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Environmental Protection Agency

Office of Emergency and Remedial Response
Washington DC 20460

Office of Research and Development
Office of Health and Environmental Assessment
Environmental Criteria and Assessment Office
Cincinnati OH 45268

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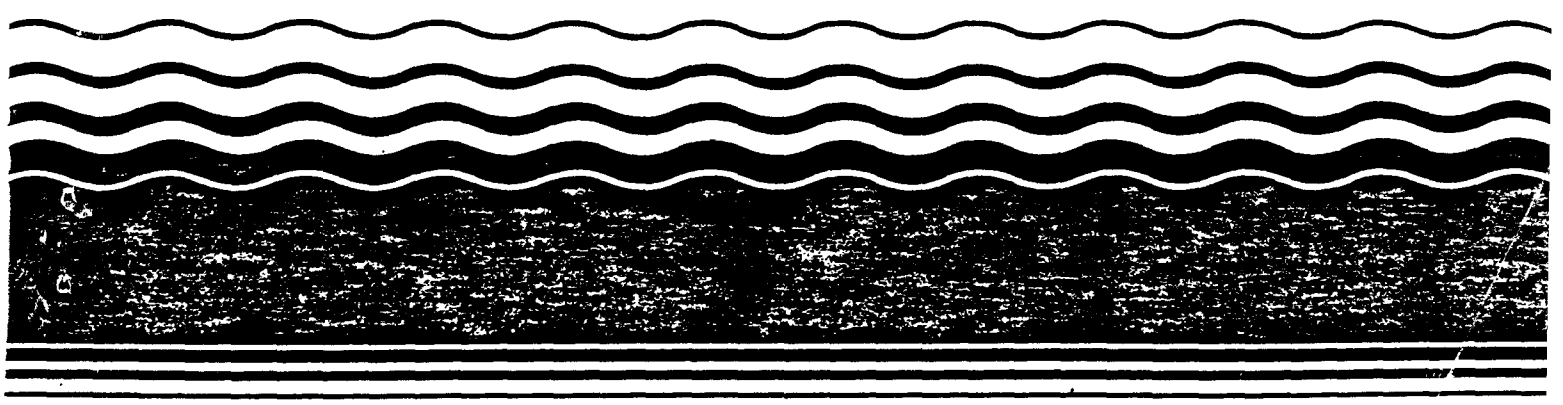
HEALTH EFFECTS ASSESSMENT FOR VINYL CHLORIDE



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U.S. Environmental Protection Agency
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DISCLAIMER

This report has been funded wholly or in part by the United States Environmental Protection Agency under Contract No. 68-03-3112 to Syracuse Research Corporation. It has been subject to the Agency's peer and administrative review, and it has been approved for publication as an EPA document. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

PREFACE

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with vinyl chloride. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on-line literature searches of the Chemical Abstracts, TOXLINE, CANCERLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to September, 1984. Secondary sources of information have also been relied upon in the preparation of this report and represent large-scale health assessment efforts that entail extensive peer and Agency review. The following Office of Health and Environmental Assessment (OHEA) sources have been extensively utilized:

U.S. EPA. 1980a. Ambient Water Quality Criteria for Vinyl Chloride. Environmental Criteria and Assessment Office, Cincinnati, OH. EPA 440/5-80-078. NTIS PB 81-117889.

U.S. EPA 1982. Health and Environmental Effects Profile for Vinyl Chloride. Prepared by the Environmental Criteria and Assessment Office, Cincinnati, OH, OHEA for the Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. 1983a. Reportable Quantity Document for Vinyl Chloride. Prepared by the Environmental Criteria and Assessment Office, Cincinnati, OH, OHEA for the Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. 1983b. Review of Toxicologic Data in Support of Evaluation for Carcinogenic Potential of: Vinyl Chloride. Prepared by the Carcinogen Assessment Group, OHEA, Washington, DC for the Office of Solid Waste and Emergency Response, Washington, DC.

The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data were available. Values were not derived or larger uncertainty factors were employed when the variable data were limited in scope tending to generate conservative (i.e., protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, the AIS or acceptable intake subchronic, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval that does not constitute a significant portion of the lifespan). This type of exposure estimate has not been extensively used or rigorously defined, as previous risk assessment efforts have been primarily directed towards

exposures from toxicants in ambient air or water where lifetime exposure is assumed. Animal data used for AIS estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure.

The AIC, acceptable intake chronic, is similar in concept to the ADI (acceptable daily intake). It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan [see U.S. EPA (1980b) for a discussion of this concept]. The AIC is route specific and estimates acceptable exposure for a given route with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CSs) for noncarcinogens have also been calculated where data permitted. These values are used for ranking reportable quantities; the methodology for their development is explained in U.S. EPA (1983c).

For compounds for which there is sufficient evidence of carcinogenicity, AIS and AIC values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980b). Since cancer is a process that is not characterized by a threshold, <u>any</u> exposure contributes an increment of risk. Consequently, derivation of AIS and AIC values would be inappropriate. For carcinogens, q_1^*s have been computed based on oral and inhalation data if available.

ABSTRACT

In order to place the risk assessment evaluation in proper context, refer to the preface of this document. The preface outlines limitations applicable to all documents of this series as well as the appropriate interpretation and use of the quantitative estimates presented.

Vinyl chloride following inhalation exposure has been shown to be carcinogenic in humans, rats, mice and hamsters. Using data for tumor incidence in rats, a q_1^* for humans of 2.5×10^{-2} $(mg/kg/day)^{-1}$ was estimated.

No data are available concerning oral exposure in humans and cancer risk. On the basis of total tumors in female rats fed vinyl chloride-containing diets, a human q_1^* of 2.3 $(mg/kg/day)^{-1}$ was estimated for oral exposure.

ACKNOWLEDGEMENTS

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LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
AIC	Acceptable intake chronic
AIS	Acceptable intake subchronic
bw	Body weight
CAS	Chemical abstract service
CNS	Central nervous system
CS	Composite score
FEL	Frank-effect level
GOT	Glutamic oxaloacetic transaminase
GPT	Glutamic pyruvic transaminase
LOAEL	Lowest-observed-adverse-effect level
MED	Minimum effective dose
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
ppm	Parts per million
PVC	Polyvinyl chloride
TLV	Threshold limit value
TWA	Time-weighted average
VCM	Vinyl chloride monomer

1. ENVIRONMENTAL CHEMISTRY AND FATE

The relevant physical and chemical properties and environmental fate of vinyl chloride (CAS No. 75-01-4), also known as chloroethene, are given below.

Chemical class:	halogenated aliphatic hydrocarbon (purgeable halocarbon)
Molecular weight:	62.5
Vapor pressure:	2660 mm Hg at 25°C (Callahan et al., 1979)
Water solubility:	2760 mg/ℓ at 25°C (Horvath, 1982)
	1100 mg/kg at 28°C (U.S. EPA, 1980a)
Octanol/water partition coefficient:	24 (estimated) (U.S. EPA, 1980a)
Bioconcentration factor:	2.97 (estimated) (U.S. EPA, 1980a)
Half-lives in	
Air:	1.2 days (Singh et al., 1981)
Water:	several minutes to a few hours (Callahan et al., 1979) 1-5 days (estimated)

The estimated half-life values for vinyl chloride in aquatic media have been derived from the reaeration rate ratio (0.675) and the oxygen reaeration rate of 0.19-0.96 day^{-1} given by Mabey et al. (1981).

The fate of vinyl chloride in soil is not known with certainty. Evaporation is expected to be the predominant loss mechanism from the soil surface. The half-life for soil evaporation should be longer than its evaporative half-life from water. Despite its expected low soil sorption rate and insignificant biodegradation rate (Callahan et al., 1979; Mabey et al., 1981), the probability of groundwater contamination through leaching of vinyl chloride from soil is low (Page, 1981).

2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL MAMMALS

2.1. ORAL

Although quantitative data are not available, Withey (1976) and Watanabe et al. (1976a) have reported rapid absorption of vinyl chloride from the gastrointestinal tract into the blood of dosed rats.

