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VINYL CHLORIDE MONOMER

BACKGROUND INFORMATION

PHYSICAL AND CHEMICAL PROPERTIES

Chemical Formula: C2H3Cl
Molecular Weight: 62.50
Chemical Names: Chloroethylene
Synonyms: VCM
Freezing point:
Melting point: -153.8°
Boiling point: -13.37°
Physical state: colorless gas; liquefies in a freezing mixture
Vapor density:
Vapor pressure: at 20°; 2530 mm Hg.
Solubility: sol in alc., ether, carbon tetrachloride, benzene

General characteristics:

Vinyl chloride is an inert gas, which has no tendency to diffuse.

Conversion factors:

1 mg/L = 391 ppm; 1 ppm = 2.56 mg/m^3 ; at 20°C and 735 mm Hg pressure 0.1 mg/L = 39.1 ppm and 1 ppm = 2.5 mg/m^3; and 1% volume of vinyl chloride = 25 mg/L.

SUMMARY OF TOXICITY INFORMATION

EFFECTS ON HUMANS

Acute Toxicity

The acute toxicity of vinyl chloride was reviewed by Selikoff and Hammond, 1975; Torkelson and Rowe, 1981; EPA, 1984). The principle routes of exposure are dermal and inhalation. Liquid vinyl chloride in contact with skin produces frostbite. Central nervous system depression occurs in humans at vinyl chloride concentrations of 8000 to 10000 ppm. At concentrations of 10 to 20 % vinyl chloride produces anesthesia, cardiac and respiratory effects. These concentrations are not considered to be toxic to the liver, but may initiate carcinogenesis. Vinyl chloride is rapidly absorbed from the lung and transported to body tissues

Autopsies on humans dying from overexposures to vinyl chloride revealed congestion of the liver, spleen, and kidneys (Danziger, 1960). According to Lester et al., 1960, the short-term (five minutes) exposure limit (STEL) to which a human may be exposed to without producing symptoms of acute toxicity was between 8,000 and 13,000 ppm. Exposure concentrations ranging from 0-200 ppm over longer periods of time were observed to produce a dose relationship in the occurrence of dizziness, nausea, headache, tingling sensation in arms and legs, and fatigue (Spirtas et al., 1975). The relationship between short-term exposure (ppm hrs) and the appearance of clinical symptoms classified as "vinyl chloride disease" is not well characterized because most of the published epidemiologic studies do not present quantified exposure data. The studies of Ott et al., 1975, and Buffler et al., 1979 contain some exposure values.

Subchronic and Chronic Toxicity

Workers repeatedly exposed to vinyl chloride develop a wide range of symptoms which include a vasospastic disorder in the hands similar to Raynaud's syndrome; occupational acroosteolysis, which include club-like swellings and loss of bone from the terminal phalanges, scleroderma-like skin changes, and dermatitis; acrocyanosis, consisting of vascular changes and impaired thermoregulation; positive cold test reactions; capillaroscopic alterations; paresthesias; and central nervous system symptoms. The symptoms are accompanied by circulatory disturbances, thrombocytopenia, splenomegaly, and changes in the liver. Most of the abnormalities disappear after the workers are removed from exposure (Veltman et al., 1975; Wilson, et al., 1967, Harris and Adams, 1967; Lilis et al., 1975)

Epidemiology Studies

Creech and Johnson (1974) were first to describe angiosarcoma of the liver (LAS) among workers exposed to vinyl chloride. The clustering of three cases in one vinyl chloride polymerization facility indicated an abnormally high incidence of this cancer. The Centers for Disease Control (CDC) reported 168 deaths from LAS during the years 1964-1974. The causes of LAS was unknown in 75% of the cases. The three major known causes were vinyl chloride exposure, arsenic exposure, and thorotrast (ThO_2) treatment. Vinyl chloride monomer made up >14% of the cases (Falk et al., 1981)

Infante (1981) evaluated eight epidemiology studies for cancer mortality. Four of eight studies established a correlation between liver cancer death and vinyl chloride exposure. Excess CNS cancer deaths were confirmed in five studies. A third significant cause of death was lung cancer. Information on lymphatic and hematopoietic system cancer was unconfirmed but suggestive.

