

Vinyl chloride; CASRN 75-01-4

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the [IRIS assessment development process](#). Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the [guidance documents located on the IRIS website](#).

STATUS OF DATA FOR Vinyl chloride

File First On-Line 08/07/2000

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	08/07/2000
Inhalation RfC (I.B.)	yes	08/07/2000
Carcinogenicity Assessment (II.)	yes	08/07/2000

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name — Vinyl chloride

CASRN — 75-01-4

Last Revised — 08/07/2000

The oral Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. It is expressed in units of mg/kg-day. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to the Background Document for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of substances that are also carcinogens. Therefore, it is

essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

I.A.1. Oral RfD Summary

Critical Effect	Experimental Doses*	UF	MF	RfD
Liver cell polymorphism	NOAEL: 0.13 mg/kg-day NOAEL (HED): 0.09 mg/kg-day	30	1	3E-3 mg/kg-day
Rat chronic feeding study	LOAEL: 1.3 mg/kg-day LOAEL (HED): 0.9 mg/kg-day			
Til et al., 1983, 1991				

* Conversion Factors and Assumptions -- The PBPK model of Clewell et al. (1995a,b) was used to convert the administered animal dose to the human equivalent dose (HED). At the HED, the time-integrated liver concentration of reactive metabolites calculated by the model is predicted to be equal to or less than that achieved for the animal NOAEL or LOAEL.

I.A.2. Principal and Supporting Studies (Oral RfD)

The vinyl chloride (VC) PBPK model of Clewell et al. (1995a,b) was used in this RfD assessment as well as in the accompanying RfC and cancer assessments. Use of this model allows improved calculation of the human dose that would be expected to result in the same level of toxicity as that observed in animals. Its use is based on the assumption that equal tissue concentrations of reactive metabolite would result in the same level of toxicity. As indicated in the RfC file, the PBPK model was also used to perform route-to-route extrapolation of the doses used in the oral study of Til et al. (1983, 1991).

Til, HP; Immel, HR; Feron, VJ. (1983) Lifespan oral carcinogenicity study of vinyl chloride in rats. Final report. CIVO Institutes. TNO Report No. V 83.285/291099, TSCATS Document FYI-AX-0184-0353, Fiche No. 0353.

Til, HP; Feron, VJ; Immel, HR. (1991) Lifetime (149-week) oral carcinogenicity study of vinyl chloride in rats. Food Chem Toxicol 29:713-718.

Til et al. (1983, 1991) incorporated VC into the diet of Wistar rats, administering diets containing 1% polyvinyl chloride (PVC) with varying proportions of VC monomer. Diets were available to experimental animals for 4 hours per day. Food consumption and VC concentrations were measured several times during the feeding period to account for loss of VC from the diet through volatilization. This information was used to calculate the ingested dose. Evaporative loss averaged 20% over 4 hours. The ingested dose was adjusted downward by the amount of VC measured in the feces to arrive at the bioavailable doses of 0, 0.014, 0.13, or 1.3 mg VC/kg-day, which were fed to Wistar rats (n = 100, 100, 100, and 50/sex/group, respectively) for a lifetime. Rats were weighed at 4-week intervals throughout the study. All males surviving 149 weeks and all females still alive until week 150 were killed in extremis. A variety of lesions were observed histologically at the highest dose level of 1.3 mg/kg-day, including increased incidences of angiosarcomas, neoplastic nodules, hepatocellular carcinoma, cellular foci (clear-cell, basophilic, and eosinophilic), liver-cell polymorphism, and cysts. Of the above lesions, all except cysts and liver cell polymorphism are considered neoplastic or preneoplastic. Cysts, described as proliferating bile duct epithelium, are not considered precursors of hepatocellular tumors because tumors did not develop from this location. Liver cell polymorphism is considered to be a noncarcinogenic cytotoxic effect (Schoental and Magee, 1957, 1959). The incidence of female rats having "many" hepatic cysts was 3/98 in controls, 4/100 at 0.014 mg/kg, 9/96 at 0.13 mg/kg, and 24/49 at 1.3 mg/kg. The incidence of male rats with liver cell polymorphism characterized as moderate or severe was 5/99 in controls, 5/99 at 0.014 mg/kg, 8/99 at 0.13 mg/kg, and 13/49 at 1.3 mg/kg; the corresponding incidence in females was 16/98, 16/100, 12/96, and 24/49. Benchmark dose analysis was attempted but was not successful with these data. The LOAEL based on these endpoints is clearly at the highest dose of 1.3 mg/kg-day and the NOAEL at the next highest dose of 0.13 mg/kg-day.

