

General Description

At standard temperature and pressure, vinyl chloride (VC) is a nonirritating, colourless gas. It is generally odourless below 10 000 mg/m³ (3900 ppm), but a sweetish odour may be detected by some sensitive individuals between 200 and 500 mg/m³. The gas is easily liquefied under pressure and is usually stored or shipped as a liquid.

Vinyl chloride is highly stable in the absence of sunlight or oxygen. Above 400 °C, it dissociates into acetylene and hydrochlorine. In the atmosphere VC reacts with hydroxyl radicals and ozone, ultimately forming formaldehyde, carbon monoxide, hydrochloric acid and formic acid. On the basis of measured reaction rates with hydroxyl radicals and their concentration in air, it is estimated that the half-time of VC in the atmosphere is about 20 hours (1).

Sources

The principal emission sources, in order of importance, are VC production plants, polyvinyl chloride (PVC) polymerization facilities, and plants where PVC products are fabricated. Minor sources include storage and handling facilities for VC and PVC and plants producing ethylene diamine or ethylene dichloride. In the United States, VC emissions have been reported from municipal landfills, but the exact source of emission is unclear and systematic survey data are unavailable.

Approximately 5 million tonnes of VC were produced in the whole of Europe in 1981. The levels of emission from VC and PVC production facilities depend upon the processes and control technology employed. The use of the best available technology can reduce emissions to less than 1% of production volume, but emissions from facilities in some countries exceed this value (1).

Occurrence in air

The general background of VC in western Europe resulting from known production sources is estimated from dispersion model calculations to range from 0.1 µg/m³ to 0.5 µg/m³ (1). These levels are lower than the detection limit (0.8 µg/m³) of the best analytical procedure (gas chromatography / mass spectroscopy) (2). The same models would predict that average annual concentrations around well controlled sources would range from 1 to 10 µg/m³ at distances of 1-5 km from the source and exceed 10 µg/m³ only within 1 km. The 99-percentile 24-hour concentrations around such sources would be about 10 times higher than the above averages (1). Dispersion models reasonably predict source-related, average concentrations. However, measurements over limited time periods can differ considerably, owing to fluctuating meteorological conditions. Poorly controlled, source-related environmental concentrations are reflected by measurements made in the United States in the mid-1970s near VC and PVC production facilities. Here, plant boundary concentrations often exceeded 1 mg/m³ (3).

Conversion factors

$$\begin{aligned} 1 \text{ ppm} &= 2.589 \text{ mg/m}^3 \\ 1 \text{ mg/m}^3 &= 0.386 \text{ ppm} \end{aligned}$$

Routes of Exposure

Air

Currently, general population exposure comes overwhelmingly from industrial production sources, the primary route of entry being inhalation. Assuming a daily inhalation of 20 m³ air, the vast majority of the population would inhale 2-10 µg of VC daily. Individuals living within 5 km of well controlled production sources could be exposed to 10-100 times as much. Previously, VC was produced as a propellant in aerosol cans and episodic indoor air pollution from this source was considerable (4). However, this type of use has been discontinued.

Occupational exposure

Approximately 10 000 individuals are occupationally exposed to VC during monomer or polymer production. Generally, exposures are lower than 10 mg/m³. The yearly average for the entire occupationally exposed population is considerably less than this value.

Smoking

Vinyl chloride has been found in the smoke of cigarettes (1.3-16 ng/cigarette) and of small cigars (14-27 ng) (5). Charcoal filter tips reduce VC in cigarette smoke.

Drinking-water

There is very little information on current concentrations of VC in water systems. Because of its volatility and reactivity, VC would not be expected to remain in significant concentrations in drinking-water. It has been detected only occasionally in samples of drinking-water taken in 100 cities of the Federal Republic of Germany. The highest level, 1.7 µg/litre, was tentatively ascribed to dissolution from PVC tubing (1).

