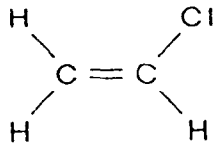
VINYL CHLORIDE

CAS: 75-01-4

Chloroethene; Chloroethylene; Vinyl chloride monomer

C_2H_3Cl



TLV–TWA, 5 ppm (13 mg/m^3)

A1 — Confirmed Human Carcinogen

1946–1947: MAC–TWA, 500 ppm

1948–1962: TLV–TWA, 500 ppm

1963–1971: TLV–Ceiling, 500 ppm

1970: TLV–TWA, 200 ppm, proposed

1972–1977: TLV–TWA, 200 ppm

1974: TLV, none; A1c Human Carcinogen; proposed

1978–1979: TLV, none; A1c Carcinogen

1978: TLV–TWA, 5 ppm; A1a Human Carcinogen; proposed

1980–present: TLV–TWA, 5 ppm

1980–1986: A1a Carcinogen

1985: A1, Confirmed Human Carcinogen; proposed

1987–present: A1, Confirmed Human Carcinogen

1992: Documentation revised

Chemical and Physical Properties

Vinyl chloride is a colorless, highly flammable gas with an ethereal odor. An odor threshold of 3000 ppm has been reported.[1] Chemical and physical properties include:[2–4]

- Molecular weight: 62.50
- Specific gravity: 0.9106 at 20°C
- Freezing point: –153.8°C
- Boiling point: –13.4°C
- Vapor pressure: 2530 torr at 20°C
- Vapor density: 2.15 (air = 1.0)
- Flash point: –77.8°C, open cup
- Explosive limits: upper, 22%; lower, 4% by volume in air
- Solubility: slightly soluble in water; soluble in alcohol or ether
- Reactivity: polymerizes in light or in the presence of catalyst
- Decomposition products: on combustion, degrades to hydrogen chloride, carbon monoxide, carbon dioxide, and traces of phosgene.

Vinyl chloride is usually handled as a liquid under pressure. Given its high vapor density, spilled vinyl chloride is slow to disperse and it will collect in low-lying areas.

Major Uses or Sources of Occupational Exposure

Production of vinyl chloride in the United States was 9.1 billion pounds in 1988.[5] Projected U.S. production in 1993 is 11.0 billion pounds. The National Institute for Occupational Safety and Health (NIOSH)[6] estimated that 81,314 U.S. workers employed in 3711 facilities were potentially exposed to vinyl chloride each day.

The principal use of vinyl chloride is as a raw material for the manufacture of polyvinyl chloride resins. It is also employed in organic syntheses and in production of vinyl chloride/vinyl acetate copolymers. Because vinyl chloride is a gas at room temperature and pressure, the common route of occupational exposure is inhalation.[7] The use of vinyl chloride as an aerosol propellant, refrigerant, or a component of pharmaceuticals or cosmetics and the like was banned in the United States in 1974. Of interest is the fact that vinyl chloride is one component of cigarette smoke.[8]

The U.S. Agency for Toxic Substances and Disease Registry (ATSDR)[9,10] has published toxicological profiles for vinyl chloride. The International Agency for Research on Cancer (IARC)[4,11] has reviewed the toxicity and carcinogenicity of vinyl chloride. Only those studies judged most relevant to derivation of the TLV for this compound are discussed here.

Animal Studies

Acute

Vinyl chloride has long been considered to be very low in toxicity by acute inhalation. Lehmann and Flury[12] summarized the early literature and reported work by Schauman who considered vinyl chloride to be a candidate surgical anesthetic. Schauman reported little pathological change even after repeated exposure to anesthetic concentrations. Further work on the anesthetic potential of vinyl chloride indicated that vinyl chloride was unsafe for use as a surgical anesthetic in dogs; in addition, because of its flammability, poor efficacy, and its ability to cause cardiac irregularities at anesthetic concentrations, vinyl chloride was not suitable for use as an anesthetic in humans.