PBPK MODELING: The PBPK model used was developed by Clewell et al. (1995a,b). The basis of the model and of this assessment is the production of reactive metabolites, most likely chloroethylene oxide, through two saturable pathways: one by cytochrome P450 IIE1 and the other by other isozymes of cytochrome P450. Because VC liver toxicity is related to production of reactive metabolites, the appropriate dose metric for liver toxicity endpoints was the total amount of the metabolite generated, divided by the volume of the tissue in which the metabolite is produced, that is, mg metabolite/L liver (Andersen et al., 1987).

The human dose corresponding to the NOAEL in animals was determined by first calculating the value of the dose metric for the NOAEL in the animals, i.e., the value of the total metabolites per liver volume for rats exposed to 0.13 mg/kg-day under the protocol of the study. This metric was then directly compared with that generated by the PBPK model from the results of a sample scenario of a continuous human exposure of 1 ppm ingestion in water by a 70 kg person, or 0.0286 mg VC/kg-day. PBPK outputs also demonstrated that the

relationship between this dose metric and oral intake was linear in the dose range of interest (up to around 25 mg/kg-day). The metric generated from the simulated human scenario was 1.01 mg/L liver. The metric generated from the rat NOAEL was 3.00 mg/L liver (from the average of the male value of 3.03 and the female value of 2.96), which was then converted by a simple proportion to the corresponding human continuous exposure of 0.09 mg/kg-day = NOAEL human equivalent dose (HED). The modeling predicts that an average daily exposure of a human to this NOAEL(HED) would generate the same concentration of metabolites in the liver as was calculated for the rats at the study NOAEL. Further details of the PBPK model development and results and the conversions between animal and human doses are in the Vinyl Chloride Toxicological Review and Appendices B and D.

I.A.3. Uncertainty and Modifying Factors (Oral RfD)

UF = 30. An uncertainty factor of 10 was used for protection of sensitive human subpopulations and 3 for animal-to-human extrapolation. The uncertainty factor for intraspecies variability includes the variability in risk estimates that would be predicted by the PBPK model for different individuals through variability in physiology, level of activity, and metabolic capability. A factor of 3 rather than a default of 10 was used for interspecies extrapolation because, although PBPK modeling refines the animal-to-human comparison regarding the toxicokinetic portion (delivered dose), it does not address the uncertainty regarding the toxicodynamic portion (differential tissue sensitivity) of interspecies extrapolation. Uncertainty relating to toxicodynamics exists for the basic mode of action for noncancer liver effects, that is, whether the epoxide or its rearrangement product (the aldehyde) are causal of the noncancer liver toxicity. The limited evidence of human susceptibility to certain hepatic effects of VC from the problematic study of Ho et al. (1991) also supports retaining the toxicodynamic portion of the interspecies UF (see Toxicological Review Section 4.1.2). No uncertainty factor for database insufficiency is considered necessary, because adequate chronic, developmental, and multigeneration reproductive studies exist. The total uncertainty factor is 30.

MF = 1.

I.A.4. Additional Studies/Comments (Oral RfD)

The Feron et al. (1981) study preceded that of Til et al. (1983, 1991). Because effects were noted at the lowest concentration, the study was repeated by Til et al. using lower doses. Compound and diet were administered to Wistar rats (n = 80, 60, 60, and 80, respectively) as in Til et al. at bioavailable doses of 0, 1.7, 5.0, or 14.1 mg VC/kg-day for a lifetime. All surviving animals were necropsied at week 135 (males) or week 144 (females). Significant clinical signs of toxicity in the 5.0 and 14.1 mg/kg-day groups included lethargy, humpbacked

posture, and emaciation. Significantly increased mortality was seen consistently in males at 14.1 mg/kg-day, and in females at 5.0 and 14.1 mg/kg-day. Relative liver weight was significantly increased at 14.1 mg/kg-day, but not reported for the other dose groups. A variety of liver lesions in male and female rats were observed histologically to be dose-related and the incidence was statistically significant. These lesions included cellular foci (clear-cell, basophilic, and eosinophilic), neoplastic nodules, hepatocellular carcinoma, angiosarcoma, necrosis, cysts, and liver cell polymorphism. Several of these endpoints were significantly increased in the group exposed to 1.7 mg/kg-day, including liver-cell polymorphisms and cysts, both of which were observed in the principal study of Til et al. and are not considered preneoplastic. This oral study defines a NOAEL of 1.7 mg/kg-day and a LOAEL of 5.0 mg/kg-day for liver effects that are not thought to be preneoplastic. Using the PBPK model of Clewell et al. (1995b), a NOAEL(HED) and LOAEL(HED) of 1.1 mg/kg-day and 9.2 mg/kg-day, respectively, were calculated. The results of Feron et al. (1981) are consistent with the results reported in the principal study of Til et al. (1983, 1991), in that the same noncancer liver endpoints were observed.