2.2. INHALATION

Rapid absorption and equilibration of vinyl chloride from the lungs into the bloodstream have been reported for rats exposed to the compound by inhalation (Duprat et al., 1977; Watanabe et al., 1976b; Bolt et al., 1977). Within 10 minutes following inhalation exposure of rats to 20,000 ppm of [^{14}C] vinyl chloride for 5 minutes, [^{14}C] was found in several tissues of the exposed animals (Duprat et al., 1977). In a brief review of a study regarding the inhalation uptake of vinyl chloride by rats (Withey and Collins, 1976), the U.S. EPA (1980a) stated that in 200 g rats, the concentration of vinyl chloride in blood produced by intaking 1.97 ppm was equivalent to that produced by gavage treatment with 4.5 mg/kg/day. This relationship held true for gavage doses ranging from 2-25 mg/kg/day.

3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

3.1. SUBCHRONIC

3.1.1. Oral. Feron et al. (1975) administered vinyl chloride monomer by gavage to groups of 15 male and 15 female Wistar rats at a level of 0, 30, 100 or 300 mg/kg bw, 6 days/week, for 13 weeks. Both males and females given the highest dose level had significantly increased liver-to-body weight ratios in the absence of hepatic damage. Males given the highest dose level also had significantly decreased adrenal-to-body weight ratio. Several hematological and biochemical changes were reported, but Feron et al. (1975) expressed reservations about the toxicological significance of these changes. The reported hematological and biochemical changes included a significantly decreased number of leucocytes in the mid- and high-dose groups of females; significantly decreased blood sugar in the mid- and high-dose groups of both sexes; and significantly decreased serum GOT, serum GPT and urinary GOT in the high-dose group of males. Hepatocellular rough endoplasmic reticulum of both sexes of high-dose groups was hypertrophic. No treatment-related effects were reported for the lowest dose groups. The authors considered 30 mg/kg to be the NOEL of this experiment but also stated that a somewhat higher no-effect level could be expected.

3.1.2. Inhalation. Several subchronic inhalation studies of vinyl chloride have been summarized by U.S. EPA (1983a). Due to the time limitations of this project, the subchronic studies discussed below were taken, in part, from that document.

A three-part subchronic inhalation study of rats, guinea pigs, rabbits and dogs revealed toxic effects in rats and rabbits exposed to 50-500 ppm of vinyl chloride, but not in guinea pigs or dogs (Torkelson et al., 1961). In the first part of the study, 10 male and 10 female rats were exposed to 500

ppm (1278 mg/m³) of vinyl chloride for 7 hours/day, 5 days/week, for 4.5 months. Five unexposed rats of each sex served as controls. This exposure level resulted in central lobular granular degeneration in the liver and interstitial and tubular changes in the kidneys. The average liver weight of both sexes of experimental animals was increased over controls; however, this increase was statistically significant in males only ($p=0.001$).

In the second part of the study, rats (20-24 males, 24 females), guinea pigs (10 male, 8 female), rabbits (3 male, 3 female) and dogs (1 male, 1 female) were exposed to 100 or 200 ppm (255.6 or 511.2 mg/m³) of vinyl chloride for 7 hours/day, 5 days/week, for 6 months. In addition, groups of five male rats were exposed to 100 or 200 ppm of vinyl chloride for 0.5, 1, 2 or 4 hours/ day, 5 days/week, for 6 months. Both unexposed and air-exposed controls were used for each species. At the 200 ppm, 7 hours/day level, the livers of both sexes of rabbits were affected by exposure to vinyl chloride, characterized by central lobular granular degeneration in both sexes and necrosis with foamy vacuolation in males or necrosis with periportal cellular infiltration in females. Increased mean liver weights were observed in male and female rats exposed to 100 or 200 ppm of vinyl chloride for 7 hours/day ($p<0.005$, as compared with controls).

In the third part of the study, rats (24 male, 24 female), guinea pigs (12 male, 12 female), rabbits (3 male, 3 female) and dogs (1 male, 1 female) were exposed to 50 ppm (127.8 mg/m³) of vinyl chloride for 7 hours/day, 5 days/week, for 6 months. In addition, groups of 10 male rats were exposed to 50 ppm of vinyl chloride for 1, 2 or 4 hours/day, 5 days/week, for 6 months. Both unexposed and air-exposed controls were used for each species.

For all species tested, there was no difference between treated or control animals in regard to mortality, growth, organ weights, or microscopic examination of tissues. This study suggests a NOEL for rats of 50 ppm and a LOAEL of 100 ppm of vinyl chloride for increased liver weights, and a NOEL for dogs and guinea pigs of 200 ppm of vinyl chloride.

A total of 27 CD-1 Charles River white male mice were exposed to 2500-6000 ppm (6391 or 15,337 mg/m^3) of vinyl chloride for 5 hours/day, 5 days/week, for 5 or 6 months (Suzuki, 1978). Resultant alveologenic tumors in mice were examined by light and electron microscopy to characterize the toxic changes that occur before tumor formation. Suzuki (1980) reported a series of pathological changes including proliferation and hypertrophy of the terminal bronchiolar cells (ciliated and Clara cells), hyperplasia of the alveolar epithelium, degeneration of alveolar septal cells, and occasional peribronchiolar or bronchiolar inflammation. These changes occurred in the lungs of almost all of the treated mice, regardless of whether they were exposed to 2500 or 6000 ppm of vinyl chloride.

Sokal et al. (1980) investigated the effects of chronic inhalation exposure to vinyl chloride with male rats (strain and number not reported). The rats were exposed to 0, 50, 500 or 20,000 ppm of vinyl chloride for 5 hours/day, 5 days/week, for 10 months. Morphological lesions in the liver and testes, depression of body weight gain, increased organ weights, and slight hematological and biochemical changes in the blood were observed in treated animals. The abstract of this study did not distinguish between level of exposure and toxic effects, and the paper was not available for further review.

Following acute toxicity determinations for vinyl chloride, Prodan et al. (1975) studied the long-term effects of vinyl chloride in guinea pigs (strain and sex not reported) in a subchronic inhalation study. Groups of 10 guinea pigs were exposed to 0 or 10% (0 or 100,000 ppm; 0 or 255,624 mg/m^3) vinyl chloride vapors for 2 hours/day for a period of 90 days. There was a statistically significant ($p<0.01$) slowed growth in exposed animals when compared to controls. Vinyl chloride had a narcotic effect on treated animals, resulting in decreased spontaneous activity. There was a significant increase in mean kidney weight in those guinea pigs exposed to 10% vinyl chloride, but the mean liver weight was similar to that of controls. Hepatocellular lesions covering the entire lobule but more dense toward the center, hepatocellular necrosis, and fibroblastic and Kupfferian proliferation were observed in the livers of experimental animals during histopathological examination. Moderate lesions of the glomeruli, marked lesions in the renal tubules, a strong cellular reaction in the spleen (marked by almost total disappearance of the red pulp), and pulmonary fibrosis were also noted in guinea pigs exposed to 10% vinyl chloride. Hematological parameters of treated animals paralleled those of control animals.

In another subchronic inhalation study, Lester et al. (1963) exposed groups of 15 male and 15 female Sherman rats to 0 or 2.0% (0 or 20,000 ppm; 0 or 51,125 mg/m^3) vinyl chloride vapors for 8 hours/day, 5 days/week, for 3 months. No differences in body weight, hemoglobin values, hematocrit and prothrombin values, monocytes, eosinophils, or external appearance were noted between experimental and control animals. The only differences noted in rats exposed to 2% vinyl chloride in comparison to those not exposed to

vinyl chloride were a significant increase in mean liver weight and a significant decrease in mean spleen weight. There was no evidence of tumorigenesis in any organs or tissues examined histopathologically.