As a result of two deaths related to vinyl chloride exposure in Canada,[13] the acute inhalation toxicity of vinyl chloride was studied by Mastromatteo et al.[14] Exposure of mice, rats, and guinea pigs at 10, 20, or 30 volume percent (100,000–300,000 ppm) vinyl chloride for 30 minutes caused concentration-dependent mortality (Table 1). Some pulmonary edema, inflammation, hyperemia, congestion, and engorgement were observed,[14] but hepatic and renal involvement were remarkably low. Deaths were due to central arrest in narcosis.

TABLE 1. Number of Deaths in Different Groups of Five Mice, Rats, and Guinea Pigs Exposed for 30 Minutes to Varying Concentrations of Vinyl Chloride in Air[14]

Vinyl Chloride Concentration (% by volume in air)	Laboratory Animal			
	Mice	Rats	Guinea Pigs	Total
10	0/5	0/5	0/5	0/15
20	1/5	0/5	0/5	1/15
30	5/5	1/5	1/5*	11/15
40	—	—	2/5*	2/5

*A delayed death occurred within 24 hours following exposure.

Subchronic

A summary of the report by Torkelson et al.[15] on the effect of repeated exposure of laboratory animals to vinyl chloride states that vinyl chloride was found to have a slight capacity to cause liver and kidney injury on repeated exposures. Male and female rats showed micropathological changes after repeated daily 7-hour exposures at 500 ppm for 4.5 months. Repeated 7-hour exposures at 200 ppm for 6 months resulted in micropathological changes in the livers of rabbits and statistically significant increases in the average weight of the livers of male and female rats, but no detectable changes in dogs and guinea pigs. Repeated 7-hour exposures at 100 ppm resulted in slight increases in the average weight of rat livers, but the other species were not affected. All species studied tolerated repeated daily 7-hour exposures at 50 ppm for 6 months with no detectable injury.

Also repeated daily 1-hour exposures at 200 and 100 ppm of vinyl chloride were without effect; longer exposures caused a slight increase in liver weight.

The authors[15] concluded that "The standard for evaluating regular daily 7- or 8-hour exposures may be defined as the concentration below which practically all analytical results must fall. The value of 100 ppm is suggested as this standard for vinyl chloride, with a time-weighted average for all exposures not to exceed 50 ppm."

Lester and associates[16] took exception with the basis for the conclusion drawn by Torkelson et al.[15] that 50 ppm should be a maximum TWA exposure for workers. Based on exposures of rats at 2 volume percent for 3 months and 5 volume percent for 19 days, Lester et al.[16] concluded that 500 ppm was acceptable as a TLV–TWA despite minor changes observed in rat liver. They also believed that these changes were "within the normal range and were not pathologic in nature."

Chronic/Carcinogenicity

Several bioassays have confirmed the carcinogenicity of inhaling vinyl chloride. In each case, the incidence of specific tumor types increases with dose until a plateau is reached. Exposures to higher concentrations have little additional effect. This is because the action of the metabolites is responsible for the carcinogenicity rather than the actions of the parent molecule. The rates of formation of the carcinogenic metabolites are limited and dose-dependent,[17–19] and once the enzyme systems responsible for vinyl chloride activation are saturated, administration of a greater dose does not result in a corresponding increase in tumor incidence.[20,21]

In an attempt to produce acroosteolysis in animals, Viola[22] exposed rats 4 hours/day, 5 days/week at 30,000 ppm (3%) vinyl chloride vapor. In his report on the results of 12 months exposure, he described metaplastic changes in the bones which he considered similar to the human disease acroosteolysis. He made no mention of having observed cancer in these animals until the Tenth International Cancer Congress in May 1970. In abstracts and subsequently in May 1971, Viola and co-workers[23] reported tumors of the skin, lungs, and bones occurring first after 10 months of exposure. The authors[23] summarized this work as follows:

> Rats (Ar/IRE Wistar strain) exposed for 12 months to vapors of vinyl chloride developed tumors of the skin, lungs, and bones. The cutaneous tumors, which always appeared in the area in which submaxillary and parotid glands are located, have been histologically recognized as epidermoid carcinomas, papillomas, and mucoepidermoid carcinomas. The morphological characteristics of lung tumors, which occurred in a lower percentage, were mainly of the adenocarcinoma type, with the exception of a single epidermoid tumor originating from the epithelial covering cells. In a minor number of rats, a large proliferation of cartilaginous tissue diagnosed as osteochondroma developed in the metacarpal and metatarsal regions of the fourlimbs.

The report by Viola et al.[23] is apparently the first publication in which carcinogenic activity had been ascribed to vinyl chloride exposure in either humans or animals. Although there were obvious deficiencies in

Viola's study, such as very impure samples, the presence of food and bedding in the exposure chamber, the excessive exposure concentration, and problems with statistical evaluation and interpretation of the lesions, the report was of serious concern and resulted in additional animal and epidemiologic studies in Italy.[24-26]

The work of Maltoni and Lefemine[25,26] on vinyl chloride was first reported at an Occupational Safety and Health Administration (OSHA) hearing in February 1974; it was also included in the 1974 proceedings of the Second International Symposium on Cancer Detection and Prevention. In these studies, groups of rats, mice, and and hamsters were exposed to vinyl chloride in air at concentrations of 50 to 10,000 ppm. Maltoni and Lefemine[25] reported carcinomas of the Zymbal gland and nephroblastomas and angiosarcomas of the livers of rats inhaling concentrations of 250 to 10,000 ppm, but none at 50 ppm. Subsequent, unpublished information[26] revealed "one liver angiosarcoma, one extrahepatic angiosarcoma and one nephroblastoma, in three animals of the first experiment, exposed at 50 ppm of VC [vinyl chloride] for one year, and surviving 135 weeks from the beginning of the treatment." The authors[26] concluded:

> . . . a dose–response relationship clearly emerges, as far as angiosarcomas and nephroblastomas are concerned, in the lower dose ranges: from 500 ppm to 50 ppm for angiosarcomas, and from 250 ppm to 50 ppm for nephro-blastomas. A comparison of the results available at the present moment in rats exposed for 12 months and 4 months (BT1 and BT3 experiments) shows that the neoplastic response, as far as angiosarcomas and nephroblastomas are concerned, is affected by the length of exposure to VC.

In their experiment BT3, Maltoni and Lefemine[25,26] reported *in utero* production of angiosarcomas in offspring of pregnant rats exposed at 10,000 ppm and 6000 ppm.

Reproductive/Developmental

No influence of vinyl chloride on male mouse fertility could be detected in acute inhalation studies;[27] however, repeated exposures at 100 to 500 ppm, 5 to 6 hours/day for 10 to 12 months were associated with oligospermia and damage to the rat seminiferous epithelium.[28,29]

Offspring of pregnant rats, mice, and rabbits that inhaled up to 2500 ppm vinyl chloride throughout organogenesis showed some evidence of fetotoxicity (delayed ossification) at maternally toxic concentrations (and, in the case of the mice, elevated maternal mortality).[30,31] Other such studies[32] have failed to demonstrate a dose–response relationship with regard to embryolethality or terata.