No other studies were located of oral administration of VC to animals or of oral exposure of humans to VC. However, the observation of nonneoplastic effects in the liver following exposure to VC is supported by several inhalation animal studies, as well as by occupational studies. These studies are discussed in the RfC summary and the Toxicological Review and are only briefly summarized here. The oral equivalents, in mg/kg-day, were estimated from the inhalation scenarios by the PBPK model and are presented for comparative purposes with the principal study.

Bi et al. (1985) exposed Wistar rats (apparently 75 per group) to 0, 10, 100, or 3000 ppm VC (99.99% pure), 6 hours/day, 6 days/week for up to 12 months, with interim sacrifices at 3 months (n = 8), 6 months (n = 30), 9 months (n = 6), and 12 months (n = 10), and sacrifice of surviving animals at 18 months (6 months after the end of exposure). This report presented histopathology results for the testes but not the liver. Body weight was significantly decreased in the mid- and high-exposure groups. Relative liver weight was increased in a concentration-dependent manner after 6 months (LOAEL at 10 ppm), but was affected only in the 3000 ppm group at 12 months, and no significant effect on liver weight was reported at 18 months. There was a concentration-related increase in the incidence of damage to the testicular seminiferous tubules (incidence at 0, 10, 100, or 3000 ppm was 18.9%, 29.7%, 36.5%, and 56%, respectively), with significant increases at the two highest levels. This damage consisted of cellular alterations, degeneration, and necrosis. The NOAEL(HED) for testicular damage is estimated at 1.4 mg/kg-day and the LOAEL(HED) for liver alterations at 0.9 mg/kg-day.

Sokal et al. (1980) exposed male Wistar rats (7-34/sex/group) to 0, 50, 500, or 20,000 ppm of VC 5 hours/day, 5 days/week for 10 months. Relative liver weight was increased at 500 and

20,000 ppm, and absolute liver and testes weight were increased at 20,000 ppm. Treatment-related histological changes developed in the liver and testes. After 10 months, significant increases in polymorphism of hepatocytes (2/28, 5/21, 18/34, and 10/17 in 0, 50, 500, and 20,000 ppm groups, respectively) and proliferation of reticulo-endothelial cells lining the sinusoids (3/28, 3/21, 13/34, and 8/17 in 0, 50, 500, and 20,000 ppm groups, respectively) were observed. These effects were also seen at 6 months in the 500 and 20,000 ppm groups (incidences not reported). Damage to the spermatogenic epithelium was significantly higher than in controls following exposure to 500 ppm (3/28, 3/21, 13/34, and 5/17 in the 0, 50, 500, and 20,000 ppm groups, respectively; NOAEL at 50 ppm). The NOAEL(HED) for liver alterations is estimated at 3.1 mg/kg-day and for testicular alterations, 4.8 mg/kg-day.

In a related study, male Wistar rats (7-10/group) were exposed under dynamic conditions to nominal concentrations of 50, 500, or 20,000 ppm VC or to air only, 5 hours/day, 5 days/week for 10 months with interim sacrifices at 1, 3, and 6 months (Wisniewska-Knypl et al., 1980). Tissue examinations were limited to the liver. Relative liver weight was increased at all sacrifice times at 500 and 20,000 ppm. Ultrastructural alterations, including lipid droplet formation and accumulation, were seen at all exposure levels (LOAEL at 50 ppm). The LOAEL(HED) for lipid accumulation is estimated at 2.6 mg/kg-day.

Increased liver weight was also observed in rats exposed to concentrations of 100 ppm or higher for up to 6 months, and rabbits exposed to 200 ppm or higher exhibited histological changes (characterized as granular degeneration and necrosis with some vacuolization and cellular infiltration, NOAEL at 50 ppm, LOAEL at 100 ppm) in the centrilobular area of the liver (Torkelson et al., 1961). Histopathological lesions of the liver (centrilobular granular degeneration) also occurred in rats exposed to 500 ppm. For females, the NOAEL(HED) for increased liver weight was 3.1 mg/kg-day; the LOAEL was 6.6 mg/kg-day.