3.2. CHRONIC

3.2.1. Oral. Feron et al. (1981) administered vinyl chloride monomer to five groups of 60-80 male and 60-80 female Wistar rats by incorporating polyvinyl chloride powder with a high content of vinyl chloride monomer into the diet or by gastric intubation of a 10% vinyl chloride monomer in soya-bean oil. The dietary levels of vinyl chloride monomer provided doses of 0, 1.7, 5.0 and 14.1 mg/kg/day as determined by measured food consumption, and the gastric intubation dose level was 300 mg/kg bw given 5 days/week. Animals were treated for their lifespan. A dose-related increase in mortality was reported, with decreased survival at all dose levels. There was also an increase in a variety of neoplastic and non-neoplastic treatment-related hepatic lesions at all dose levels. Other treatment-related effects at the 14.1 mg/kg/day and 300 mg/kg bw levels included shortened blood-clotting times, slightly increased serum alpha-foetoprotein levels, hepatomegaly, and increased splenic hematopoietic activity. Feron et al. (1981) concluded that the NOEL for vinyl chloride to rats was <1.7 mg/kg/day, the lowest dose tested in this study.

3.2.2. Inhalation. Numerous chronic inhalation studies of vinyl chloride in humans and experimental animals have been summarized by U.S. EPA (1983a). Due to the time limitations of this project, the chronic studies discussed below were taken, in part, from that document.

There are numerous clinical indications that chronic inhalation exposure to vinyl chloride is toxic to humans (U.S. EPA, 1980a). Hepatitis-like changes, angioneurosis, Reynaud's syndrome, dermatitis, acro-osteolysis,

thyroid insufficiency, and hepatomegaly have been reported (Cordier et al., 1966; Dinman et al., 1971; Filatova et al., 1958; Harris and Adams, 1967; Marsteller and Lebach, 1975; Tribukh et al., 1949; Wedrychowiez, 1976; Wilson et al., 1967). Other long-term effects include functional disturbances of the CNS with adrenergic sensory polyneuritis (Smirnova and Granik, 1970); thrombocytopenia, splenomegaly, liver malfunction with fibrosis, pulmonary changes (Lange et al., 1974); alterations in serum enzyme levels (Makk et al., 1976); portal hypertension attributed to an abnormality of the portal vein radicles, or hepatic sinusoids (Blendis et al., 1978); and angiosarcoma or fibrosis of the liver and acro-osteolysis, all of which are accompanied by microvascular abnormalities (Maricq et al., 1976).

Chronic inhalation studies of experimental animals exposed to vinyl chloride yield toxic effects similar to those seen in humans, involving the liver, spleen, kidneys, hematopoietic system and skeletal system. In a three-part study, Feron et al. (1979a,b) and Feron and Kroes (1979) investigated the toxic effects of chronic inhalation exposure to vinyl chloride in Wistar rats. Groups of 62 male and 62 female rats were exposed to 0 or 5000 ppm (0 or 12, 781 mg/m^3) of vinyl chloride for 7 hours/day, 5 days/week, for 52 weeks. In the first part of the study, growth, mortality, hematology, clinical chemistry and organ weights were examined (Feron et al., 1979a). In rats exposed to 5000 ppm of vinyl chloride, treatment-related toxic effects included slight growth retardation; slightly shortened blood clotting time; increased potassium contents of the blood serum; increased blood nitrogen urea levels; increased kidney, heart and spleen weights; slight signs of anemia; and mortality. In the second part of the study, the experimental animals were examined for morphological changes in the respiratory tract, ceruminous glands, brain, kidneys, heart and spleen (Feron and

Kroes, 1979). Rats exposed to 5000 ppm of vinyl chloride had tubular nephrosis, mild focal degeneration of the myocardium, increased hematopoietic activity in the spleen, and tumors of the brain, lungs, ceruminous glands and nasal cavity. The third part of the study, in which the morphological changes in the liver were examined, indicated degenerative, hyperplastic and neoplastic changes (including hepatocellular carcinoma) in hepatic parenchyma, and angiosarcoma of the liver in rats after exposure to 5000 ppm of vinyl chloride (Feron et al., 1979b). It seems likely that the mortality observed among treated animals may have been due to the carcinogenic response. Neither a NOEL nor a NOAEL for vinyl chloride in rats can be suggested from this study, as the only exposure level tested (5000 ppm) was a FEL for increased mortality, among other effects.

Viola (1970) exposed groups of 25 male Wistar albino rats to 0 or 30,000 ppm of vinyl chloride (equivalent to 0 or 76,690 mg/m^3) for 4 hours/day, 5 days/week, for 12 months. Histological examination was performed on the paws, brain, liver, kidneys and thyroid. Metatarsal bone metaplasia and chondroid metaplasia were observed in treated animals. The skin covering the paws was affected by epidermal hyperkeratosis, basal layer vacuolization and degeneration, disappearance of the cutaneous adnexa, and epidermal edema. Diffuse degenerative lesions of the grey and white matter of the brain and atrophy of the granular layer of the cerebellum were also observed in animals exposed to 30,000 ppm of vinyl chloride. The livers of treated animals were characterized by increased volume, diffused interstitial hepatitis, abnormal proliferation of Kupffer's cells (often hypertrophic) and partial necrosis. The kidneys were marked by signs of tubulonephrosis that were sometimes accompanied by chronic interstitial nephritis. The thyroid was affected by colloid goiter and an increase in parafollicular

cells. Similar histopathological changes were not seen in the skeleton or organs of control animals. The only exposure level tested in this study (30,000 ppm) also represents a FEL.

3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

3.3.1. Oral. Pertinent data regarding the teratogenicity of orally administered vinyl chloride could not be located in the available literature.

3.3.2. Inhalation. Vinyl chloride was not teratogenic when administered by inhalation to rats, mice or rabbits (Ungvary et al., 1978; John et al., 1977, 1981). The discussion of these studies that appears below was taken, in part, from U.S. EPA (1983a).

In a teratogenicity study in CFY rats, Ungvary et al. (1978) exposed groups of 13-28 pregnant rats to 0 or 4000 mg/m³ (~1500 ppm) vinyl chloride for 24 hours/day during days 1-9, 8-14 or 14-21 of gestation. Significantly increased ($p \sim 0.05$) fetal mortality and fetotoxic effects were observed in the offspring of dams exposed to vinyl chloride during the first third of pregnancy (days 1-9 of gestation). Similar effects were not seen in offspring of dams exposed in the second or last third of pregnancy. No teratological effects related to vinyl chloride exposure were noted in any of the experimental groups.

John et al. (1977, 1981) performed a teratogenicity study with pregnant CF_1 mice, Sprague-Dawley rats and New Zealand white rabbits. Initially, groups of 30-40 bred mice, 20-35 bred rats and 15-20 bred rabbits were exposed to 500 ppm (~1278 mg/m³) vinyl chloride for 7 hours/day on days 6-15 (mice and rats) or 6-18 (rabbits) of gestation. Using the same exposure period, mice were subsequently exposed to 50 ppm (~128 mg/m³) vinyl chloride and rats and rabbits to 2500 ppm (~6390 mg/m³) vinyl chloride.

These exposures resulted in maternal toxicity, but no significant embryonal or fetal toxicity or gross teratogenic abnormalities were observed in the offspring of exposed dams. There were excess occurrences of minor skeletal abnormalities and increased fetal deaths at the higher exposure levels; however, neither of these effects occurred at a statistically significant increased incidence when compared with respective control animals.

3.4. TOXICANT INTERACTIONS

Metabolism of vinyl chloride by rats in vivo is inhibited by pretreatment with ethanol or pyrazole, which is an inhibitor of alcohol dehydrogenase, xanthine oxidase and other enzymes (Hefner et al., 1975; Carter and Isselbacher, 1972). In rats, simultaneous chronic ingestion of ethanol and inhalation exposure to vinyl chloride increased the incidence of liver tumors and tumors in other sites as compared to the incidence expected for exposure to only vinyl chloride (Radike et al., 1977). Jaeger (1975) found that the effects on rats of 4-hour inhalation exposures to 200 ppm of vinylidene chloride and 1000 ppm of vinyl chloride were less severe than those seen after exposure to only 200 ppm of vinylidine chloride. The toxicological endpoint used for comparison was serum alanine α-ketoglutarate transaminase levels.