Food

In the mid-1970s VC was also identified as a contaminant of foods and liquids packaged in PVC material (6). However, with the implementation of more stringent manufacturing specifications for PVC, such contamination decreased substantially and it is estimated that the maximum intake per person in foods and liquids would now be less than 0.1 µg/day (7).

Relative significance of different routes of exposure

The most important exposure route is air contamination from VC and PVC production facilities. General environmental levels of VC from all sources in Europe are likely to lead to average exposures of 2-10 µg/day. Exposures from food and water are less than 0.1 µg/day. Heavy smokers may inhale additionally up to 0.5 µg/day.

Kinetics and Metabolism

Vinyl chloride is rapidly absorbed through the lungs and is carried by the blood stream to all organs. The highest concentrations of metabolites are found in the liver, kidneys and spleen (8,9). Studies in rats indicate that this process saturates, with proportionately less VC being metabolized at concentrations exceeding 1000 mg/m³ than at lower concentrations (10).

First-order kinetics describes the metabolism of VC up to about 200 mg/m³. The metabolism is believed to proceed through the micro-somal mixed-function oxidase system, forming chloroethylene oxide which rapidly rearranges to chloroacetaldehyde (11). The activated metabolite binds to cellular macromolecules (12) or nucleotides (13). Detoxification occurs primarily by oxidation in the liver to polar compounds, which can be conjugated to glutathione and/or cysteine and excreted in the urine (14). No significant accumulation of VC

occurs in the body. From studies of its metabolism in rats VC is estimated to have a biological half-time of 20 minutes (9).

Health Effects

Reviews of the health effects of VC include that of IARC, the Dutch criteria document (1), the clinically oriented review by Lebach & Marsteller (15) and a review of VC mortality by Nicholson et al. (16).

Effects on experimental animals and *in vitro* test systems

Toxicological effects

The acute toxicity of VC is low; at higher concentrations a narcotic effect occurs. Two-hour LC₅₀ values for different animal species vary from 300 to 600 g/m³ (1). In chronic exposure VC can induce a variety of toxic effects. These are mainly related to the liver, the central nervous system (CNS) and the cardiovascular system.

Teratology studies, after VC inhalation, have been carried out in mice, rats and rabbits. No significant effects on malformations or anomaly rates resulted from exposures to VC at 130-6470 mg/m³ (50-2500 ppm) for up to 24 hours per day for up to 12 days during different periods of pregnancy (17-19). Other experiments have suggested some signs of embryotoxicity of VC in rats (20) and in mice (19). Vinyl chloride has been shown to be a transplacental carcinogen in the rat at exposures of 15 000 or 26 000 mg/m³ for 4 hours per day on days 12-18 of pregnancy (21).

Mutagenic and carcinogenic effects

Vinyl chloride is one of the best studied chemicals in relation to animal species. Studies by Maltoni et al. (21) on nearly 7000 animals over a 10-year period provide a data base virtually unmatched in experimental carcinogenesis. In these studies, VC was found to produce a statistically significant excess of Zymbal gland carcinomas, liver angiosarcomas, nephroblastomas, neuroblastomas, mammary gland adenocarcinomas and forestomach papillomas in concentrations ranging from 13 to 77 000 mg/m³. Liver haemangiosarcomas were found in experiments at concentrations as low as 25 mg/m³. The risk increased linearly up to approximately 1300 mg/m³, at which point 10% of the animals developed haemangiosarcoma. Thereafter, the rate of increase in risk lessened, but 30% of the animals developed haemangiosarcoma at 77000 mg/m³. The saturation of the haemangiosarcoma risk seen in the experimental animal data may be attributed to the shortened lifespan due to toxic effects in the heavily exposed animals (they did not live long enough to fully show their cancer risk). Further, the nonlinear metabolism of VC would affect the carcinogenic dose-response relationship.