A review of 20 epidemiological studies by Purchase et al., 1987 involving about 45,000 workers occupationally exposed to VCM showed that neoplasms of the liver increased in incidence in the majority of studies. For brain cancer the association between exposure to VCM and increased incidence was less clear because of the lower relative risk. Neoplasms of the respiratory tract, digestive system, lymphatic and haemopoietic system, buccal cavity, and

pharynx cardiovascular system and colon/stomach were reported to show an increased incidence in one or more studies, but to show no increase, or in some cases a decrease, in incidence in other studies.

In view of the increased incidence of breast neoplasms in rodents exposed to VCM, the studies of Chaizze et al., 1980, who did not confirm these findings in humans, are of importance. The register of LAS cases now contains records of 99 persons with confirmed LAS and occupational exposure to VCM. The average latent period between first exposure to VCM and death from LAS is 21.9 years. The majority of cases occurred in autoclave workers, who are recognized as having been exposed to extremely high levels. Although precise estimates of the pattern of cases roughly suggests that extremely high exposures were necessary for the induction of LAS. Estimation of the exposure levels likely to cause a lifetime risk of LAS of 10^{-6} on the basis of these data give extremely low levels (down to 3.9×10^{-7} ppb which appear to be unrealistic estimates for man. Part of the reason for this is that laboratory studies have shown that VCM is metabolized in the liver (and elsewhere in the body) to the reactive metabolite chloroethylene oxide. The rate of conversion is limited at high levels of exposure giving inaccurate estimates of the slope of the dose-response curve.

A recent epidemiology study was performed by Wong et al., 1991 using the records of 10173 men from 37 U.S. plants manufacturing vinyl chloride, polyvinyl chloride, homopolymers or copolymers. The men worked at least one year and were exposed to vinyl chloride between 1942 and January 1, 1973. Mortality was followed between 1942 and 1982. Of the 1,536 who died, an excess number of liver and bilary tract tumors, angiosarcomas, and brain/CNS cancers were observed. A significant increase in emphysema and chronic obstructive pulmonary disease (COPD) were also observed. The length of time the men were exposed to vinyl chloride fell into three categories; 1) less than 10 yrs, 2) 10-20 yrs, and 3) more than 20 yrs. Liver cancer was significantly elevated in the later two categories with 20 observed vs 1.62 expected and 11 observed vs 0.86 expected, respectively. Deaths in the less than 10 yr category were elevated (6 vs 3.30 expected) but not significantly. Brain and CNS cancer was significantly elevated in the greater than 20 years exposure group with 6 observed deaths vs 1.55 expected. The other two groups had elevated rates which were not significant. The reverse was true for emphysema/COPD. A significant difference was observed for employees with less than 10 years exposure (25 vs 11.97 expected) and not observed for the other two groups. A higher incidence of liver cancer was observed when there was a latency period of 30 years when compared to latencies of 20-30 years and less than 20. A further examination of the statistics, arranging by year of first exposure, revealed the men were most likely to develop liver cancer if exposed before 1950. Overall, the study reported an increase in liver cancer and possibly brain/CNS cancer with exposure to vinyl chloride.

Effects on Animals

Acute and Subchronic Inhalation

Acute 2 hour inhalation LC50s were reported as 27,419 ppm in mice, 47,640 ppm in rats, 236,215 ppm in guinea pigs, and 263,215 ppm in rabbits. Respiratory failure was the principal cause of death and all exposed animals displayed lung, liver and kidney damage (Calif Air Resources Board, 1990).

Male and female ICR mice and Fisher 344 rats were exposed for one hour to vinyl chloride at concentrations of 50, 500, 5000, and 50000 ppm by) Hehir et al., 1981. The male mice exhibited no signs of toxicity except for twitching, hyperactivity, and ataxia at 50000 ppm. Twenty five percent of the female mice developed respiratory problems and ataxia at 50000 ppm. Prior to these poisoning symptoms, the females were hyperactive. All animals recovered within 24 hours and there were no changes in death rate or body weight.