A two-generation inhalation reproductive study, done in accordance with GLP, was performed in rats (CD, 30/sex/group) exposed by whole-body inhalation for 6 hours/day to concentration levels of 0, 10, 100, and 1100 ppm VC monomer (CMA, 1998). Evaluation for the parental animals included body weights, food consumption, and estrous cycling as well as fertility, reproductive performance, and sperm assessments. Both F1 and F2 pups were examined and weighed at birth and on several days during lactation. At weaning, one pup/sex/litter was randomly selected, sacrificed, and given a macroscopic exam. No adverse effect of the measured parameters was seen in the parental generations, and no adverse effect of treatment was indicated in the F1 and F2 pups. Liver effects typical of VC (increased weights, hypertrophy, and occurrence of altered hepatocellular foci) were noted in parental animals at 1100 and 100 ppm, but not at 10 ppm, with increased incidence occurring in the P2 as opposed to the P1 animals. Whether this increased incidence in P2 animals was due to in utero or juvenile susceptibility (the P1 animals were not exposed during these periods whereas the P2

animals were) or to a longer duration (P2 animals were exposed longer than were P1 animals) is not clear. However, tumor incidence has been documented to increase at maturity among laboratory animals treated with VC during the first 6 months of life when compared with those exposed during the second or third 6-month period of life (Maltoni et al., 1981; Drew et al., 1983). The NOAEL for reproductive effects is >1100 ppm. PBPK analysis (Section 4.3 and Appendix D of the Toxicological Review) indicates that liver effects are seen in Til et al. (1991) at doses to the liver that are much lower than the NOAEL for liver effects (10 ppm; NOAEL(HED)=1 mg/kg-day) in this reproductive study.

Several epidemiology and case studies have associated chronic occupational exposure to VC with impaired liver function and/or biochemical or histological evidence of liver damage, notably subcapsular, portal and perisinusoidal fibrosis, hyperplasia of hepatocytes and sinusoidal cells, and portal hypertension (Buchancova et al., 1985; Doss et al., 1984; Gedigk et al., 1975; Lilis et al., 1975; Marsteller et al., 1975; Popper and Thomas, 1975; Tamburro et al., 1984). Ho et al. (1991) reported VC-related liver dysfunction in 12 of 271 workers who were exposed to environmental levels of 1-20 ppm, with a geometric mean of 6 ppm; latent periods from first exposure to the first abnormal test ranged from 1 to 13 years. These studies are described in more detail in the Toxicological Review.

Data on potential reproductive or developmental effects of VC following oral exposure of animals or humans are not available. However, because VC is rapidly absorbed and distributed throughout the body following both oral and inhalation exposure, and because a PBPK model with route-to-route extrapolation capabilities is employed, data from inhalation studies can be used to predict potential effects from oral exposure.

Insufficient data exist to evaluate the teratogenicity of VC in humans. Several epidemiology studies have investigated the effects of VC exposure on the incidence of fetal loss and birth defects (Hatch et al., 1981; Infante et al., 1976; Waxweiler et al., 1977); however, no solid association has been found. Studies of communities near VC plants (Edmonds et al., 1978; Theriault et al., 1983) have found no clear association between parental residence in a region with a VC plant and incidence of birth defects in the exposed community.

Inhalation experiments in animals have associated developmental toxicity only with concentrations at or above those associated with maternal toxicity and above those concentrations extrapolated by the PBPK model to a human equivalent concentration (HEC) that are associated with liver effects in the principal study of Til et al. (1983, 1991) of 2.5 mg/m³ or a HED of 0.09 mg/kg-day. John et al. (1977) exposed pregnant mice to 0, 50, or 500 ppm on gestation days 6 to 15. Exposure to 500 ppm induced maternal effects, including increased mortality, reduced body weight, and reduced absolute (but not relative) liver weight. Fetotoxicity also occurred in mice at 500 ppm, and was manifested as significantly increased

fetal resorption, decreased fetal body weight, reduced litter size, and retarded cranial and sternal ossification. There was no evidence of a teratogenic effect in mice at either concentration. Pregnant rats exposed to 500 ppm on gestation days 6 through 15 had reduced body weight, and one rat exposed to 2500 ppm died. Fetal body weight was significantly decreased at 500 ppm, and an increased incidence of dilated ureters was observed at 2500 ppm. No signs of maternal or developmental toxicity were observed in pregnant rabbits exposed to 500 or 2500 ppm. In another study, rats were exposed continuously to 1500 ppm during the first, second, or third trimester of pregnancy (Ungvary et al., 1978). During the first third of pregnancy, maternal toxicity was manifested by increased relative liver weight; increased fetal mortality and embryotoxic effects were also observed. There were no embryotoxic or teratogenic effects following exposure during the second or last trimester. In a dominant lethal study of VC, reduced fertility was observed at a concentration (250 and 1000 ppm) above the concentration that caused liver effects in rats (Short et al., 1977).

As discussed in the RfC summary, human and animal studies indicate that absorption following inhalation exposure occurs rapidly, with peak retention reached within 15 minutes. No human studies of absorption of ingested VC were located, although the principal study (Til et al., 1983, 1991) reported that absorption of VC monomer in animals following oral exposure is nearly quantitative. Peak blood levels were reached within 10 minutes when VC was administered to male rats by gavage in an aqueous solution at doses up to 92 mg/kg. In the same study, more complex and slightly delayed absorption was observed following VC gavage in oil, although peak blood levels were reached within 40 minutes (Withey, 1976). At 72 hours after a single gavage dose of 100 mg/kg VC in oil, unmetabolized VC was detected in exhaled air, indicating that metabolism was saturated (Watanabe and Gehring, 1976; Watanabe et al., 1976).