The effect of age was investigated by Maltoni and co-workers, who exposed 21-week-old breeders and newborn Sprague-Dawley rats to 25 600 and 15 000 mg VC per m³ for 4 hours per day, 5 days per week, for 5 weeks. Malignancies were found only among the newborn animals. Fifteen liver haemangiosarcomas and 20 hepatomas were found among 44 rats exposed to 25 600 mg/m³; 17 haemangiosarcomas and 20 hepatomas were found among 42 exposed at 15 400 mg/m³. In contrast to these results, Groth et al. (22) found that the incidence of angiosarcoma increased with age at the start of exposure in an experiment in which Sprague-Dawley rats were exposed to 2400 mg/m³ for 7 hours per day, 5 days per week, for 24 weeks. The difference between the two studies may indicate a greatly increased sensitivity of newborns compared with older animals.

Interaction effects in the incidence of neoplasms in the rat have been demonstrated by

Radike et al. (23), who administered VC, ethanol, and VC with ethanol to groups of 80 male Sprague-Dawley rats. Forty of 80 rats exposed to VC and ethanol developed angiosarcomas, compared with 18 in the groups exposed to VC and none in those exposed to ethanol.

Vinyl chloride has been shown to be carcinogenic in mice (21), hamsters (21) and rabbits (24). In some strains, the haemangiosarcoma incidence in mice is similar to that in rats, but hamsters are much less sensitive. In contrast to rats, some strains of mice are highly susceptible to an increase in lung malignancies caused by VC exposure. In other mice strains, VC induces haemangiosarcomas in many tissues (21,25). In fact, liver haemangiosarcomas are in the minority.

Vinyl chloride and its metabolites 2-chloroethylene oxide, 2-chloroethylene aldehyde and 2-chloroethanol are mutagenic in various test systems (26).

Effects on humans

Toxicological effects

Between 1949 and 1974, a variety of effects of exposure to VC were documented. The symptoms observed included Raynaud's phenomenon, a painful vasospastic disorder of the hands, acro-osteolysis, primarily of the terminal phalanges of the hands, and pseudoscleroderma. Hepatomegaly and noncirrhotic portal fibrosis with portal hypertension and splenomegaly were also noted among individuals exposed to VC in polymerization facilities. The above symptoms were largely confined to people very heavily exposed to VC during reactor cleaning and were not found among individuals exposed to lower VC concentrations in the PVC processing industry. None of the above manifestations is of concern for individuals exposed in environmental circumstances.

VC is a narcotic agent and loss of consciousness can occur from exposures approaching 25 000 mg/m³. This was the case among 4.5% of workers examined at a PVC polymerization facility (27). At lesser concentrations (about 2300 mg/m³), euphoria, dizziness, somnolence and narcosis were commonly reported (28). At approximately 100 mg/m³, 10% of workers exposed in a workshift experienced dizziness and 17% somnolence; lesser percentages of other CNS disorders were reported.

Several investigators reported a higher incidence of chromosomal aberrations in peripheral lymphocytes cultured from workers exposed to high levels of VC (26). Three studies of communities close to PVC plants suggested an association between such locations and an increased risk of malformations, particularly of the CNS (29-31). However, none of the studies produced a clearcut association, and other uncontrolled variables, including other industrial pollutants, may account for the differences observed. A single study (32) of workers exposed to VC, showing an increase in fetal death rates in their wives, was more convincing, but it had a number of methodological problems. Further studies are required before any definite conclusions can be reached. Sanockij et al. reported that, among wives of workers exposed to VC, the number of miscarriages increased, while the number of spermatozoa in the ejaculate of exposed males decreased (33).

Mutagenic and carcinogenic effects

Twelve cohort studies of workers exposed to VC have been published. The size of the cohorts varied greatly, from 304 to 9677, in a large industry-sponsored study in the United States (34). A notable feature of all the studies is that the populations followed were relatively young or recently employed, even though many plants in the studies started production in the 1940s. Most workers were hired after 1950, when United States and western European production increased sixfold in 10 years. Thus, data on effects 25 or more years after the beginning of exposure are limited.