4. CARCINOGENICITY

4.1. HUMAN DATA

4.1.1. Oral. Pertinent data regarding the carcinogenicity of oral exposure to vinyl chloride in humans could not be located in the available literature.

4.1.2. Inhalation. Numerous case reports and epidemiology studies on the carcinogenicity of vinyl chloride to humans have been summarized by IARC (1979), U.S. EPA (1980a, 1983b) and Infante (1981). For the purposes of this document, only those studies presenting sufficient data on the exposed population and a substantial number of cancer cases have been reviewed for the assessment of carcinogenic risk. The exposure and cancer incidence data are summarized in Table 4-1. These data have been previously summarized by U.S. EPA (1983b).

Infante (1981) reviewed epidemiological data that indicate an association between liver cancer, brain cancer, lung cancer, and hematopoietic and lymphatic cancers and vinyl chloride exposure. Waxweiler et al. (1976) reported that 7 of 136 deaths among 1287 workers exposed to vinyl chloride for $\geq$5 years were due to biliary and liver cancer. All seven deaths occurred after a latency period of 15 years. The incidence of biliary and liver cancer among this group of workers was considered to be significantly increased ($p<0.01$) when compared to the expected number of 0.4 cases in this group. Similarly, three brain and CNS cancers were reported after a 15-year latency, while only 0.6 were expected ($p<0.05$). Respiratory system cancers numbered 11, while 5.7 were expected ($p<0.05$). Lymphatic and hematopoietic system cancer occurred in three workers exposed to vinyl chloride, which is suggestive of an increased incidence (1.7 expected) but is not statistically significant.

TABLE 4-1

Epidemiology Studies on Deaths due to Cancer Among Vinyl Chloride Workers

Size of Exposed Population	Size of Control Population	Sex	Level of Exposure	Duration of Exposure	Target Organ	Tumor Type	Number of Cases Observed*	Number of Cases Expected	Relative Risk (p value)	Reference
1287	U.S. death rates	M,F	NR	>5 years	liver and biliary	cancer	7	0.4	16.0 (p<0.01)	Waxweiler et al., 1976
					brain and CNS	cancer	3	0.6	5.0 (p<0.05)	
					lymphatic and hematopoietic	cancer	3	1.7	1.8 (NS)	
					respiratory system	cancer	11	5.7	1.9 (p<0.05)	
750	1969 Swedish population	M	periodically up to 15,000 ppm	>10 years	liver/pancreas	cancer	4	0.68	p<0.005	Bryen et al., 1976
				<1 to >10 years	brain	cancer	2	0.33	p<0.043	
				<1 to >10 years	lung	cancer	3	1.78	p<0.26	
7409	death rates for England and Wales	M	<25 to >200 ppm	6-20 years	liver	cancer	4	1.64	2.44	Fox and Collier, 1977
161	161	M	NR	NR	liver and biliary tract	cancer	8	0.7	11.0	Monson et al., 1974
					brain	cancer	5	1.2	4.2	
					lung	cancer	13	7.9	1.6	
					digestive	cancer	13	8.3	1.6	
					lymphatic and hematopoietic system	cancer	5	3.4	1.5	

*Incidence of tumors after 15-year latency

NS = Not significant; NR = Not reported

In a cohort study of 750 workers exposed to vinyl chloride for >10 years, Bryen et al. (1976) reported four liver/pancreatic cancers, two of which were confirmed liver angiosarcomas, compared to 0.68 cases expected ($p=0.005$). An additional case of hepatic hemangiosarcoma occurred after the data were compiled, and was therefore not included in the reported cases. Two cases of brain cancer were reported compared to 0.33 expected ($p<0.043$). The increased incidence of lung cancer (3 observed vs. 1.78 expected) was not statistically significant.

Fox and Collier (1977) examined the mortality of 7409 workers exposed to vinyl chloride in the production of polyvinyl chloride in eight factories. A total of four deaths due to liver cancer were reported, compared to 1.64 expected. Three of these cases occurred in a factory engaged in polyvinyl chloride production since 1944 (the longest period of those factories examined), while only 0.13 would have been expected ($p<0.01$) (Infante, 1981). It was noted, however, that 75% of this study cohort had been employed for <10 years, which does not allow for a sufficient latency period and therefore underestimates the observed risk of cancer.

Of 161 deaths among vinyl chloride workers, there were 8 liver and biliary cancers (0.7 expected; 11.0 risk ratio), 5 brain cancers (1.2 expected; 4.2 risk ratio), 13 lung cancers (7.9 expected; 1.6 risk ratio), 13 digestive tract cancers (8.3 expected; 1.6 risk ratio), and 5 lymphatic and hematopoietic cancers (3.4 expected; 1.5 risk ratio) (Monson et al., 1974). The authors did not report statistical comparisons of these data, but did note an excess frequency of liver, lung and brain cancers. It was also reported that the frequency of all cancers increased with length of exposure and latency (Monson et al., 1974).

4.2. BIOASSAYS

4.2.1. Oral. An oral study (Feron et al., 1981) in which vinyl chloride was given in the diet or by gavage was used by the U.S. EPA (1984) to derive a q_1^* for oral exposure. In the dietary study groups of 60 male and 60 female 5-week-old Wistar rats were fed diets containing 10% PVC powder (PVC, containing not more than 0.3 ppm), which acted as a carrier for liquid VCM. A control group of 80 males and 80 females was given a diet containing PVC without added VCM. The VCM used in this study was >99.97% pure. Diets were prepared daily and offered for 6 hours each day. In addition, another control group (80 males and 80 females) was fed diets containing PVC without VCM ad libitum and an additional treatment group (60 males and 60 females) was given VCM in soya oil at 300 mg/kg bw/day. A vehicle control (soya oil) group was not used in this experiment. The feeding trials lasted for 135 weeks for males and 144 weeks for females. Gavage treatment was performed 5 days/week for 83 weeks.

Body weights and food consumptions were measured periodically throughout the study. Fecal VCM was subtracted from VCM intakes on the assumption that it represented VCM enclosed in PVC granules and not available to the body. Dietary levels of VCM of 0, 20, 60 and 200 ppm resulted in actual exposure of 0, 1.7, 5.0 and 14.1 mg VCM/kg bw/day. Complete histopathological examinations were performed on tissues and organs of 20 males and 20 females from the control (restricted feeding), high-dose diet and gavage groups at termination. In addition, all gross lesions and tumors were histopathologically examined as were selected tissues from 10 males and 10 females from these groups sacrificed at 26 and 52 weeks.

A statistically significant dose-related decrease in survival became evident in rats fed diets containing VCM at 80 weeks of treatment. Survival was also reduced in gavage-treated rats but statistical analyses were not performed because a vehicle control group had not been maintained. The U.S. EPA (1984) reported the incidences of liver and lung tumors by type and the q_1^* associated with each individual tumor in rats fed VCM in the diet. These data are presented in Tables 4-2 (males) and 4-3 (females). A dose-related increased incidence of hepatocellular carcinomas, and liver and lung angiosarcomas were noted in rats of both sexes. A high incidence of angiosarcoma of the lung (19/60 males, 23/60 females) was also noted in gavage-treated rats. A significantly increased incidence ($p<0.05$ at the two highest dose levels; Fisher Exact Test) of liver angiosarcomas was seen in Sprague-Dawley rats (40/sex/dose level) given vinyl chloride by gastric intubation (in olive oil) at levels of 0, 3.33, 16.65 or 50 mg/kg bw, 4-5 times/week, for 52 weeks (Maltoni, 1977a; Maltoni et al., 1975). Survival at 85 weeks after the beginning of treatment was 35 control, 39 low-dose, 32 mid-dose and 23 high-dose animals. After 120 weeks, the number and types of tumors reported were 1 Zymbal gland tumor in the control group; 1 intra-abdominal angiosarcoma in the low-dose group; 9 liver angiosarcomas, 2 Zymbal gland carcinomas, and 3 nephroblastomas in the mid-dose group; and 16 liver angiosarcomas, 2 nephroblastomas, 1 Zymbal gland carcinoma, 1 thymic angiosarcoma, and 1 intra-abdominal angiosarcoma in the high-dose group. The individual incidences for each sex were not segregated in the available summaries of this study (IARC, 1979; U.S. EPA, 1983b). The incidences of hepatic angiosarcoma and renal nephroblastoma are summarized in Table 4-4.