Genotoxicity Studies

In the presence of hepatic mixed function oxidase enzymes, vinyl chloride is a base-substitution mutagen in *Salmonella typhimurium*.[33-35] Its metabolites, 2-chloroethylene oxide and 2-chloroacetaldehyde, are direct-acting mutagens in *S. typhimurium*,[36] in *Escherichia coli*,[37] in *Schizosaccharomyces pombe*,[38] and in cultured Chinese hamster ovary (CHO) cells.[39]

Increased numbers of chromosomal aberrations[40] and increased hepatic cell proliferation with ethenoadenosine and ethenocytidinc DNA adducts occur in rats after inhaling[41-46] or ingesting[47] vinyl chloride. Clastogenesis[48] and ethenodeoxy adducts similar to those in rats have been isolated from the livers of vinyl chloride-exposed mice.[49]

Epidemiologic and clinical studies have confirmed increased clastogenesis,[50] chromosomal aberrations,[51-53] and sister-chromatid exchange[54] in peripheral lymphocytes of vinyl chloride-exposed workers. These alterations appear to be transient and reversible.[53,55] In some of these instances, worker exposures had been on the order of 1000 to 2000 ppm.[52] Given the available data, Hansteen et al.[53] concluded that the no-observed-effect level (NOEL) for human chromosomal aberration associated with occupational vinyl chloride exposure was 1 ppm.

Pharmacokinetic/Metabolism Studies

Vinyl chloride is metabolized by microsomal cytochrome P-450 to chloroethylene oxide and 2-chloroacetaldehyde (via 2-chloroethanol) and it is excreted in humans as urinary thiodiglycolic acid.[56] The half-time for elimination of vinyl chloride as thiodiglycolic acid is 4 to 5 hours;[57] this metabolism is saturable and the excretion of thiodiglycolic acid plateaus.

The products of *in vitro* vinyl chloride metabolism by human cytochrome P-450 are mutagenic in prokaryotic cells; human liver catalyzed metabolism was 84% as efficient as rat liver enzymes in carrying out these conversions; however, a ninefold individual variation was observed.[58]

The elimination of vinyl chloride follows first-order kinetics. Elimination of vinyl chloride in exhaled air proceeds with a half-time of 20 to 30 minutes.[57]

Human Studies

Controlled Exposures

A single, 3-minute inhalation exposure at 25,000 ppm caused confusion, headache, and dizziness among volunteers.[59] Among volunteers inhaling 4000 ppm for 5 minutes, no such complaints were recorded;[60] however, after similar exposures at 8000 or 20,000 ppm, the volunteers complained of nausea, dizziness, and headache.[60] When young adult males inhaled 2.9 to 23.5 ppm by mask for 6 hours, 42% of the inspired vinyl chloride was retained.[61] Following cessation of exposure, only

3% to 5% of the parent compound was exhaled unchanged.[61]

Case History Reports

As with many liquified gases, contact of the skin, conjunctiva, or cornea with escaping compressed vinyl chloride can produce freezing frostbite.[13,62] Exposure to extremely high (but unknown) concentrations can cause death.[13]

Despite the early reports ascribing low toxicity to vinyl chloride, injury during the production of polyvinyl chloride (PVC) resins was reported as early as 1949. Significantly, this report came from Europe where production of PVC preceded U.S. production by several years, and today, the quantity produced in Europe still exceeds U.S. production by about twofold. A 1949 paper by Tribukh et al.[63] reported numerous effects in PVC workers in what must be considered primitive production facilities by today's standards. These authors[63] found a "considerable number of cases of hepatitis among workers"; however, this report was more concerned with the consequences of exposure to hepatotoxic chemicals other than vinyl chloride (e.g., chlorinated diphenyl and chlorinated naphthalenes).

Since 1949, numerous articles describing conditions and problems in PVC production plants have appeared, particularly in the Eastern European literature. Filatova and Gronsberg,[64] Suciu et al.,[65] Gabor et al.,[66] Grigorescu and Toba,[67] Antonyuzhenko,[68] and Kudryavtseva[69] have all described the consequences of apparent gross chronic exposure. These papers and abstracts are difficult to interpret because there are generally poor descriptions of the exposure conditions and analyses of the workroom air; thus, no dose–response relationships can be determined. The injuries and effects described by the authors are neither consistent with the levels of exposure claimed by the authors nor are the levels of exposure consistent with past or even present-day chemical technology. Furthermore, exposures to mixtures of chemicals are involved which makes it impossible to ascribe the effects described to any one particular compound. For example, Suciu et al.[65] described nervous disorders, including euphoria with whistling and laughing, incoordination, and dizziness similar to alcohol intoxication. However, these authors[65] ascribe the results to exposure on the order of 5.5 mg/m^3 (2 ppm v/v), a finding inconsistent with other publications which indicate these effects only if concentrations greatly exceed 10,000 to 20,000 ppm v/v.