The mice were held with no further exposure until 8 and 18 months of age and then sacrificed for gross and histopathological examination. Bronchio-alveolar adenomas were increased in the 50000 and 5000 ppm groups (i.e.,33% and 17% as opposed to 10% incidence in the controls) and slightly elevated in the 500 ppm group (12.9%). Neoplastic lesions were observed at 5000 ppm.

A second group of mice and rats was given 10 one-hour exposures to 500 ppm or 100 one hour exposures to 50 ppm of VC. All animals were observed for the remainder of their lives, 18-24 months. The one hour exposures at high levels, 5000 and 50000 ppm, increased the incidence of pulmonary adenomas and carcinomas in mice. Repeated exposures to low doses of vinyl chloride resulted in an increased incidence of pulmonary adenomas and carcinomas in mice given 10 one-hour exposures to 500 ppm. At the lower dose of 50 ppm x 100 one-hour exposure, no significant increase in tumors was observed. Fischer rats exposed under the same conditions as the mice failed to elicit a tumorigenic response.

Chronic Inhalation

Maltoni et al., 1981 tested the long term effects of age, strain, species, ingestion, and injection of VC carcinogenicity. In the studies involving age, strain, and species the animals were exposed by inhalation. In studies involving the long term effects of exposure by inhalation, VC was administered to Sprague-Dawley rats at concentrations up to 10000 ppm. In the 17 week study, at the highest two concentrations, 6000 and 10000 ppm, the incidence of Zymbal gland carcinoma was 15.5 and 15.0%, respectively. Incidence was slightly higher in males than females. Neuroblastoma was increased to 15.5, 20,0 and 8.3% in the 10000, 6000, and 2500 ppm exposure groups, respectively. In the 52 week Sprague-Dawley rat studies, the investigators reported the liver angiosarcomas shown in Table 1.

Table 1. Schedule of long-term experiments on the effects of exposure by inhalation for 1 year to different doses of VC on adult Sprague-Dawley rats

Length of Study	Concentration in Air, ppm	LAS Incidence[a/] Male	Female
4 hr/day, 5d/wk	0	0/22	0/29
52 weeks (BT1)	50	0/26	1/29
	250	1/28	2/26
	500	2/22	6/28
	2500	6/26	7/24
	6000	3/17	10/25
	10000	3/21	4/25
4 hr/day, 5d/wk	0	0/61	0/68
52 weeks (BT2)	100	0/37	1/43
	150	1/36	5/46
	200	7/42	5/44
4 hr/day, 5d/wk, 52 weeks (BT6)	30000	5/22	13/24
4 hr/day, 5d/wk	0	0/29	0/38
52 weeks (BT9)	50	7/70	12/110
4 hr/day, 5d/wk	0	0/25	0/44
52 weeks (BT15)	1	0/48	0/55
	5	0/43	0/47
	10	0/42	1/46
	25	1/41	4/40
LAS Incidence in Historical Controls		1/364	2/541

[a/] Number in denominator = number of animals alive when first liver angiosarcoma was observed

According to Maltoni et al., 1981, VC causes tumors in all the animal systems tested. The neoplastic response was affected by treatment schedule, duration of treatment, species, sex, and strain of animals tested. VC showed a clear cut dose response relationship down to 50 ppm. VC produced carcinogenic effects on embryos via the placenta. Newborn animals were extremely responsive developing hepatocarcinomas and angiosarcomas.

Pulmonary Effects

A total of 27 male CD-1 Charles River white mice were exposed to vinyl chloride via inhalation to determine pulmonary effects by Suzuki (1981). The animals were exposed to 0, 2500, and 6000 ppm vinyl chloride for 5 hours/day, 5 days/week for 5 months. A second study exposed 7 mice to 2500 ppm and 6 mice to 6000 ppm in the same manner for an additional month with a two day recovery period. In a third experiment, 7 mice were exposed to 2500 and one to 6000 ppm in the same manner, but allowed a 37-day recovery period. Sixteen mice were used as controls. Out of the three groups, 26/27 exposed mice developed pulmonary tumors. Only one animal, 6000 ppm group, failed to develop a lung tumor.