TABLE 4-2

Type and Incidence of Statistically Significant Treatment-Related Changes in the Liver and Lung of Male Wistar Rats Exposed to VCM in the Diet. Values of q_1^* and Concentration from Multistage Extrapolation Model Included[a]

	Treatment Group (mg/kg/day)				q_1^*[b]
	0	1.7	5.0	14.1	$(mg/kg/day)^{-1}$
Number of rats examined[c]	55	58	56	59	
Liver					
Neoplastic nodules	0	1	7	23	2.1×10^{-1}
Hepatocellular carcinomas	0	1	2	8	8.8×10^{-2}
Angiosarcomas	0	0	6	27	1.3×10^{-1}
Total liver tumors[d]	0	2	13	50	3.0×10^{-1}
Lung					
Angiosarcomas	0	0	4	19	1.1×10^{-1}
Total animals with tumors	0	2	17	58	2.9×10^{-1}

[a]Source: Adapted from Feron et al., 1981

[b]Human equivalent $q_1^* = q_1^*(a)(W_h W_a)^{1/3}$ in $(mg/kg/day)^{-1}$

[c]Found dead or killed in extremis or terminally

[d]Sum of neoplastic nodules and liver angiosarcomas

TABLE 4-3

Type and Incidence of Statistically Significant Treatment-Related Changes in the Liver and Lung of Female Wistar Rats Exposed to VCM in the Diet. Values of q_1^* and Concentration from Multistage Extrapolation Model Included[a]

	Treatment Group (mg/kg/day)				
	0	1.7	5.0	14.1	q_1^{*b} $(mg/kg/day)^{-1}$
Number of rats examined[c]	57	58	59	57	
Liver					
Neoplastic nodules	2	26	39	44	1.3
Hepatocellular carcinomas	0	4	19	29	5.0×10^{-1}
Angiosarcomas	0	0	2	9	8.8×10^{-2}
Total liver tumors[d]	2	26	41	53	1.9
Lung					
Angiosarcomas	0	0	1	5	5.8×10^{-2}
Total animals with tumors	2	26	42	56	2.3

[a]Source: Adapted from Feron et al., 1981

[b]Human equivalent $q_1^* = q_1^*(a)(W_h W_a)^{1/3}$ in $(mg/kg/day)^{-1}$

[c]Found dead or killed in extremis or terminally

[d]Sum of neoplastic nodules and liver angiosarcomas

TABLE 4-4

Tumor Incidences in Sprague-Dawley Rats Dosed with Vinyl Chloride by Gavage[a]

Sex	Dose or Exposure[b] (mg/kg)	Duration of Treatment (weeks)	Duration of Study (weeks)	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence (p value)
NR	50	52	136	NR	olive oil	liver	angiosarcoma	16/80 ($p<0.05$)[c]
						kidney	nephroblastoma	2/80
NR	16.5	52	136	NR	olive oil	liver	angiosarcoma	9/80 ($p<0.05$)[c]
						kidney	nephroblastoma	3/80
M,F	0.0	52	136	NA	olive oil only	liver	angiosarcoma	0/150
						kidney	nephroblastoma	0/150

[a]Source: Maltoni, 1977b

[b]Exposure to vinyl chloride by gavage was once daily in olive oil 4-5 days/week for 52 weeks

[c]Fisher exact test was performed by Syracuse Research Corporation

NA = Not applicable; NR = Not reported

ation. There are numerous inhalation studies on the carcino-
vinyl chloride in experimental animals. Inhalation exposures to
ride have resulted in increased incidences of various tumors,
pulmonary adenomas and adenocarcinomas, angiosarcomas of the liver
er sites, lymphomas, mammary carcinomas, and neuroblastomas of the brain, in mice, rats and hamsters (Wagoner, 1983). Inhalation exposure to vinyl chloride at concentrations as low as 10 ppm have resulted in hepatic and extrahepatic angiosarcomas, whereas mammary carcinomas are produced at even lower concentrations (e.g., 1 or 5 ppm) (Wagoner, 1983). Due to the limitations of this project, only the most substantial studies will be reviewed and used as a basis for evaluating carcinogenic risk associated with inhalation exposure to vinyl chloride. The reader is referred to the summaries by U.S. EPA (1980a, 1982, 1983b) and IARC (1979).

Maltoni and Lefemine (1974a,b, 1975) investigated the carcinogenic effects of inhaled vinyl chloride in rats exposed to concentrations ranging from 50-10,000 ppm for 5 days/week, for 52 weeks. The animals were observed for tumor development for their lifespan (length of experiment equal to 135 weeks). The total tumor incidences after 135 weeks, reported by U.S. EPA (1980a) as the basis for deriving a human cancer based criterion for vinyl chloride, were 6/58 controls, 10/59 at the 50 ppm level, 16/59 at the 250 ppm level, 22/59 at the 500 ppm level, 32/59 at the 2500 ppm level, 31/60 at the 6000 ppm level, and 38/61 at the 10,000 ppm level. Differential responses between the sexes were not reported. The tumor types included hepatic angiosarcomas, renal nephroblastomas, Zymbal gland carcinomas, and others unspecified. These tumor incidences are summarized in Table 4-5.

TABLE 4-5

Incidence of Tumors in Sprague-Dawley Rats Exposed 4 Hours/Day, 5 Days/Week, for 52 Weeks by Inhalation to Various Concentrations of Vinyl Chloride: Results after 135 Weeks*

Concentration (ppm)	Number of Animals		Liver		Kidney		Zymbal Gland		Other	Total Number of Rats with One or More Tumors
	Total	Corrected	Angio-sarcomas	Average Latency (weeks)	Nephro-blastomas	Average latency (weeks)	Carcinomas	Average Latency (weeks)		
10,000	69	61	9	64	5	59	16	50	25	38
6,000	72	60	13	70	4	65	7	62	19	31
2,500	74	59	13	78	6	74	2	33	18	32
500	67	59	7	81	4	83	4	79	11	22
250	67	59	4	79	6	80	0	0	9	16
50	64	59	1	135	1	135	0	0	12	10
No treatment	68	58	0	0	0	0	0	0	10	6

*Source: Maltoni and Lefemine, 1975

Viola et al. (1971) reported an increased incidence of skin carcinomas, lung carcinomas and osteochondromas in Wistar rats exposed to 30,000 ppm of vinyl chloride by inhalation. Since then, studies by Maltoni (1977b), Maltoni et al. (1981), Lee et al. (1978) and Hong et al. (1981) have also provided evidence of the carcinogenicity of vinyl chloride in experimental animals. These five studies are summarized in Tables 4-6 through 4-10.

Maltoni (1977b) reported an increased incidence of hepatic angiosarcoma and renal nephroblastoma in Sprague-Dawley rats exposed by inhalation. Kidney nephroblastomas were seen in animals exposed to 6000 or 10,000 ppm of vinyl chloride, whereas an increased incidence of liver angiosarcoma was reported in groups exposed to concentrations as low as 100 ppm. More recently, Maltoni et al. (1981) reported kidney nephroblastomas in groups of rats exposed by inhalation to 25 ppm of vinyl chloride, while control groups had none. Liver angiosarcomas were evident in rats exposed to 100 ppm of vinyl chloride by inhalation. Similar tumors were not seen in rats exposed to 0, 1 or 5 ppm of vinyl chloride. For groups of Swiss mice exposed by inhalation to 50, 250, 500, 2500, 6000 or 10,000 ppm of vinyl chloride, Maltoni et al. (1981) reported a dose-related incidence of liver angiosarcomas and lung tumors. In Golden hamsters exposed at the same levels, papillomas and acanthomas of the forestomach were produced by vinyl chloride exposure.