Therefore, based on the above case reports, the following conclusions can be made regarding the result of massive and apparently repeated exposures:

1. Vinyl chloride and related vinyl monomers possess a narcotic action and produce, depending upon concentration, characteristic neurologic manifestation, a state of euphoria (12%), followed by a state of inebriation similar to that of ethanol intoxication. In certain cases, narcosis can appear. After leaving the workplace, somnolence (45%) persists; hypersomnia has been described. Vinyl chloride acts on the skin and produces a sensation of heat.
2. After repeated exposure, a neurologic asthenia developed in which somnolence predominates.
3. After a variable period of time, dyspeptic disturbances ensue. At first, these are not characteristic and include epigastric pain (16%), swelling, discomfort, and a feeling of heaviness in the right hypochrondium (7%) or the left (5%). Anorexia has been described in some of these patients.

   In 30% of the cases, congestive hepatomegaly appears, which may mimic toxic hepatitis without jaundice; some cases may become chronic.

   In 6% of the cases, the hepatomegaly is accompanied by splenomegaly. The proteinogram and the aldolases are the most sensitive clinical tests and show changes similar to those of acute hepatitis (e.g., increase in α-globulins and of the β- and γ-globulins).

   The thymol test, Greenstedt's reaction, and the zinc sulfate test are positive only in few of the patients.
4. After 3 years of exposure, a syndrome typical of ulcer without radiologic changes becomes manifest in some 9% of the cases.
5. In 6% of the cases, Raynaud's syndrome has appeared, particularly among the young men. Plethysmography shows inhibition of the vasomotor centers in 50% of these individuals.
6. Allergic dermatitis in 4.4% and scleroderma in 3.6% have been observed.
7. The clinical and laboratory findings are of importance in differential diagnosis because, in numerous cases, diseases appear in humans that cannot be reproduced in common laboratory animals (e.g., Raynaud's syndrome and scleroderma). Vinyl chloride and the vinyl monomers have played a part in the production of these disease manifestations as demonstrated by the fact that the sudden and frequent appearance of suc manifestations in workers in the PVC division of several plants, as well as in normal, relatively young individuals employed in certain PVC production operations, ended in the majority of the cases after the institution of protective measures and change of work.[65]

In 1967, reports appeared describing acroosteolysis in workmen engaged in polymerization of vinyl chloride. Harris and Adams[70] reported two cases in Europe, Wilson et al.[71] reported 37 cases in the B.F. Goodrich Company, and Juhe et al.[72] described a syndrome consisting of (arranged in decreasing order of occurrence) thrombocytopenia, splenomegaly, hepatic involvement, dyspnea, circulatory obstruction, and skin and bone tox-

icities.

In January 1974, the B.F. Goodrich Company notified its employees, NIOSH, the Kentucky State Department of Labor, and the public that three workers had died of hepatic angiosarcoma. The report of the first subject has been published by Creech and Johnson.[73] The employee, a 36-year-old male, was hospitalized January 5, 1970, and died September 27, 1971. He had worked in PVC production from November 1955 until the onset of his illness; his history, clinical course, and pathologic findings are consistent with those of others who died of angiosarcoma.

