have been detected in DNA from rats and mice exposed to VC (*123,128–131*). Highly variable background levels of εA and εC were found in all the tissues examined (*132,133*). After exposure of rats to VC, significantly elevated levels of εA and εC were measured in most tissues, except the brain; there were also no significant increases of εA levels in the kidney and spleen (*121,134*).

The liver is one of the primary targets for VC-induced carcinogenesis in rats and humans. Mutations have been found in liver tumors associated with VC exposure. Mutations, all A:T → T:A transversions, have been described in the *p53* gene in three human ASL cases (Table 8). In human ASL, the Ki-*ras* gene is also activated through a G:C → A:T mutation at base 2 of codon 13 (Table 9). Ki-*ras* gene activation has not been found in rat ASL (*141,142*). However, 44% of rat ASL cases were found to contain a mutated *p53* gene: most mutations were base pair substitutions that involved mainly A:T base pairs (*137*). The data suggest the existence of hot spots for mutations in the *p53* gene; one mutation found in two rat ASL cases was equivalent to the same mutation characterized in one human ASL case associated with VC exposure. In rat HCC induced by VC, the Ha-*ras* gene is activated through an A:T → T:A transversion in codon 61 (Table 9).

The mutation spectra observed in liver tumors (ASL and/or HCC) that are associated with VC exposure in humans and rats are clearly distinct from those observed in sporadic liver tumors or in hepatic tumors associated with other exposures. In rats, the substitution mutations found at A:T base pairs in the *ras* and *p53* genes are consistent with the promutagenic properties of εA and with the accumulation and persistence of this lesion in hepatic DNA (*121*). Altogether, available data suggest that etheno adducts

Table 7. Absolute risk of angiosarcoma of the liver per 100,000 ppm-years.[a]

Years since first employment	Cumulative exposure (ppm-years)			
	< 2,000	2,000–5,999	6,000–9,999	≥ 10,000
0–19	1.0	6.8	24.4	44.8
20–24	4.7	32.0	115.6	212.5
≥ 25	6.2	42.2	152.3	280.0

[a]Data from Simonato et al. (*113*).

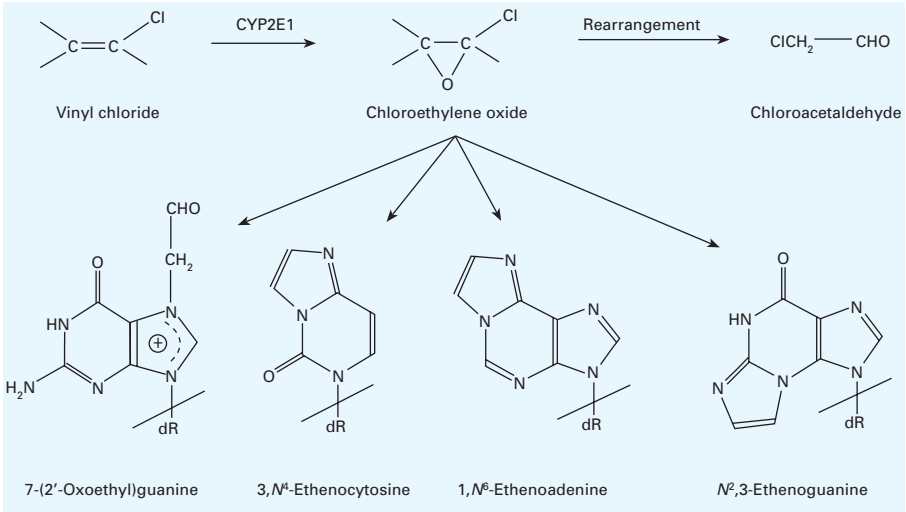

Figure 2. Vinyl chloride reactive metabolites and nucleic acid adducts formed from them *in vivo* [adapted from Ciroussel et al. (*123*)].

could be involved in the initiation of hepatocarcinogenesis by VC.