In groups of 36 male and 36 female CD rats, lung and liver hemangiosarcomas were produced in groups of animals exposed by inhalation to 250 or 1000 ppm of vinyl chloride (Lee et al., 1978). This study indicated that females of this strain were more susceptible to the carcinogenic effect of vinyl chloride. Rats treated with 0 or 50 ppm of vinyl chloride did not

TABLE 4-6

Tumor Incidences in Male Wistar (Ar/IRE) Rats Exposed to 30,000 ppm of Vinyl Chloride by Inhalation[a]

Dose or Exposure[b] (ppm)	Duration of Treatment	Duration of Study	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence
30,000	12 months	>12 months	99%	vapor/air	skin	epidermoid carcinoma	15/26
					lung	carcinoma	6/26
					bone	osteochondroma	5/26
0	NA	>12 months	NA	air only	skin	epidermoid carcinoma	0/25
					lung	carcinoma	0/25
					bone	osteochondroma	0/25

[a]Source: Viola et al., 1971

[b]Exposure was for 4 hours/day, 5 days/week for 12 months.

NA = Not applicable

TABLE 4-7

Tumor Incidences in Sprague-Dawley Rats Exposed to 100-10,000 ppm of Vinyl Chloride[a]

Exposure Route	Dose or Exposure[b] (ppm)	Duration of Treatment (weeks)	Duration of Study (weeks)	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence
Inhalation	10,000	52	155	vapor/air	liver kidney	angiosarcoma nephroblastoma	9/60 5/60
Inhalation	6,000	52	155	vapor/air	liver kidney	angiosarcoma nephroblastoma	13/60 4/60
Inhalation	200	52	143	vapor/air	liver	angiosarcoma	12/120
Inhalation	150	52	143	vapor/air	liver	angiosarcoma	5/120
Inhalation	100	52	143	vapor/air	liver	angiosarcoma	1/120
NA	0	52	143-155	air only	liver kidney	angiosarcoma nephroblastoma	0/500 0/120

[a]Source: Maltoni, 1977b

[b]Exposure to vinyl chloride by inhalation was for 4 hours/day, 5 days/week for 52 weeks

NA = Not applicable; NR = Not reported

TABLE 4-8

Tumor Incidences in Sprague-Dawley Rats, Swiss Mice and Syrian Golden Hamsters Exposed to Various Concentrations of Vinyl Chloride by Inhalation[a,b]

Sex	Dose or Exposure[c] (ppm)	Duration of Treatment (weeks)	Duration of Study (weeks)	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence
				RATS			
M,F	30,000	52	68	air/vapor	liver kidney	angiosarcoma nephroblastoma	18/60 NR
M,F	10,000	52	135	air/vapor	liver kidney	angiosarcoma nephroblastoma	7/60 5/60
M,F	6,000	52	135	air/vapor	liver kidney	angiosarcoma nephroblastoma	13/59 5/59
M,F	2,500	52	135	air/vapor	liver kidney	angiosarcoma nephroblastoma	13/60 6/60
M,F	500	52	135	air/vapor	liver kidney	angiosarcoma nephroblastoma	6/60 6/60
M,F	250	52	135	air/vapor	liver kidney	angiosarcoma nephroblastoma	3/59 5/59
M,F	200	52	143	air/vapor	liver kidney	angiosarcoma nephroblastoma	12/120 7/120
M,F	150	52	143	air/vapor	liver kidney	angiosarcoma nephroblastoma	6/119 11/119
M,F	100	52	143	air/vapor	liver kidney	angiosarcoma nephroblastoma	1/120 10/120
M,F	50	52	135	air/vapor	liver kidney	angiosarcoma nephroblastoma	1/60 1/60
M,F	25	52	147	air/vapor	liver kidney	angiosarcoma nephroblastoma	5/120 1/120

TABLE 4-8 (cont.)

Sex	Dose or Exposure[c] (ppm)	Duration of Treatment (weeks)	Duration of Study (weeks)	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence
				RATS (cont.)			
M,F	10	52	147	air/vapor	liver kidney	angiosarcoma nephroblastoma	1/119 0/119
M,F	5	52	147	air/vapor	liver kidney	angiosarcoma nephroblastoma	0/119 0/119
M,F	1	52	147	air/vapor	liver kidney	angiosarcoma nephroblastoma	0/118 0/118
M,F	0	NA	135-147	air only	liver kidney	angiosarcoma nephroblastoma	0/363 0/363
				MICE			
M,F	10,000	30	81	air/vapor	liver lung	angiosarcoma tumor	10/56 46/56
M,F	6,000	30	81	air/vapor	liver lung	angiosarcoma tumor	13/60 47/60
M,F	2,500	30	81	air/vapor	liver lung	angiosarcoma tumor	16/59 40/59
M,F	500	30	81	air/vapor	liver lung	angiosarcoma tumor	14/60 50/60
M,F	250	30	81	air/vapor	liver lung	angiosarcoma tumor	18/60 41/60
M,F	50	30	81	air/vapor	liver lung	angiosarcoma tumor	1/60 6/60
M,F	0	NA	81	air only	liver lung	angiosarcoma tumor	0/150 15/150

TABLE 4-8 (cont.)

Sex	Dose or Exposure[c] (ppm)	Duration of Treatment (weeks)	Duration of Study (weeks)	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence
				HAMSTERS			
M,F	10,000	30	109	air/vapor	forestomach	papilloma/acanthoma	10/30
M,F	6,000	30	109	air/vapor	forestomach	papilloma/acanthoma	10/30
M,F	2,500	30	109	air/vapor	forestomach	papilloma/acanthoma	17/30
M,F	500	30	109	air/vapor	forestomach	papilloma/acanthoma	9/30
M,F	250	30	109	air/vapor	forestomach	papilloma/acanthoma	4/30
M,F	50	30	109	air/vapor	forestomach	papilloma/acanthoma	3/30
M,F	0	NA	109	air only	forestomach	papilloma/acanthoma	3/60

[a]Source: Maltoni et al., 1981

[b]Purity of compound was >99.9%

[c]Exposure was for 4 hours/day, 5 days/week

NA = Not applicable; NR = Not reported

TABLE 4-9

Tumor Incidences in CD Rats and CD-1 Mice Exposed to 50-1000 ppm of Vinyl Chloride by Inhalation[a]

Sex	Dose or Exposure[b] (ppm)	Duration of Treatment (months)	Duration of Study (months)	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type[b]	Tumor Incidence (p value)
				RATS				
M	50	12	12	99.8%	vapor/air	liver	hemangiosarcoma	0/36
						lung	hemangiosarcoma	0/36
F	50	12	12	99.8%	vapor/air	liver	hemangiosarcoma	0/36
						lung	hemangiosarcoma	0/36
M	250	12	12	99.8%	vapor/air	liver	hemangiosarcoma	2/36
						lung	hemangiosarcoma	0/36
F	250	12	12	99.8%	vapor/air	liver	hemangiosarcoma	10/34 ($p<0.05$)
						lung	hemangiosarcoma	3/34
M	1000	12	12	99.8%	vapor/air	liver	hemangiosarcoma	6/34
						lung	hemangiosarcoma	4/34
F	1000	12	12	99.8%	vapor/air	liver	hemangiosarcoma	15/36 ($p<0.05$)
						lung	hemangiosarcoma	9/36
M	0	NA	12	NA	air only	liver	hemangiosarcoma	0/35
						lung	hemangiosarcoma	0/35
F	0	NA	12	NA[c]	air only	liver	hemangiosarcoma	0/35
						lung	hemangiosarcoma	0/35

TABLE 4-9 (cont.)