There is indirect evidence that intermittent exposures to vinyl chloride on the order of thousands of ppm have not been infrequent in PVC plants in the U.S. and in Russia. No data on the past (or even present) concentrations of vinyl chloride in plants where angiosarcoma cases have occurred, or not occurred, appear to be available. One report[74] indicates that 21 of 26 early cases of angiosarcoma occurred in former reactor cleaners. Vinyl chloride exposures during reactor cleaning were apparently associated with the majority of acroosteolysis cases investigated by Cook and associates.[75]

Other reports have related at least four cases of respiratory cancer among vinyl chloride workers, but no dose–response relationship has come forward.[76]

In a study of 7000 men exposed to vinyl chloride in PVC manufacture between 1940 and 1974, Fox and Collier[77] found no evidence of cancers due to vinyl chloride at sites other than the liver. There were four liver cancers, including two angiosarcomas.

Delorme and Theriault[78] described ten cases of hepatic angiosarcoma among workers in vinyl chloride polymerizing plant in Quebec; these cases all had developed extensive hepatic fibrosis. Details of 64 cases were presented by Spirtas and Kaminski.[79]

Matufuji[80] noted that, in contrast to the U.S. and European countries where 70 angiosarcomas cases associated with vinyl chloride exposure had been reported, no cancer, but many poisoning cases, had been reported in the USSR.

Epidemiological Studies

In 1967, the University of Michigan was retained by the Manufacturing Chemists Association to investigate acroosteolysis occurring in workers engaged in the polymerization of vinyl chloride. The results of a large-scale epidemiological study of workers then currently employed in vinyl chloride and polyvinyl chloride production have been described in detail.[75,81,82]

Dinman et al.[81] summarized the data as follows:

> An epidemiological study was performed covering 5011 employees with 21,510 man-years experience in various phases of vinyl chloride (VC) and polyvinyl chloride (PVC) manufacturing in 32 plants throughout the United States and Canada. The total number of definitive cases of acroosteolysis (AOL) was 25; 16 other individuals were under suspicion. This condition is clearly associated with the hand cleaning of polymerizers. Workers engaged in other phases of VC or PVC manufacturing do not appear to be at risk of developing AOL. The importance of Raynaud's phenomenon as a concomitant of AOL is emphasized. Several statistical approaches for rapid medical survey are suggested. Acroosteolysis appears to be a systemic rather than local disease. Presently, neither the etiological agent nor its portal of entry is known.

Cook et al.[75] described the polyvinyl chloride production process in considerable detail and concluded that, although no etiological agent could be identified, "There appeared to be a correlation between the extent of degassing prior to entry into the reactor" and the incidence of acroosteolysis.

Kramer and Mutchler[83] presented a paper at the 1968 Gordon Research Conference which drew the following conclusion:

> Our findings suggest that repeated exposure to vinyl chloride at TWA levels of 300 ppm or above for a working lifetime together with a very low level of vinylidene chloride may result in slight changes in certain physiologic and clinical laboratory parameters. The possibility of some impairment in liver function tests must be considered, even though no overt clinical disease was evident in any of the individuals studied. We shall continue our study, but suggest that similar studies to help clarify the effects of this material be performed for other worker populations exposed to vinyl chloride alone.

Since that time, a number of reports[84–86] have been published demonstrating Raynaud's syndrome and acroosteolysis particularly among workers cleaning vinyl chloride reactor tanks. The disease is characterized by hypertrophy of cells of the arteries of the fingers, local inflammation, and impaired circulation.[87] Although generally confined to the hands, some patients have experienced such changes in the toes, legs, arms, and mandible. This condition resolves, generally within about 4 months, after cessation of exposure.[88,89]

Epidemiological studies on U.S. workers have been conducted by Tabershaw–Cooper Associates for the Manufacturing Chemists Association.[90] The authors summarized those data as follows:

> This historical prospective mortality study of 8384 men who had at least one year of occupational exposure to vinyl chloride before December 31, 1972, demonstrated that cancers of the

digestive system (primarily angiosarcoma), respiratory system, brain, and cancers of unknown site, as well as lymphomas, occurred more often than expected in those members of the study population with the greatest estimated exposure. The mortality from other cancers was lower than that of the general male population, with the exception of cancers of the buccal cavity and pharynx. The explanation for the latter finding is not apparent. The other major findings of the study are: 1) the overall mortality of the study population was approximately 75% of what would be expected in a comparable population of U.S. males; 2) no cause of death showed a statistically significant excess over what would be expected in a comparable U.S. male population; and 3) no deaths identified as angiosarcoma of the liver were found other than those previously identified.