In a companion inhalation study by Suzuki (1981), four groups of 30 mice were exposed to 0, 1, 10, and 100 ppm vinyl chloride for 5 hours/day, 5 days/week for 4 weeks. Ten animals from each group were sacrificed immediately after exposure, 12 weeks after and 40 weeks after exposure. Alveologenic tumors were observed in 5 of 9 at 100 ppm, 2 of 9 at 10 ppm, 1 of 9 at 1.0 ppm and at 0 of 10, at 0 ppm

Age Related Effects

Sprague-Dawley rats of four different ages (6, 17-18, 32-33, and 51-53 weeks) were exposed 7 hours/day, 5 days/week for 24.5 weeks to 948 ppm vinyl chloride in breathing air (Groth et al., 1981). Animals were sacrificed at 3, 6, and 9 months. Liver angiosarcomas, pituitary adenomas and mammary tumors were the most frequent tumors in the test group, while pituitary adenomas and mammary tumors were the most frequent in the controls. Liver angiosarcomas were not observed until the 16th week. Tumor onset and incidence increased with the age of the animals with females being more susceptible than males.

Reproductive Effects

The effects of vinyl chloride on reproduction were assessed in pregnant CD-1 mice, Sprague-Dawley rats, and New Zealand white rabbits during gestation days (gd) 6-15 for mice and rats and gd 6-18 for rabbits (John et al., 1981). Mice were exposed to 0, 50, and 500 ppm, while rats and rabbits were exposed to 0, 500, and 2500 ppm daily for 7 hours. Mice, rats, and rabbits were sacrificed on gd 18, 21, and 29, respectively. Maternal toxicity was seen in all three species at the highest doses. Toxic effects observed include decreases in weight gain, food consumption, liver weight, and death. Prior to termination of the study 5 of 29 mice, 1 of 17 rats, and 1 of 7 rabbits died in the higher exposure groups. Fetal resorptions were observed in mice exposed to 500 ppm vinyl chloride. Other effects in this group considered related to maternal toxicity were decreased litter size and fetal body weight. The NOEL in mice was 50 ppm.

Implantation and the percentage of pregnant dams were not affected in exposed rats. A decrease in fetal body weight and an increase in fetal crown-rump lengths were noted in the 500 ppm group. No effects on reproduction were observed in rabbits. Vinyl chloride was considered to be nonteratogenic in mice even though skeletal development was delayed (John et al., 1981).

In a separate study by John et al., 1981, breeder Sprague-Dawley rats were exposed 4 hrs/day to vinyl chloride at concentrations of 6000 and 10000 ppm during gd 12 to 18. Males were also exposed in this study. The offspring had a clearly higher incidence of malignant tumors at both doses then their parents. Tumor incidence in offspring was 29.6% at 10000 ppm and 21.9% at 6000 ppm, while the tumor incidence in the parents was 6.7% at both dose levels.

METABOLISM AND PHARMACOKINETICS

The metabolism of vinyl chloride in animals have been studied by a number of investigators (Watanabe et al., 1978; Gehring et al., 1978; Watanabe et al., 1976a; Du, et al., 1982; Watanabe et al., 1976b). The metabolic pathway initially involves the P-450 catalyzed oxidation of vinyl chloride to chloroethylene oxide (CEO), hydrolysis of CEO to chloroethanol, and oxidation of the alcohol to chloroacetaldehyde (CAA). These two products, CEO and CAA, react with glutathione to produce the glutathione conjugate of acetaldehyde. Glutathione-S-epoxide transferase (GEST) and glutathione-S-arylalkyl transferase (GAST) catalyze the reactions with CEO and CAA, respectively. The acetaldehyde conjugate gives rise to two known metabolites, N-acetyl-S- (2-hydroxyethyl) cysteine and thiodiglycolic acid, excreted in urine. The kinetics of the P-450 catalyzed reactions have not been directly studied because of the difficulties involved in measuring CEO, chloroethanol, and CAA in tissues or tissue homogenates.