Sex	Dose or Exposure[b] (ppm)	Duration of Treatment (months)	Duration of Study (months)	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type[b]	Tumor Incidence (p value)
				MICE				
M	0	NA	12	NA	air only	respiratory tract	bronchioloalveolar adenoma	1/26
						liver	hemangiosarcoma	0/26
F	0	NA	12	NA	air only	respiratory tract	bronchioloalveolar adenoma	0/36
						liver	hemangiosarcoma	0/36
M	50	12	12	99.8%	vapor/air	respiratory tract	bronchioloalveolar adenoma	8/29
						liver	hemangiosarcoma	3/29
F	50	12	12	99.8%	vapor/air	respiratory tract	bronchioloalveolar adenoma	4/34
						liver	hemangiosarcoma	0/34
M	250	12	12	99.8%	vapor/air	respiratory tract	bronchioloalveolar adenoma	10/29
						liver	hemangiosarcoma	7/29 ($p<0.05$)
F	250	12	12	99.8%	vapor/air	respiratory tract	bronchioloalveolar adenoma	12/34
						liver	hemangiosarcoma	16/34 ($p<0.05$)
M	1000	12	12	99.8%	vapor/air	respiratory tract	bronchioloalveolar adenoma	22/33
						liver	hemangiosarcoma	13/33 ($p<0.05$)
F	1000	12	12	99.8%	vapor/air	respiratory tract	bronchioloalveolar adenoma	26/36
						liver	hemangiosarcoma	18/36 ($p<0.05$)

[a]Source: Lee et al., 1978

[b]Exposure was for 6 hours/day, 5 days/week

NA = Not applicable

TABLE 4-10

Tumor Incidences in CD Rats and CD-1 Mice Exposed to Various Concentrations of Vinyl Chloride by Inhalation[a]

Sex	Dose or Exposure[b] (ppm)	Duration of Treatment (months)	Duration of Study (months)	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type[c]	Tumor Incidence
				RATS				
M,F	50	6 or 10[d]	18 or 22[d]	99.8%	air/vapor	liver	hepatocellular carcinoma	0/66
							hemangiosarcoma	0/66
						lung	bronchioloalveolar tumor	0/66
							hemangiosarcoma	0/66
M,F	250	6 or 10[d]	18 or 22[d]	99.8%	air/vapor	liver	hepatocellular carcinoma	2/68
							hemangiosarcoma	5/68
						lung	bronchioloalveolar tumor	2/68
							hemangiosarcoma	2/68
M,F	1000	6 or 10[d]	18 or 22[d]	99.8%	air/vapor	liver	hepatocellular carcinoma	7/72
							hemangiosarcoma	14/72
						lung	bronchioloalveolar tumor	4/72
							hemangiosarcoma	7/72
M,F	0	6 or 10[d]	18 or 22[d]	99.8%	air/vapor	liver	hepatocellular carcinoma	1/72
							hemangiosarcoma	0/72
						lung	bronchioloalveolar tumor	0/72
							hemangiosarcoma	0/72
				MICE				
M,F	50	1	13	99.8%	air/vapor	lung	bronchioloalveolar tumor	3/32
						liver	hemangiosarcoma	1/32
M,F	250	1	13	99.8%	air/vapor	lung	bronchioloalveolar tumor	19/32
						liver	hemangiosarcoma	0/32
M,F	1000	1	13	99.8%	air/vapor	lung	bronchioloalveolar tumor	20/32
						liver	hemangiosarcoma	0/32

TABLE 4-10 (cont.)

Sex	Dose or Exposure[b] (ppm)	Duration of Treatment (months)	Duration of Study (months)	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type[c]	Tumor Incidence
				MICE (cont.)				
M,F	0	1	13	99.8%	air/vapor	lung	bronchioloalveolar tumor	3/32
						liver	hemangiosarcoma	0/32
M,F	50	3	15	99.8%	air/vapor	lung	bronchioloalveolar tumor	12/32
						liver	hemangiosarcoma	0/32
M,F	250	3	15	99.8%	air/vapor	lung	bronchioloalveolar tumor	21/32
						liver	hemangiosarcoma	4/32
M,F	1000	3	15	99.8%	air/vapor	lung	bronchioloalveolar tumor	5/20
						liver	hemangiosarcoma	16/20
M,F	0	3	15	99.8%	air/vapor	lung	bronchioloalveolar tumor	2/32
						liver	hemangiosarcoma	0/32
M,F	50	6	18	99.8%	air/vapor	lung	bronchioloalveolar tumor	3/16
						liver	hemangiosarcoma	1/16
M,F	250	6	18	99.8%	air/vapor	lung	bronchioloalveolar tumor	12/20
						liver	hemangiosarcoma	9/20
M,F	1000	6	18	99.8%	air/vapor	lung	bronchioloalveolar tumor	14/24
						liver	hemangiosarcoma	13/24
M,F	0	6	18	99.8%	air/vapor	lung	bronchioloalveolar tumor	11/56
						liver	hemangiosarcoma	1/56

[a]Source: Hong et al., 1981

[b]Exposure for 6 hours/day, 5 days/week

[c]Showed dose-related response; significant at $p<0.05$

[d]Duration of exposure was for 6 or 10 months, followed by a 12-month latency period. The results presented are for the combined treatment-duration group.

develop similar tumors. Lee et al. (1978) also reported an increased incidence of bronchioalveolar adenoma and hepatic hemangiosarcomas in male and female CD-1 mice exposed to 50, 250 or 1000 ppm of vinyl chloride by inhalation for 6 hours/day, 5 days/week.

In a study examining the carcinogenic effect of vinyl chloride at various doses (50, 250 or 1000 ppm) by inhalation for various durations of treatment (6 or 10 months treatment period for rats; 1, 3 or 6 months treatment period for mice), Hong et al. (1981) reported elevated numbers of lung and liver hemangiosarcomas, hepatocellular carcinomas and bronchioloalveolar tumors in rats treated with 250 ppm of vinyl chloride for 6 or 10 months duration. All four tumor types showed a significant dose-related response in rats. In mice, only hemangiosarcomas showed a dose-related response. One month of exposure to 250 or 1000 ppm of vinyl chloride for 6 hours/day, 5 days/week, followed by a 12-month latency period, was sufficient to produce an increased incidence of bronchioloalveolar tumors in mice.

4.3. OTHER RELEVANT DATA

The mutagenicity of vinyl chloride has been reviewed by IARC (1979), U.S. EPA (1980a), Bartsch and Montesano (1975), Bartsch et al. (1976) and Fishbein (1976). Vapors of vinyl chloride induced reverse mutations in Salmonella typhimurium in the presence of a 9000 x g supernatant from rat liver (Andrews et al., 1976; Bartsch et al., 1975; Garro et al., 1976; Malaveille et al., 1975; McCann et al., 1975; Rannug et al., 1974) from mouse liver (Bartsch et al., 1975; Garro et al., 1976; Malaveille et al., 1975), and from human liver biopsy specimens (Bartsch et al., 1975, 1979; Malaveille et al., 1975). Vinyl chloride vapors induced mutations in the S. typhimurium assay without metabolic activation, but the mutagenic response was much higher with metabolic activation (Andrews et al., 1976; Bartsch et al., 1975; McCann et al., 1975).

When tested in aqueous or methanolic solution, vinyl chloride was negative in the S. typhimurium test system (Bartsch et al., 1975; Rannug et al., 1974) but induced reverse mutations in Escherichia coli K12 (Greim et al., 1975), forward mutations in Schizosaccharomyces pombe and mitotic gene conversions in Saccharomyces cerevisiae in the presence of mammalian metabolic activation (Loprieno et al., 1976, 1977).

Both vapors and an ethanol solution of vinyl chloride were negative in a mutagenicity assay with Neurospora crassa, regardless of whether metabolic activation was present or not (Drozdowicz and Huang, 1977). Forward mutations were induced in V79 Chinese hamster cells by vinyl chloride in the presence of a mammalian metabolic activation system (Drevon et al., 1977). Vinyl chloride vapors induced a significantly increased frequency of recessive lethals in Drosophila melanogaster (Magnusson and Ramel, 1976; Verburgt and Vogel, 1977) but not dominant lethals, translocations or sex-chromosome loss (Verburgt and Vogel, 1977). No dominant lethal mutations were observed in male CD-1 mice exposed to various levels of vinyl chloride by inhalation (Anderson et al., 1976, 1977).