This was the first epidemiological study[90] which suggested that vinyl chloride-induced cancer in humans may also be associated with cancers at sites other than those in the liver.[77] The central nervous system (CNS),[91–94] hematopoietic system,[91,95–97] and respiratory system[92,98] have been implicated as at risk for vinyl chloride-induced carcinogenesis. The risk for cancers of the respiratory tract is disputed because these studies[91,98,99] failed to account for tobacco use other than to note that the tumors found are not those usually associated with cigarette smoking.[93]

TLV Recommendation

Acute inhalation of vinyl chloride has caused CNS depression and death. In animals, chronic inhalation of vinyl chloride produced cancers of the liver, kidney, skin, lung, and bones. Skin contact has produced local frostbite in workers. Repeated exposure of workers to vinyl chloride has caused increased liver enzyme concentrations, restricted blood flow, bone degeneration in the fingers, liver and spleen enlargement, nervous system disturbances, CNS depression, decreased respiratory function, and emphysema. Cancer of the liver (hemangiosarcoma) has shown a clear cause and effect relationship with occupational exposure to vinyl chloride.[73,77,93–95,97,100–103] Although not as firmly established as vinyl chloride-induced angiosarcoma, cancers of the lung, brain, mouth, and pharynx have also been observed in workers exposed to vinyl chloride.

A number of quantitative analyses of excess cancer risk associated with chronic exposure to vinyl chloride have been published. Depending upon the particular statistical treatment selected, estimates of human cancer risk associated with chronic exposure to vinyl chloride can differ. The U.S. Environmental Protection Agency (EPA)[104] calculated an upper bound cancer potency (q_1^*) of 2.95×10^{-1} $(mg/kg/day)^{-1}$ from the rat inhalation hepatic angiosarcoma data published by Maltoni et al.[105] and an upper bound ingestion potency[106] of 2.3×10^{-1} $(mg/kg/day)^{-1}$ based on the Feron et al.[107] rat liver and lung tumor data. These analyses, based on the U.S. linearized "multistage" model, have been the subject of severe criticism because they 1) are not validated, 2) are derived from mathematical assumptions rather than from knowledge of the biochemical mechanism of action, 3) show wide variations or risk with small changes in model parameters, and 4) give the impression of precision that cannot be justified from the assumptions upon which such linear models are based. For the case of carcinogen risk assessment, EPA[108] stated:

> The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the one-hit, Weibull, logit or probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

Given that human hepatic angiosarcoma arises from local sinusoidal hyperplasia (which occurs in conjunction with fibroblast proliferation and interstitial hemorrhagic necrosis due to overt hepatotoxicity), it appears that cell proliferation, a response which cannot be accommodated by linear, one-hit models, plays a significant role in the production of vinyl chloride-induced hepatic angiosarcoma.[109] It is apparently the progression of vinyl chloride-induced hepatic fibrosis with chronic high-dose exposure that forms the basis of these cancers in human beings.[110,111] Such hepatic degeneration is more severe among those exposed for longer durations or exposed most recently.[112] Because human angiosarcoma occurs spontaneously in the U.S. at 0.11 to 0.14 case/1 million people per year,[113] Gehring and co-workers,[21] using a probit model based on studies with rats, calculated a lifetime incidence of hepatic angiosarcoma associated with an 8 hour/day, 5 days/week, 35-year exposure at 1 ppm to be 1.5×10^{-8} (or 0.015 theoretical excess cases per 1 million people).