These reactions are rate limiting, obeying Michaelis-Menten kinetics as demonstrated by dose dependent decreases in urinary metabolites and increases in the amount of VC eliminated via the lung in a rat single dose oral as shown in Table 2 and in six hr inhalation studies as shown in Table 3.

Table 2. Percentage of Administered ^{14}C Activity Recovered Following a Single Oral Dose of Vinyl Chloride (VC)[a/]

	Dose (mg/kg)		
Dose (mg/kg)	0.05	1.0	100
Expired:			
as VC	1.43±0.13[b/]	2.13±0.22	66.64±0.67
as CO2	8.96±0.59	13.26±0.47	2.52±0.13
Urine	68.34±0.54	59.30±2.75	10.84±0.95
Feces	2.39±0.52	2.20±0.39	0.47±0.06
Carcass/tissues	10.13±1.93	11.10±0.47	1.83±0.14
Cage wash[c/]	0	0.84±0.45	0
Total Recovery	91.25±2.47	88.83±1.98	82.30±0.43

[a/]Percentage of dose excreted over 72 hr
[b/]Mean SE five rats per dose.
[c/]Distilled water wash of metabolism cage at termination of the study.
Table 2 taken from Watanable et al. 1976b.

Table 3. Percentage ^{14}C Activity Eliminated during 72 hr following Inhalation Exposure to Vinyl Chloride for 6 hr in rats

	Percentage ^{14}C			
	Exposure concentration			
	10 ppm		1000 ppm	
Expired				
as VC	1.61[a/]	(4)[b/]	12.26[a/]	(814)[b/]
as CO2	12.09	(30)	12.30	(817)
Urine	67.97	(169)	56.3	(3739)
Feces	4.45	(11)	4.21	(280)
Carcass and tissues	13.84	(34)	14.48	(977)
Cage wash[c/]	0.15	(<1)	0.23	(15)
Total VC recovered	100	(248)	100	(6642)

[a/]Expressed as percentage of the total ^{14}C activity recovered
[b/]Microgram equivalents vinyl chloride
[c/]Water, acetone wash of the metabolism cage at termination of the experiment.
Table 3 taken from Watanabe et al. 1976a.

The percentage decrease in urinary metabolites was not as large in the inhalation study as it was in the oral study because the majority of the absorbed ^{14}C-labeled VC was eliminated by the lung during the six hr exposure period. The fate of the ^{14}C-labeled VC present is tissues after 6 hr of exposure is shown in Table 3. At the 10 and 1000 ppm exposure levels, tissues were rapidly depleted of ^{14}C-labeled VC equivalents as shown in Table 4.

Table 4. Percentage of 14C Activity per Gram Tissue 72 hr Following an Inhalation Exposure to [^{14}C]Vinyl Chloride for 6 hr in Rats

	Percentage ^{14}C activity			
	Exposure concentration			
Tissue	10 ppm		1000 ppm	
Liver	0.139[a/]	(0.35)[b/]	0.145[a/]	(9.63)[b/]
Skin	0.072	(0.18)	0.115	(7.64)
Carcass	0.048	(0.12)	0.049	(3.26)
Plasma	0.051	(0.13)		ND
Muscle	0.052	(0.13)	0.038	(2.52)
Lung	0.065	(0.16)	0.046	(3.06)
Fat	0.026	(0.07)		ND
Kidney	0.079	(0.20)	0.057	(3.79)

[a/]Expressed as percentage of total ^{14}C activity per gram of tissue.
[b/]Microgram equivalents of vinyl chloride per gram of tissue.
Table 4 taken from Watanabe et al. 1976a