The primary route of VC metabolism is by the action of cytochrome P450 IIEI on VC to form a highly reactive epoxide intermediate, chloroethylene oxide (CEO), which spontaneously rearranges to form chloroacetaldehyde (CAA). These intermediates are detoxified mainly through conjugation with glutathione catalyzed by glutathione S-transferase (Hefner et al., 1975; Bolt et al., 1976; Jedrychowski et al., 1984; Watanabe et al., 1978). The conjugated products are excreted in urine as substituted cysteine derivatives (Bolt et al., 1980; Hefner et al., 1975). Although VC has often been cited as a chemical for which saturable metabolism should be considered in the risk assessment, saturation appears to become important only at very high exposure levels (greater than 250 ppm by inhalation or 25 mg/kg-day orally) compared with levels associated with the most sensitive noncancer effects or tumorigenic levels, and thus has little impact on the risk estimates.

Several different PBPK models for VC have been described in the literature. These models are described in detail and compared in the accompanying Toxicological Review Appendix A.

The PBPK model used in this assessment was developed to support a cancer risk assessment based on the pharmacokinetic and metabolic data available in the literature for VC (Clewel et al., 1995a,b). The initial metabolism of VC was hypothesized to occur via two saturable pathways, one representing low capacity-high affinity oxidation by cytochrome P450 IIE1 and the other representing higher capacity-lower affinity oxidation by other isozymes of P450, producing in both cases CEO as an intermediate product. The parameter values for the two metabolic pathways describing the initial step in VC metabolism were determined by simulation of gas uptake data from mice, rats, hamsters, monkeys, and controlled human inhalation exposures, as well as from data on total metabolism and glutathione depletion in both oral and inhalation exposures. Successful simulation of pharmacokinetic data from a large number of studies over a wide range of concentrations using primarily inhalation exposure and different measures of effect (decreased chamber concentrations of VC, decreased serum levels of GSH) served as evidence that the PBPK model was valid over the exposure range of interest, especially for inhalation exposure scenarios. One limitation of the model is the lack of pharmacokinetic data via the oral route available for simulation and model validation. Model parameters for deriving dose metrics via the oral route have therefore been established such that the dose metrics generated would be "conservative," that is, predictive of higher human risk from animal results. This model, including the parameters and the rationale for their choice, pharmacokinetic data and model fit to these data, the sensitivity analysis of the model, and the actual dose metrics derived, is presented in the appendices of the Toxicological Review.

For more detail on Susceptible Populations, exit to [the toxicological review, Section 4.7 \(PDF\)](#).

I.A.5. Confidence in the Oral RfD

Study — High

Database — Medium to high

RfD — Medium

The overall confidence in this RfD assessment is medium. Confidence in the study of Til et al. (1983, 1991) is high because it used adequate numbers of animals, was well controlled, and reported in detail on the histological effects on the liver and their absence in other tissues (e.g., testes) at these same exposure levels. The critical effects, liver alterations and histopathology, are corroborated by other long-term studies including oral studies (Feron et al., 1981), inhalation studies (Sokal et al., 1980), and a reproductive study (CMA, 1998).

The confidence in the database is medium to high. The route-to-route capability of the PBPK model allows use of inhalation data, such as the developmental studies, to fill gaps in the oral

database. The multigeneration reproductive study (CMA, 1998) and the dominant lethal study of Short et al. (1977) indicate at least in animals that if reproductive effects were to occur from exposure to VC, they would occur at a much higher exposure than that producing liver effects.

Concern for the confidence of dose metrics derived by the PBPK model from the oral study of Til et al. is offset by procedures instituted within the model when calculating oral dose metrics, including assumption of a maximum rate of VC uptake (i.e., designating it a zero-order process) and spreading the applied dose over a 24-hour period, which would minimize the concentration and maximize the likelihood that the parent VC would be metabolized to reactive species (i.e., the basis of this assessment, mg VC metabolized).

The high degree of confidence in the principal study of Til et al. (1983, 1991), combined with the medium to high assessment of the database and less than high confidence in the qualitative aspects of the PBPK model, is considered to result in an overall medium confidence in the RfD

For more detail on Characterization of Hazard and Dose Response, exit to [the toxicological review, Section 6 \(PDF\)](#).