Increased incidence of cancer in all sites is reported in most of the studies, although it does not achieve a 0.05 level of significance except in the study by Waxweiler et al. (35). In the study by Ott et al. (36), a highly exposed subgroup with 15 years' latency had 8 cancer deaths compared with 3.2 expected ($P < 0.05$). The absence of significant findings in other studies may be attributed to their low power or to the inclusion of a large number of individuals with very short or recent exposures.

One remarkable finding in virtually all the studies is the absence of significantly elevated mortality from chronic liver disease. The generally benign results reported in other studies contrast sharply with the severe liver disease from VC exposure documented in clinical studies (15). Hepatomegaly, hepatic fibrosis, portal hypertension and bleeding oesophageal varices have commonly been found in individuals heavily exposed to VC, even without exposure to alcohol.

In the case of liver cancer, the overall data are consistent and striking. Haemangiosarcomas of the liver were reported in 8 of the 12 studies. In each of these, a very large and highly significant standard mortality rate (SMR) for liver cancer was seen. Methodological limitations can account for negative data in the other four studies. The large SMRs observed, however, result largely from low values for the expected number of cases rather than from a high incidence of observed cases. In all 12 studies, only 35 separate liver haemangiosarcomas were identified. As the overall excess number of deaths from liver and biliary cancer in all studies was 54, some haemangiosarcomas may not have been identified. The low numbers must also be seen in the light of the limited follow-up times in most studies.

The evidence for lung cancer is less clear. Some studies indicate an increase in lung cancer, but at a level that does not achieve statistical significance, except in the 15-year-latency population of Waxweiler et al. (35). This, in part, may be the result of the low power of many of the studies. Only two have an 80% power to detect an overall risk of 1.5. Of significance, however, are the very low SMRs in the groups studied by Theriault & Allard (37), Reintl et al. (38), and Nicholson et al. (16), cohorts in which many haemangiosarcomas were found. The four largest studies, although in some cases limited by the inclusion of short-term and recently employed workers, are also noteworthy for SMRs close to 100. Where available, data on subcohorts with longer latency (> 15 years) suggest some increased risk.

In a number of studies, cancers of the brain and the CNS were found to be significantly elevated, although the results differed considerably from study to study. Again, negative data may be simply the result of limited long-term follow-up or the low power of the study. In contrast to lung cancer, however, the largest study group had a significantly elevated risk of malignant tumours of the brain and the CNS. The human data are also modified by the recent finding of brain and CNS tumours resulting from various types of chemical plant exposure (39). Excess brain malignancies, but not the etiological agents, have been identified in workers at several chemical/petrochemical plants in Texas and Louisiana, USA. Exposure to VC was documented for some cases, but it did not account for the overall findings. Since individuals in many of the VC studies considered here were exposed to other chemicals and petrochemicals, the possible role of these agents cannot be excluded.

Similar results are obtained for malignancies of the lymphatic and haematopoietic system. Here again, the analysis is limited by the few deaths and disparate results reported in different studies. Overall, there would appear to be an elevated risk, but the influence of confounding exposures precludes any definitive statement to this effect.

Animal data show VC to be a multi-site carcinogen (21). While the epidemiological data are somewhat equivocal, VC should be considered potentially carcinogenic in humans in the lung, brain, and lymphatic and haematopoietic system, as well as the liver. Nevertheless, in all of the epidemiological studies reported to date, the number of excess cases at these nonhepatic sites is no more than the number of liver haemangiosarcomas found.

Nicholson et al. (16) have recently completed a follow-up (to the end of 1981) of a group of 491 workers at two polymerization plants. Eighty deaths occurred during follow-up beginning 10 or more years after employment. Of the 80 deaths, 9 were from haemangiosarcoma of the liver, 6 of which occurred after 1974. From an analysis of this very limited group, it would appear that haemangiosarcoma risk increases as approximately the square of time from the start of exposure in individuals exposed for 5 or more years.