Analysis of Dose Response

VC has been shown to be carcinogenic and toxic in both oral and inhalation experimental bioassays, as well as in human epidemiologic studies. For VC, dose–response analyses have been based on data of ASL because it is the most critical and sensitive effect.

The bioassays that have most often been used as the basis for dose–response analysis in animals are the rat inhalation studies of Maltoni et al. (*34*,*35*) (involving a wide range of exposure levels and a large number of animals) and the oral studies of Feron et al. (*31*) and Til et al. (*32*,*33*). Risk evaluations derived from animal data can be compared with human epidemiologic data on ASL [e.g., Simonato et al. (*113*)].

Risk Assessment Based on Human Epidemiologic Data

Simonato et al. (*113*) performed a regression analysis from epidemiologic data to assess the relative risk of liver cancer and ASL in occupational exposure to VC using the variables cumulative exposure (ppm-years) and years since first employment. On the basis of this regression analysis, Simonato et al. (*113*) calculated the absolute risk of ASL per 100,000 (Table 7). For example, for workers exposed for > 25 years to < 80 ppm (i.e., < 2,000 ppm-years), there is a risk of 6.2 as compared to those who are exposed for only a few years at the same exposure level. At higher exposure levels (2,000–5,999 ppm-years), the risk increases to 42.2.

Physiologically Based Pharmacokinetic Model

In order to perform quantitative risk assessment using animal bioassays, physiologically based pharmacokinetic models (PBPKs) have been developed to derive the concentration of active metabolite at the critical target site, the liver, and to extrapolate this from animals to humans. The PBPK model should be validated by taking into account the known metabolic pathways and by using experimentally determined metabolic constants.

Clewell et al. (*143*) developed a model in which the initial metabolism of VC was hypothesized to occur via two saturable pathways (one representing high-affinity, low-capacity oxidation by CYP2E1 and one representing low-affinity, high-capacity oxidation by other P450 isozymes), producing CEO as an intermediate product in both cases. Chloroacetaldehyde (from CEO) was modeled as the major substrate of glutathione conjugation, with a lesser amount of CEO as the substrate of glutathione *S*-epoxide transferase. The model was similar to that proposed by Chen and Blancato (*144*) with regard to number and type of compartments, physiologic parameters, and the assumption that metabolism of VC takes place only in the liver; the authors used partition coefficients from the literature (*145*). The metabolic parameters for the two oxidative pathways were estimated from gas uptake experiments (*146*); in this model, it was assumed that the reactive VC metabolites further degrade to carbon dioxide, react with glutathione, or react with cellular macromolecules. Parameters for subsequent metabolism were taken from the PBPK model for vinylidene chloride (*147*).

This PBPK model (*143*) was used to predict the total production of reactive metabolites from VC in the animal bioassays and in human exposure scenarios. These measures of internal exposure were then used in the linearized multistage model (LMS) (*148*) to predict the risk associated with lifetime exposure to VC in air or drinking water.

Risk Assessments Based on Animal Studies

Inhalation Exposure Studies

The 95% upper confidence limit for excess lifetime risk associated with continuous inhalation of 1 μg/m^3 of VC is 8.4 μg/L × 10^{-5} in the current U.S. Environmental Protection Agency (U.S. EPA) health effects assessment summary tables (HEAST) (*149*), which are currently being updated. This is based on the studies of Maltoni et al. (*34*), but not using a PBPK model.

Reitz et al. (*150*) developed a PBPK model based on the study of Maltoni et al. (*34*), but using a single saturable pathway to predict the measures of delivered dose in rats. Reitz et al. (*150*) calculated lifetime average daily doses and fit them to an empirical dose–response model (a linearized multistage model). The 95% upper confidence limits for excess lifetime risk associated with continuous inhalation of 1 μg/m^3 VC calculated from this PBPK-based approach was 5.7 × 10^{-7}. Thus, the value calculated using the PBPK model differs from the HEAST risk estimation [8.4 μg/L × 10^{-5} (*149*)] by two orders of magnitude.