I.A.6. EPA Documentation and Review of the Oral RfD

Source Document — U.S. EPA, 2000

This assessment was peer reviewed by external scientists. Their comments have been evaluated carefully and incorporated in finalization of this IRIS Summary. A record of these comments is included as an appendix to the Toxicological Review of Vinyl Chloride in Support of Summary Information on the Integrated Risk Information System (IRIS) (U.S. EPA, 2000). [To review this appendix, exit to the toxicological review, Appendix E, Summary of and Response to External Peer Review Comments \(PDF\)](#)

Agency Consensus Date - 07/20/2000

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfD for vinyl chloride conducted in August 2003 did not identify any critical new studies. IRIS users who know of important new studies may provide that information to the IRIS Hotline at hotline.iris@epa.gov or 202-566-1676.

I.A.7. EPA Contacts (Oral RfD)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (fax), or hotline.iris@epa.gov (Internet address).

I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

Substance Name — Vinyl chloride
CASRN — 75-01-4
Last Revised — 08/07/2000

I.B.1. Inhalation RfC Summary

Critical Effect	Experimental Doses*	UF	MF	RfC
Liver cell polymorphism	NOAEL: 0.13 mg/kg-day NOAEL(HEC): 2.5 mg/m ³	30	1	1E-1 mg/m ³
Rat chronic feeding study	LOAEL: 1.3 mg/kg-day LOAEL(HEC): 25.3 mg/m ³			
Til et al., 1983, 1991				

*Conversion Factors and Assumptions: MW = 62.5. The NOAEL/LOAEL(HEC) were calculated for a gas: extrarespiratory effect based on the PBPK model of Clewell et al. (1995a,b). The continuous human exposure concentration (HEC) that achieved a time-integrated liver concentration of metabolites less than or equal to that achieved for the animal simulation is defined as the HEC. The model parameters, assumptions, and results are explained below and at length in the accompanying Toxicological Review for Vinyl Chloride (U.S. EPA, 2000).

I.B.2. Principal and Supporting Studies (Inhalation RfC)

The chronic dietary study of Til et al. (1983, 1991) in rats is the principal study for both the inhalation RfC and oral RfD. The rationale for basing an inhalation RfC on an oral study is

based on evidence for a mode of action common to exposures from either route (liver toxicity) and availability of PBPK models to perform route-to-route extrapolations. The critical effect, increases in the incidence of liver cell polymorphism and cysts, is reported in both oral studies (lifetime feeding studies of Feron et al., 1981; Til et al., 1983, 1991) and inhalation studies (10-month inhalation study of Sokal et al., 1980). In addition, the existing inhalation studies report no direct effects at the portal of entry (i.e., the respiratory tract). The inhalation database for VC, although deficient in chronic inhalation studies from which an RfC could be derived, has nevertheless allowed for development of PBPK models capable of converting VC exposures not only from animals to human equivalents but also from route to route. Use of this PBPK model is based on the principal assumption that equal tissue concentrations of reactive metabolite would result in the same level of toxicity whether in animals or humans, or from inhalation or oral exposures. Complete documentation of the choice, application, assumptions, and limitations of the PBPK model used in this assessment are in the supporting Toxicological Review and appendices.

Til, HP; Feron, VJ; Immel, HR. (1991) Lifetime (149-week) oral carcinogenicity study of vinyl chloride in rats. *Food Chem Toxicol* 29:713-718.

Til, HP; Immel, HR; Feron, VJ. (1983) Lifespan oral carcinogenicity study of vinyl chloride in rats. Final report. Civo Institutes. TNO Report No. V 83.285/291099, TSCATS Document FYI-AX-0184-0353, Fiche No. 0353.

The lifetime dietary study of Til et al. (1983, 1991) was performed in order to study a range of oral doses below those delivered in a nearly identical study by Feron et al. (1981), because tumors and other pathological effects were observed at all doses in the Feron et al. study. To incorporate VC into the diet of Wistar rats, Til et al. administered diets containing 1% PVC with varying proportions of VC monomer. Diets were available to experimental animals for 4 hours per day. Food consumption and VC concentrations were measured at several times during the feeding period so as to account for the loss of VC from the diet through volatilization. This information was used to calculate the ingested dose. Evaporative loss averaged 20% over 4 hours. The ingested dose was adjusted downward by the amount of VC measured in the feces to arrive at the bioavailable doses of 0, 0.014, 0.13, and 1.3 mg/kg-day VC, which were fed to Wistar rats (n = 100, 100, 100, and 50/sex/group, respectively) for a lifetime. Rats were weighed at 4-week intervals throughout the study. All males surviving 149 weeks and all females alive until week 150 were killed in extremis. Mortality was slightly increased in the high-dose group near the end of the study. A variety of lesions were observed histologically at the highest dose level of 1.3 mg/kg-day. These included increased incidences of angiosarcomas, hepatocellular carcinomas, neoplastic nodules, cellular foci, liver-cell polymorphism, and cysts. All these may be considered as neoplastic or preneoplastic save for cysts and liver cell polymorphism. Cysts described as proliferating bile duct epithelium are not