The exposures that led to the currently observed mortality from VC were very high. Prior to 1955, it was estimated (40) that industrywide average exposures were approximately 2500 mg/m³ and decreased to about 800 mg/m³ by 1970. After 1974, substantial reductions in workplace exposures occurred following the identification of human cancer risk.

In a United States mortality study of PVC fabricators, including around 4300 deaths, an overrisk in gastrointestinal cancer was found in both sexes (41). A statistically insignificant trend towards increased risk of tumours of the digestive organs was also found in a Swedish study (42). These studies indicate that even low levels of VC exposure might represent a cancer risk to humans.

Nicholson et al. (43) have made projections of the future mortality that might occur from all VC exposures prior to 1975 in the United States and western European industry. These projections were made by assuming that the time course of VC risk follows a power law relationship with age (44,45): $R = bt^k$, where R is the incidence rate of cancer at a specific site, t is age, and b and k are constants specific to site. Incidence data according to year of first exposure, number of years of exposure, calendar year of death, and number of years from onset of exposure, were matched to results calculated using a range of values for b and k. The values of b and k that best fit the data were then utilized to calculate the future mortality, assuming that the time course of risk continues throughout the life of the exposed population. The result suggests that 200-600 individuals in the United States and 550-2800 in western Europe may die of haemangiosarcoma from all occupational exposures to VC prior to 1975. Because of the assumption of a continued increasing risk, the estimates are likely to be high.

Vinyl chloride also causes chromosome breaks (46), fragmentations and rearrangements (47) in the peripheral lymphocytes of PVC workers.

Evaluation of Human Health Risks

Exposure

Calculations based on dispersion models indicate that 24-hour average concentrations of 0.1-0.5 µg/m³ exist as background levels in much of western Europe, but such concentrations are below the current detection limit (approximately 1.0 µg/m³). In the vicinity of VC and PVC production facilities, 24-hour concentrations can exceed 100 µg/m³, but are generally less than 10 µg/m³ at distances greater than 1 km from plants. The half-time of VC in the air is calculated to be 20 hours; this figure is based on measured rates of reaction with hydroxyl radicals and their concentrations in the air (1).

Health risk evaluation

There is sufficient evidence of carcinogenicity of VC in humans and experimental animals (26). Extrapolation (or rather interpolation) to lower exposure levels can be made, based on knowledge or assumptions about the dose and time-dependence of risk. As seen in the low exposure data of Maltoni et al. (21), a linear dose-response relationship accords well with the animal data for haemangiosarcoma. The finding of at least three cases of haemangiosarcoma in PVC processors as compared with about 100 in VC or PVC production workers is compatible with a linear relationship. The average exposures in the production industry were

about 100 times lower than those in the polymerization industry, but the workforce was 10 times larger.

Data from a cohort study (16) and an analysis of the incidence of haemangiosarcoma in the USA and western Europe (43) suggest that the risk of haemangiosarcoma increases as the second or third power of time from onset of exposure. Using a model in which the risk increases as t^3 during exposure and as t^2 subsequently, estimates of the relative risk in various exposure circumstances can be calculated and used to convert limited-duration exposure risks into lifetime exposure risks.