Reitz et al. (*150*) then compared their predictions of ASL incidences in humans with different exposures to those reported by Simonato et al. (*113*). For example, in the subgroup that Simonato et at. (*113*) estimated to have the lowest exposures (0–2,000 ppm-years), the reported incidence of ASL was 6.2/100,000 (Table 7). In contrast, Reitz et al. (*150*) calculated a maximum likelihood estimate of 188–736 cases/100,000 for exposures of 500–2,000 ppm-years. Thus, this risk assessment (*150*) using a PBPK model predicted almost two magnitudes more liver cancer cases than were actually reported.

Oral Exposure Studies

The present HEAST (*149*), which uses results from the rat bioassay of Feron et al. (*31*), gives a slope factor of 1.9 per mg/kg/day and an oral unit risk of 5.4 μg/L × 10^{-5}. These values are based on the U.S. EPA evaluations of 1984 and 1985 for which a PBPK model was not used. These values are under review and are subject to change.

By using results from the rat bioassay of Til et al. (*32*) and by applying the linearized multistage model, the human lifetime exposure for a 10^{-5} excess risk of ASL was calculated to be 20 μg/day (*151*). In this report, it was assumed that, in humans, the number of cancers at other sites may equal that of ASL, so that a correction (factor of 2) for cancers other than ASL is justified. VC

Table 8. Comparison of mutation spectra in the *p53* gene in liver tumors in humans and rats.[a]

Species	Tumor origin	No. mutations /no. of cases	No. and types of mutations	Reference
Humans	VC-associated ASL	3/6	3 A:T → T:A	(*135*)
	Cells cultured from VC-associated liver tumor		[CAT → CTT] (codon 179)	(*136*)
Rats	VC-associated ASL	11/25	5 A:T → T:A 2 A:T → G:C 2 A:T → C:G 3 G:C → A:T One 12 base-pair deletion 1 Deletion	(*137*)
	HCC	1/8	1 A:T → T:A	

[a]Adapted from Barbin et al. (*137*)

Table 9. Mutagenesis of *ras* proto-oncogenes in VC-associated liver tumors in humans and rats.

Species	Tumor origin	Gene involved	Codon	No. mutations/ no. tumors	Base pair changes	Codon changes	References
Human	ASL	Ki-*ras* 2	13	15/18	G → A	GGC → GAC	(*138–140*)
Rats	ASL	Ki-*ras* 2		0/10			(*141,142*)
	HCC	H-*ras*	61	5/8	A:T → T:A	A:T → T:A	(*141,142*)

concentrations in drinking water of 5 µg/L were calculated as being associated with excess risks of 10^{-5}.

Conclusion

VC is a chemical of interest in many fields of study. Workers in some parts of the world were and may still be exposed to high levels of VC, although it is a known carcinogen and is regulated in many countries. Fortunately, it seems that ASL is correlated with only high exposures over long periods. Because ASL has a latency of approximately 20 years, mortality from ASL caused by VC exposure is still to be expected in the next few years. With further improvements in industrial hygiene in countries all over the world, perhaps VC-induced ASL mortalities will become a phenomenon of the past.

The detection of VC as a degradation product of some chlorinated solvents is an indication of the intricate problems that may be attributed to past and future chemical waste deposits. Progress in remediation processes should be able, at least in part, to resolve these problems.

Research into the mechanisms of carcinogenesis has been initiated because ASL is a rare tumor and its occurrence in VC workers can be correlated with estimated VC exposure. Studies into mutation spectra observed in rat and human liver tumors (ASL and/or HCC) have shown that etheno adducts, in particular 1,N^6-ethenoadenine (εA), have promutagenic properties and are responsible for substitution mutations found at A:T base pairs in the *ras* and *p53* genes.

Since the 1970s it has been possible to monitor exposed VC workers and to keep records of mortality cases; a large amount of data is now available for epidemiologic studies, which are being continually updated. Using animal studies and various models, researchers have attempted to predict the risk of mortality and to extrapolate predictions from animals to humans. By comparing these predictions with human ASL mortality records, current risk assessment methodology can be validated.

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