considered precursors of hepatocellular tumors because tumors did not develop from this location. Liver cell polymorphism is considered a noncarcinogenic cytotoxic effect (Schoental and Magee, 1957, 1959). The incidence of female rats having "many" hepatic cysts was 3/98 in controls, 4/100 at 0.014 mg/kg, 9/96 at 0.13 mg/kg, and 24/49 at 1.3 mg/kg. The incidence of male rats with liver cell polymorphism characterized as moderate or severe was 5/99 in controls, 5/99 at 0.014 mg/kg, 8/99 at 0.13 mg/kg, and 13/49 at 1.3 mg/kg; the corresponding incidence in females was 16/98, 16/100, 12/96, and 24/49. Benchmark dose analysis was attempted but was not successful with these data. The LOAEL based on these endpoints is clearly at the highest dose of 1.3 mg/kg-day and the NOAEL at the next highest dose of 0.13 mg/kg-day.

PBPK Modeling: The PBPK model used was developed by Clewell et al. (1995a,b). The basis of the model and this assessment is the production of reactive metabolites, most likely chloroethylene oxide, through two saturable pathways: one by cytochrome P450 IIE1 and the other by other isozymes of cytochrome P450. Because VC liver toxicity is related to production of reactive metabolites, the appropriate dose metric for liver toxicity endpoints was the amount of the metabolite generated, divided by the volume of the tissue in which the metabolite is produced, that is, mg/L liver (Andersen et al., 1987) expressed as a daily average.

The NOAEL(HEC) was derived by first calculating the value of the appropriate dose metric for the NOAEL in the animals, that is, the value of the total metabolites per liver volume for rats exposed to 0.13 mg/kg under the protocol of the study. This metric was calculated to be 3.00 mg/L liver (from the average of the male value of 3.03 and the female value of 2.96) and a factor was then used to convert this metric to a continuous human inhalation exposure. The conversion factor to a human equivalent inhalation concentration (HEC) was generated by exercising the PBPK model to determine this same dose metric for a continuous human inhalation exposure, that is, the continuous exposure concentration that would result in the same dose of metabolites to the human liver. The results from a range of exposure concentrations (1 $\mu\text{g}/\text{m}^3$ to 10,000 mg/m^3) showed that the relationship was linear up to nearly 100 mg/m^3 , with the factor in this range being 1.18 mg/L liver/1 mg/m^3 VC. Conversion of the study NOAEL of 0.13 mg/kg-day was then accomplished by dividing the animal dose metric for this concentration by the conversion factor (3.00 /1.18) to arrive at NOAEL(HEC) of 2.5 mg/m^3 . For the LOAEL(HEC) the figures and calculation are 29.9/1.18, or 25.3 mg/m^3 .

I.B.3. Uncertainty and Modifying Factors (Inhalation RfC)

UF = 30. An uncertainty factor of 10 was used for protection of sensitive human subpopulations and 3 for animal-to-human extrapolation. The uncertainty factor for intraspecies variability includes the variability in risk estimates that would be predicted by the

model for different individuals, through variability in physiology, level of activity, and metabolic capability. A factor of 3 rather than a default of 10 was used for interspecies extrapolation because, although PBPK modeling refines the animal-to-human comparison of delivered dose, it does not address the uncertainty regarding the toxicodynamic portion of interspecies extrapolation (relating to tissue sensitivity). Uncertainty relating to toxicodynamics exists for the basic mode of action for noncancer liver effects, that is, whether the epoxide or its rearrangement products (the aldehyde) are causal of the noncancer liver toxicity. The limited evidence of human susceptibility to certain hepatic effects from VC from the problematic study of Ho et al. (1991) also supports retaining the toxicodynamic portion of the interspecies UF. No uncertainty factor for database insufficiency is considered necessary, because adequate chronic, developmental, and multigenerational reproductive studies exist. The total uncertainty factor is 30 (see Toxicological Review Section 4.1.2).

MF = 1.