Estimates of cancer risk can be made from the data relating to the cohort studied by Nicholson et al. (16). A group of 491 workers at two long-established PVC production plants was studied. One plant began operations in 1936 and the other in 1946. Each cohort member had a minimum of 5 years' employment; the average work duration was 18 years. It is estimated that the average VC exposure was 2050 mg/m^3 . The overall standardized mortality rate (SMR) for cancer was 142 (28 observed; 19.7 expected); that for liver and biliary cancer was 2380 (10 observed; 0.42 expected). Using the liver cancer data, the estimated lifetime risk of death from VC exposure is 3.6×10^{-4} per mg/m^3 , or $[(23.8 - 1) \times 0.003 / (2050 \text{ mg/m}^3) \times 2.8 \times 70/18]$, where 0.003 is the lifetime risk of death from liver biliary cancer in white American males, 2.8 is the working week-total week conversion and 70/18 the work period-lifetime conversion. Since there are an equal number of cancers at other sites (averaging over 12 cohorts), the excess cancer risk is 7.2×10^{-4} per mg/m^3 . If the total cancer SMR is used directly, the risk is 4.5×10^{-4} per mg/m^3 , or $[(1.42 - 1) \times 0.2 / (2050 \text{ mg/m}^3) \times 2.8 \times 70/18]$, which is in good agreement with the above. The average of the two estimates indicates that a 10^{-6} cancer risk occurs at exposures of $1.7 \text{ } \mu\text{g/m}^3$.

The risk of cancer from VC can be calculated from data on the United States population exposed in the Equitable Environmental Health study (34). This study identified 10 173 workers who were employed for one or more years in 37 (of 43) VC and PVC production plants. The average duration of employment before 1973 was 8.7 years. Using the data of Barnes (40), a weighted exposure of 650 ppm (1665 mg/m^3) was estimated. Considering the total population at risk to be 12 000, the unit exposure lifetime risk from an average exposure of 9 years is 0.75×10^{-5} per mg/m^3 , or $[(150/12\ 000) \times (1/1665)]$.

Using a linear dose-response relationship converting to a lifetime exposure (assuming that one half of the workers began exposure at the age of 20 and one half at the age of 30), the continuous lifetime haemangiosarcoma risk is 4.7×10^{-4} per mg/m^3 , or $[0.75 \times 10^{-5} \times 2.8 \times 22.4]$, where 2.8 is the ratio of the air volume inhaled in a full week ($20 \text{ m}^3 \times 7$) to that in a working week ($10 \text{ m}^3 \times 5$) and 22.4 is the average conversion to a lifetime for a ten-year exposure beginning at an average age of 25 years, taking into account the time course of haemangiosarcoma. (Without explicit consideration of the time course, the multiplier would be $70/9 = 7.8$.) A 10^{-6} risk occurs at a concentration of $2.1 \text{ } \mu\text{g/m}^3$.

Assuming that the number of cancers in other sites may equal that of haemangiosarcomas, the best estimate for excess cancer risk is that a 10^{-6} risk occurs as a result of continuous lifetime exposure to $1.0 \text{ } \mu\text{g/m}^3$.

The risks estimated from epidemiological studies are the most relevant for human exposures. The above estimate from human angiosarcoma incidences is a conservative one, from the point of view of health, because of the use of a model that assumes that the haemangiosarcoma risk continues to increase throughout the lifetime of an exposed individual.

These risk estimates are in agreement with those made by others. The US Environmental Protection Agency has estimated that 11 cancer deaths per year would result from 4.6×10^{-6} people being exposed to 0.017 ppm ($43 \text{ } \mu\text{g/m}^3$) (48): this translates to a 10^{-6} lifetime risk at $0.25 \text{ } \mu\text{g/m}^3$. A Dutch criteria document, on the basis of animal data, estimates that a 10^{-6} risk

occurs at $0.035 \mu\text{g}/\text{m}^3$ (1).

One cautionary note should be sounded: the particular sensitivity of newborn rats to VC, referred to above, suggests that risks may be much greater in childhood than those estimated from adult exposures. However, by the age of 10 years the latter risks should prevail.

Guidelines

Vinyl chloride is a human carcinogen and the critical concern with regard to environmental exposures to VC is the risk of malignancy. No safe level can be indicated. Estimates based on human studies indicate a lifetime risk from exposure to $1 \mu\text{g}/\text{m}^3$ to be 1×10^{-6} .

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