PHYSIOLOGICALLY-BASED PHARMACOKINETICS

Four published reports (Watanabe et al., 1978; Tarkowski et al., 1980; Jedrychowski et al., 1984, 1985) provided the primary source data for developing a pharmacokinetic model for predicting tissues dose (Clement International Corporation, 1990). Chen and Blancato (1989) proposed a PB-PK model for vinyl chloride pattern after the styrene model of Ramsey and Andersen (1984). The model had four compartments, representing the liver, a fat group, richly- and poorly- perfused tissue groups with metabolism occurring primarily in the liver. Metabolism of vinyl chloride was assumed to occur via one saturable pathway following Michaelis-Menten kinetics. A second first order pathway in the liver was added to this model to evaluate the experimental results of Gehring et al., 1978 and Watanabe et al., 1978. At all doses above 25 ppm, the model predicted a greater amount of vinyl chloride metabolized than observed. The models assumed that vinyl chloride either reacted directly with glutathione or was first metabolized to CEO by P-450 enzymes and then conjugated with glutathione. According to more recent metabolism work, glutathione does not
react directly with vinyl chloride, but is metabolized to CEO by mixed function oxidases. CEO in turn may be conjugated directly with glutathione or hydrolyzed to chloroethanol, oxidized to CAA and conjugated with glutathione. The CAA conjugate gives rise to thiodiglycollic acid and N-acetyl-S-(2-hydroxyethyl)cysteine. On the basis of this information the proposed models need to be rewritten to include the following kinetics.

1. Metabolism of vinyl chloride to CEO by MFO
2. Alkylation of adenosine, guanosine, and cytosine
3. Metabolism of CEO to chloroethanol by hydrolases
4. Metabolism of chloroethanol to CAA by oxidases
5. Conjugation of CEO by glutathione
6. Conjugation of CAA by glutathione
7. Hydrolysis of CEO and CAA glutathione conjugates and acetylation to form N-acetyl-S-(2-hydroxyethyl) cysteine
8. Formation of thioglycollate from CAA

The reactions catalyzed by MFO are saturable reactions while the hydrolytic pathways are believed to obey first order kinetics. The formation of CEO from vinyl chloride appears to be the principle rate limiting step in the metabolism of VC. The amount of CEO available in the liver and other tissues for reaction with DNA is dependent upon the enzymes involved and the kinetics of the competing pathways. At this writing the kinetics of these reactions have not been estimated. An attempt was made by several investigators to determine the kinetics of glutathione conjugation by measuring the loss of this tripeptide via conjugation in conjunction with its synthesis. In the past animal kinetic data have been converted to human data by multiplying the animal Vmax values by $BW^{0.7}$. This procedure is only satisfactory when little or no human data is available.

PHARMACODYNAMICS

The development of liver angiosarcoma is believe to be due to the reaction of small amounts of CEO with DNA. The reaction of CAA with DNA was ruled out based on the results of an experiment conducted by Gwinner et al., 1983, in which the biological effects of VC exposure were compared to those of bis(chloroethyl)ether (BCEE), a metabolic precursor of CAA. The biological end-points investigated were covalent protein binding, nucleic acid (RNA and DNA) alkylation and the potency of the two chemicals to induce preneoplastic and ATPase-deficient foci in rat liver in which only animals exposed to VC developed preneoplastic hepatocellular ATPase deficient foci.

A comparison of the estimated TD50 for CEO, CAA and VC in rodents by Barbin and Bartsch (1989) confirmed that CEO is the ultimate carcinogenic metabolite of VC and suggests that only a very small proportion of metabolically generated CEO is available for DNA alkylation in vivo. The median TD50 for inhaled VC was calculated at 3.9 g/kg, for subcutaneous CEO at 72 mg/kg, and for intragastric CAA at 16 g/kg, indicating that CEO was the ultimate carcinogenic metabolite of VC. Van Muren (1989) compared the potency of VC with two-direct acting carcinogens, chloromethylmethyl ether (CME) and bis(chloromethyl) ether (BCME) and concluded that VC is a weak human carcinogen on the basis of 115 deaths due to angiosarcoma of the liver among several hundred thousand VC exposed workers compared to a total of 87 respiratory cancer deaths among only 3024 CME-BCME exposed workers.