4.4. WEIGHT OF EVIDENCE

Vinyl chloride has been shown to be a carcinogen in rats, mice and hamsters. It produces a high incidence of liver, kidney, lung and brain tumors in a dose-related response when administered by oral or inhalation routes. Similar carcinogenic effects have been reported in workers exposed to vinyl chloride. The predominant target organs are the liver, brain, lung and lympho-hematopoietic system, but a general non-specific carcinogenic effect has been suggested. IARC (1982) concluded that there is sufficient evidence for carcinogenicity in both humans and experimental animals.

Applying the criteria for evaluating the overall weight of evidence of carcinogenicity to humans proposed by the Carcinogen Assessment Group of the U.S. EPA (Federal Register, 1984) vinyl chloride is most appropriately classified as a chemical in Group A - Human Carcinogen.

5. REGULATORY STANDARDS AND CRITERIA

ACGIH (1983) has established a TLV-TWA of 5 ppm (10 mg/m^3) of vinyl chloride. The standards adopted by OSHA in 1981 are 1 ppm (2.6 mg/m^3) of vinyl chloride as an 8-hour TWA and 5 ppm (13 mg/m^3) of vinyl chloride as a ceiling concentration limit average over any period of $\leq$15 minutes (Code of Federal Regulations, 1981). Similar hygienic standards for occupational exposures in foreign countries exist; these are summarized in Table 5-1.

In the United States, vinyl chloride has been used in limited quantities as an aerosol propellant, but in 1974 it was banned from use in pesticide aerosol products (U.S. EPA, 1974), in self-pressurized household containers, and as an ingredient of drug and cosmetic products (U.S. Consumer Product Safety Commission, 1974a,b).

TABLE 5-1

Hygienic Standards for Occupational Exposure to Vinyl Chloride in Foreign Countries*

Country	Concentration (ppm)	Standard
Canada	10	8-hour TWA
	25	15-minute ceiling
Finland	5	8-hour TWA
	10	10-minute ceiling
Italy	50	8-hour TWA
The Netherlands	10	8-hour TWA
Norway	1	8-hour TWA
	5	15-minute ceiling
Sweden	1	8-hour TWA
	5	15-minute ceiling
USSR	12	NR
France		
existing factories	5	1-week TWA
	15	ceiling
new factories	1	1-week TWA
	5	ceiling
Denmark	1	8-hour TWA
Belgium	5	1-week TWA
	15	ceiling
Federal Republic of Germany		
existing factories	5	1-week TWA
	15	1-hour ceiling
new factories	2	1-week TWA
	15	1-hour ceiling
United Kingdom	10	8-hour TWA
	30	ceiling (maximum)
Switzerland	10	1-week TWA

*Sources: IARC, 1979; Bertram, 1977; Thomas, 1977

NR = Not reported

6. RISK ASSESSMENT

6.1. ACCEPTABLE INTAKE SUBCHRONIC (AIS)

Vinyl chloride is a chemical that is a known human and animal carcinogen and data are sufficient for calculation of a q_1^*. It is inappropriate, therefore, to calculate an AIS for vinyl chloride.

6.2. ACCEPTABLE INTAKE CHRONIC (AIC)

Vinyl chloride is a chemical that is a known human and animal carcinogen and data are sufficient for calculation of a q_1^*. It is inappropriate, therefore, to calculate an AIC for vinyl chloride.

6.3. CARCINOGENIC POTENCY (q_1^*)

6.3.1. Oral. A dose-related increased incidence of neoplastic nodules of the liver, hepatocellular carcinomas and angiosarcomas of the liver and the lung were observed in both male and female rats fed diets containing vinyl chloride for 135 weeks (males) or 144 weeks (females) (Feron et al., 1981). The incidences of each tumor type and the associated human q_1^* were presented in Tables 4-2 and 4-3 for males and females, respectively. The q_1^* values ranged from 8.8×10^{-2} to 1.3 $(mg/kg/day)^{-1}$ for individual tumor types. A q_1^* was also calculated for rats of each sex based on the incidence of total animals with tumors. The incidence of hepatocellular carcinoma was not included in these tallies because it was assumed that rats having hepatocellular carcinoma also bore neoplastic nodules, since neoplastic modules are considered to be preneoplastic forerunners of hepatocellular carcinomas. Furthermore, the total number of animals bearing tumors in the high-dose groups was arbitrarily reduced to one less than the total number of animals examined, so that the resulting data would fit the linear non-threshold model adopted by the U.S. EPA (1980b) for estimation of carcinogenic potency. The human q_1^*s resulting from this manipulation were

2.9×10^{-1} $(mg/kg/day)^{-1}$ (males) and 2.3 $(mg/kg/day)^{-1}$ (females). The q_1^* of 2.3 $(mg/kg/day)^{-1}$ associated with total tumors in female rats was chosen by the U.S. EPA (1984) as most conservatively representing the carcinogenic potency of vinyl chloride.

6.3.2. Inhalation. The U.S. EPA (1980a) derived a q_1^* for humans for oral exposure from the incidence of total tumors in rats exposed to vinyl chloride by inhalation (Maltoni and Lefemine, 1975). This q_1^* has been superseded by a q_1^* for oral exposure based on the incidence of total tumors in female rats fed diets containing vinyl chloride (see Section 6.3.1.). The tumor incidence data in rats exposed by inhalation in the Maltoni and Lefemine (1975) study may more appropriately be used to derive a q_1^* for humans exposed by inhalation.

Using the linear non-threshold model adopted by the U.S. EPA (1980b) and the data from the Maltoni and Lefemine (1975) study summarized in Appendix B, a human q_1^* of 2.5×10^{-2} $(mg/kg/day)^{-1}$ is calculated. This slope value, in transformed units, is the same as that developed in U.S. EPA (1980a) without inclusion of the empirically derived factor to estimate oral exposure from inhalation data. U.S. EPA (1980a) estimated a unit risk of 6.80×10^{-3} $(ppm)^{-1}$ based on the rat inhalation data. Assuming that rats breathe 0.223 m^3/day (U.S. EPA, 1980b) and weigh 0.35 kg, this unit risk can be converted to an animal q_1^* of 4.2×10^{-3} $(mg/kg/day)^{-1}$. Estimation of an equivalent human q_1^* was accomplished by using a surface area approximation: $(70/0.35)^{1/3}$, i.e., 4.2×10^{-3} $(mg/kg/day)^{-1}$ x $(70/0.35)^{1/3} = 2.5 \times 10^{-2}$ $(mg/kg/day)^{-1}$ (U.S. EPA, 1980b).

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APPENDIX A

Summary Table for Vinyl Chloride

Carcinogenic Potency	Species	Experimental Dose/Expsure	Effect	q_1^* $(mg/kg/day)^{-1}$	Reference
Inhalation	rats	50-10,000 ppm	total tumors	2.5×10^{-2}	Maltoni and Lefemine, 1975
Oral	rats	16.65 or 50 mg/kg bw	angiosarcomas	2.3	Feron et al., 1981; U.S. EPA, 1984

APPENDIX B

Cancer Data Sheet for Derivation of q_1^*

Compound: Vinyl chloride

Reference: Maltoni and Lefemine, 1975

Species, strain, sex: rats, Sprague-Dawley, male and female

Body weight: 0.35 kg (assumed)

Length of exposure (le) = 52 weeks, 4 hours/day, 5 days/week

Length of experiment (Le) = 104 weeks

Lifespan of animal (L) = 104 weeks

Tumor site and type: total tumors

Route, vehicle: inhalation

		Input	
Experimental Doses or Exposures (ppm)	(mg/m³)	Transformed Dose† (mg/kg/day)	Incidence No. Responding/No. Tested (or Examined)
0	0	0	6/58
50	127.8	4.9	10/59
250	639.1	23.9	16/59
500	1,278.1	47.8	22/59
2,500	6,390.6	239.1	32/59
6000	15,337.4	573.8	31/60
10,000	25,562.4	956.4	38/61

†Assumes rats breathe 0.223 m³/day, reflects time-weighted average exposure incorporating factors of 4 hours/24 hours, 5 days/7 days and 52 weeks/104 weeks

Unadjusted q_1^* from study = 4.2×10^{-3} $(mg/kg/day)^{-1}$

Human q_1^* = 2.5×10^{-2} $(mg/kg/day)^{-1}$