Based on the human case reports and the results of formal epidemiological studies, vinyl chloride is given the A1, confirmed human carcinogen, classification. A TLV–TWA exposure concentration of 5 ppm is recommended. It is the judgment of the TLV Committee that, if the average airborne exposure concentration to vinyl chloride does not exceed 5 ppm, there should be no detect-

able increase in the incidence of occupational cancers, specifically angiosarcoma of the liver. It is the judgment of the Committee that the cancers reported and attributed to vinyl chloride among PVC workers resulted from exposures many times the 5 ppm level. Nonetheless, of practical significance is the potentiation of vinyl chloride-induced hepatic angiosarcomas, hepatomas, and lymphosarcomas by ethanol in laboratory animals[114] and the identification of genetically susceptible individuals.[115,116] Thus, the degree of protection offered by the 5 ppm TLV among workers who consume ethanol or who have sensitive genotypes is not known.

At this time, no STEL is recommended until additional toxicological data and industrial hygiene experience become available to provide a better base for quantifying on a toxicological basis what the STEL should be. The reader is encouraged to review the section on *Excursion Limits* in the "Introduction to the Chemical Substances" of the current TLV/BEI Booklet for guidance and control of excursions above the TLV–TWA, even when the 8-hour TWA is within the recommended limits.

Other Recommendations

OSHA PEL: OSHA regulates vinyl chloride as a potential occupational carcinogen under 29 CFR 1910.1017. OSHA established a PEL–TWA of 1 ppm and a 15-minute ceiling limit of 5 ppm for vinyl chloride.[117]

NIOSH REL/IDLH: NIOSH considers vinyl chloride a potential occupational carcinogen and has established a REL of maintaining occupational exposures at the lowest reliably detectable concentration.[118,119] NIOSH has not established an IDLH value for this substance [NIOSH CARCINOGEN].

ACGIH Rationale for TLVs that Differ from the PEL or REL: From the results of calculations incorporating comparative pharmacokinetics in rodents and humans and using a threshold-based model, ACGIH believes that, if average workplace air exposure to vinyl chloride does not exceed 5 ppm, there should be no detectable increase in the incidence of cancer in exposed workers, specifically angiosarcoma of the liver. This professional judgment was supported by the conclusion that cancers reported and attributed to vinyl chloride among PVC workers resulted from vinyl chloride exposures many times the TLV. Based on studies carried out in rhesus monkeys where only 0.023% to 0.031% of the total absorbed dose could be accounted for via percutaneous absorption,[120] no assignment of the skin notation was made.

NTP Studies: NTP has completed an immunotoxicity study of vinyl chloride. Vinyl chloride has been selected for testing in the *Salmonella* assay. NTP has not conducted other genetic toxicology, short-term toxicology, or long-term toxicology and carcinogenesis bioassays on vinyl chloride.

Carcinogenic Classification

IARC: Group 1, carcinogenic to humans.
MAK: Group A1, capable of inducing malignant tumors as shown by experience with humans.
NIOSH: Carcinogen, with no further categorization
NTP: Group 1, known to be carcinogenic.
OSHA: Carcinogen, with no further categorization.
TLV: A1, confirmed human carcinogen.

Other Nations

Australia: 5 ppm, Category 1, established human carcinogen (substance under review) (1990); Federal Republic of Germany: no MAK value , Group A1, compound capable of inducing malignant tumors as shown by experience with humans; technical guiding concentration (TRK), existing installations for VC and PVC production 3 ppm, others 2 ppm (1992); Sweden: 1 ppm, short-term value 5 ppm, 15 minutes, skin, carcinogen (1990); United Kingdom: 3 ppm, annual maximum exposure limit (MEL), supplemented by a MEL–TWA of 7 ppm with proviso that the annual MEL is not exceeded (1991).

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