The principal alkylation products after incubation of DNA with ^{14}C-VC, rat liver microsomes and NADPH are 1,N^6-ethenoadenosone, 3,N^4-ethenocytidine and 7-(2-oxoethyl) guanine with the guanine derivative being the major alkylation product (Laib et al., 1981). Single exposure of rats or mice to ^{14}C-VC also confirmed 7-(2-oxoethyl)guanine as the major product (98% of the adducts) of the alkylation of liver DNA (Osterman-Golkar et al., 1977, Laib, et al., 1981).

Direct miscoding of 7-(2-oxoethyl) guanine contributes only slightly to the inductions of mutations (Barbin et al., 1985) and neither the hydrated form of 3, N^4-ethenocytosine nor 1,N^6-ethenoadenine or its hydrate are mutagenic, but 3, N^4-ethenocytosine is mutagenic.

The concentrations of 1,N^6-etheno-2'-deoxyadenosine (edAdO) and 3,N^4-etheno-2'-deoxycytidine (edCyd) expressed as molar ratios of edAdO/2'-deoxyadenosine and edCyd/2'-deoxycytidine were measured in lung and liver DNA of Sprague-Dawley rats exposed to 2000 ppm VC for 10 days, 7 hrs/day, for 9 days and 24 hrs on the tenth day. The ratios were smaller in the liver, 5.0×10^{-8} and 1.6×10^{-7}, respectively, for edAdO and edCyd than they were in the lung with ratios of 1.3×10^{-7} and 3.3×10^{-7}, respectively. The differences are believed to be related to rates of repair in the two organs (Eberle et al., 1989).

RISK ASSESSMENT

The EPA Office of Health and Environmental Assessment (OHEA) published several cancer risk estimates for the lifetime inhalation of vinyl chloride. The 1980 Ambient Water Quality

Criteria for Vinyl Chloride and the 1984 Health Effects Assessment for Vinyl Chloride used total tumors from the 1981 study of Maltoni et al.. The 1985 Health and Environmental Effects Profile for Chloroethene used only liver angiosarcomas from the Maltoni et al. (1981) study.

The 1985 EPA Health and Environmental Effects Profile used rat inhalation exposure data vs LAS tumor (liver angiosarcomas) incidence data from the studies of Maltoni et al., 1981 (see Table 1), the linearized multistage model (LMS), and surface correction to calculate a human inhalation potency of 2.95×10^{-1} $(mg/kg/day)^{-1}$ (upper bound q^*_1). The value gives an excess risk of 1.7×10^{-5} for a dose of 4.0 ug/2L of water (2.0 ppb vinyl chloride, dose of 57×10^{-6} mg/kg/day) or 3.3×10^{-6} for 0.2 ppb of vinyl chloride.

In the 1985 EPA Drinking Water Criteria document, the oral potency of vinyl chloride was estimated to be 2.3 $(mg/kg/day)^{-1}$ using all tumors (female rat neoplastic nodules and angiosarcomas) from the Feron et al. (1981) oral study, linearized multistage, and surface area correction. This potency (upper bound q^*_1) gives a risk of 1.3×10^{-4} for 2.0 ug/L of vinyl chloride in drinking water (dose of 57×10^{-6} mg/kg/day in 2 L of water). The potency value for males (all tumors) was determine to be 2.9×10^{-1}. An update of the 1985 Drinking Water Criteria document will include an assessment of the tumor data from the Til et al. (1983) study.

Chen and Blancato (1989) from EPA used the Airforce PBPK model to convert exposure concentrations in ppm into metabolized doses (chloroethylene oxide in mg/kg/day). The tumor incidence data from the inhalation studies of Maltoni et al.(1981 and 1984), Drew et al. (1983), and Hong et al. (1981) were used along with the tumor data from the oral studies of Maltoni et al. (1981 and 1984), and Feron et al. (1981). Linearized multistage was used to estimate the potency (upper bound on slope (q_1^*)). According to Chen and Blancato (1989) the upper bounds on slope for Maltoni et al. (1981, 1984) inhalation studies were 7.9×10^{-2} and 3.5×10^{-2} $(mg/kg/day)^{-1}$ for the angiosarcomas (males and females, respectively), while the oral gavage data gave slopes of 4.7×10^{-2} and 5.8×10^{-2} $(mg/kg/day)^{-1}$ for the angiosarcomas (males and females, respectively). The Feron et al. (1981) oral data gave slopes of 3.8×10^{-2} and 2.1×10^{-2} $(mg/kg/day)^{-1}$ for angiosarcomas (males and females, respectively). The combined tumors (angiosarcomas and hepatocarcinomas) gave minimum values of 5.4×10^{-2} and 1.3×10^{-1} $(mg/kg/day)^{-1}$ (males and females, respectively) and maximum values of 5.8×10^{-2} and 1.6×10^{-1} (males and females, respectively). According to these numbers, calculated from different data bases (inhalation or oral; male or female rats) the animal potency values are all comparable.

Chen and Blancato used potency slopes of 3.5×10^{-2} (mg metabolite/kg/day)$^{-1}$ and 7.9×10^{-2} (mg metabolite/kg/day)$^{-1}$ derived from female and male rat inhalation data (Maltoni et al. 1984) to predict cancer cases in humans and animals.
The predicted incidences in animals were consistent with the tumor incidences observed in Drew et al. (1983) and Hong et al. (1981). On the basis of female rat potency of 3.5×10^{-2} $(mg/kg/day)^{-1}$, drinking water containing 2.0 ug/L (57×10^{-6} mg/kg/day) gives a risk of 1.9×10^{-6} and 1.2×10^{-5}, respectively, using body weight and surface area correction. A human potency value of 7.98×10^{-2} $(mg/kg/day)^{-1}$ was estimated by Chen and Blancato (1989) using epidemiology data. This value gives an excess risk of 4.5 cancers in 1,000,000 exposed individuals ingesting 4.0 ug (2.0 L consumed/day) of vinyl chloride in 2.0 L of drinking water. The lifetime liver cancer mortality rate in the U.S. population is 1.30×10^{-3}.

The U.S. Airforce PBPK model used by Chen and Blancato (1989) was recently modified by Reitz (1994) to take into consideration up-to-date metabolic and potency information on vinyl chloride. The PBPK model was combined with the multistage model to predict the incidence of liver angiosarcoma produced in humans. The model predicted less risk than calculated by

current nonpharmacokinetic procedures. The incidence of angiosarcomas actually observed in humans is considerably lower than predicted by the new PBPK/multistage model.

On the basis of epidemiology studies vinyl chloride is believed to be less potent in humans than it is in the rat. Surface area correction of rat potency data, as applied in risk assessment, increases the human potency of vinyl chloride by a factor of 6 over the rat. At the present time no consensus has been reached by EPA concerning the proper selection of the tumor incidence data from the animal studies [total tumors (neoplastic nodules and angiosarcomas), hepatocarcinomas, and angiosarcomas] or the best study to use in risk assessment (Maltoni et al., 1981, 1984, Feron et al. 1981, Til et al. 1983, etc). Angio-sarcomas are found in exposed animals and man, and appear to be the most useful tumor. EPA has not used PBPK modeling to estimate the active metabolite (chloroethylene oxide) in their risk assessments. This procedure is necessary when the inhalation data of Maltoni et al. 1981 is used in risk assessment. EPA is currently updating the risk assessment on vinyl chloride.

According to a 1993 ATSDR Toxicology Profile for vinyl chloride, EPA requires that the amount of vinyl chloride in drinking water not exceed 0.002 mg/L per liter of water (2.0 ug/L or 2.0 ppb). For short term exposures drinking water levels should not exceed 2.6 mg/L (2.6 ppm) for 10 days.

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