I.B.4. Additional Studies/Comments (Inhalation RfC)

Bi et al. (1985) exposed Wistar rats (apparently 75 per group) to 0, 10, 100, or 3000 ppm VC (99.99% pure), 6 hours/day, 6 days/week for up to 12 months. Animals were weighed monthly and observed daily for clinical signs. Interim sacrifices were reported at 3 (n = 8), 6 (n = 30), 9 (n = 6), and 12 (n = 10) months, with surviving animals examined after 18 months (6 months after the end of exposure). Organ weights and histopathology were reported to have been assessed on lung, liver, heart, kidney, testes, spleen, and brain, but only partial organ weight information was presented, and only testicular histopathology results are discussed in the report. Body weight was significantly decreased in the mid- and high-exposure groups (320, 310, 280, and 240 g in 0, 10, 100, and 3000 ppm groups, respectively). Relative liver weight was increased in a concentration-dependent manner after 6 months. At 12 months, increased relative liver weight was observed only in the 3000 ppm group, although the power to detect this effect was limited by the small number of animals examined. No effect on liver weight persisted at 18 months after the start of the exposure. Relative kidney weight in the 3000 ppm group was increased at 3 and 12 months but not at 6 or 18 months, and in the 100 ppm group only at 18 months. Relative testes weight was decreased in the 100 and 3000 ppm groups at 6 months, but the effect was not concentration related, in that the relative testes weight was less at 100 than at 3000 ppm, and no other time points showed significant effects. The study did not report absolute organ weights, relative weights for groups with no significant differences, standard deviations, or histopathology results (except in the testes), making the organ weight differences in tissues other than the liver and testes difficult to interpret. The incidence of damage to the testicular seminiferous tubules in rats (n = 74 total) exposed to 0, 10, 100, or 3000 ppm was 18.9%, 29.7%, 36.5%, and 56%, respectively. The incidence was statistically elevated at 100 and 3000 ppm ($p < 0.05$ and $p < 0.001$, respectively) compared with controls,

and appeared to be concentration related. This damage consisted of cellular alterations, degeneration, and necrosis. Thus, 10 ppm is considered a LOAEL for liver weight changes and the NOAEL for biologically significant testicular degeneration.

In determining an HEC for testicular damage by use of the PBPK model, the effects are assumed to be caused by metabolites produced in the testes, in that cytochromes P450 are known to be present in this tissue. Because specific information on VC metabolism in testes is not available, the relative amount of metabolism in testes and liver was assumed to be the same across species, so the amount of metabolite produced in the testes would be proportional to the total metabolism. An appropriate dose metric for the testicular effects would then be the total amount of metabolite produced divided by the body weight expressed as a daily average, which was determined by the PBPK model to be 0, 1.3, 12.5, and 43.2 mg metabolites per kg body weight. Using a conversion factor for this dose metric derived for a continuous human inhalation exposure as described above (0.0308 mg/kg body weight), the NOAEL(HEC) would be $1.3/.0308 = 42 \text{ mg/m}^3$. Benchmark analysis of the incidence of testicular degeneration using the Weibull and polynomial models and the HECs calculated using the PBPK model resulted in a BMC10 for extra risk of 182 mg/m^3 . The testicular effects noted in this subchronic study are considered to occur at higher HEC concentrations than do the liver effects. In addition, it may be that testicular effects from VC exposure have concentration dependency and a route component (i.e., inhalation only), in that testicular effects were not reported in either of the lifetime oral exposure studies in which liver toxicity was prominent.

A two-generation inhalation reproductive study, done in accordance with GLP, was performed in rats (CD, 30/sex/group) exposed by whole-body inhalation for 6 hours/day to concentration levels of 0, 10, 100, and 1100 ppm (0, 26, 256, and 2816 mg/m^3) VC monomer (CMA, 1998). Evaluation for the parental animals included body weights, food consumption, and estrous cycling as well as fertility, reproductive performance, and sperm assessments. Both F1 and F2 pups were examined and weighed at birth and on several days during lactation. At weaning, one pup/sex/litter was randomly selected, sacrificed, and given a macroscopic exam. No adverse effect of the measured parameters was seen in the parental generations and no adverse effect of treatment was indicated in the F1 and F2 pups. Liver effects typical of VC (increased weights, hypertrophy, and occurrence of altered hepatocellular foci) were noted in parental animals at 1100 and 100 ppm, but not at 10 ppm, with increased incidence occurring in the P2 as opposed to the P1 animals. Whether this increased incidence in P2 animals was due to in utero or juvenile susceptibility (the P1 animals were not exposed during these periods whereas the P2 animals were) or to a longer duration (P2 animals were exposed longer than were P1 animals) is not clear. However, tumor incidence has been documented to increase at maturity among laboratory animals treated with VC during the first 6 months of life when compared with those exposed during the second or third 6-month period of life (Maltoni et al., 1981; Drew et al., 1983). The NOAEL for reproductive effects is $>2816 \text{ mg/m}^3$. PBPK analysis

(Section 4.3 and Appendix D, Table D-2, of the Toxicological Review) indicates that liver effects are seen in Til et al. (1991) at doses to the liver that are much lower than the NOAEL for liver effects (mg/m^3) in this reproductive study.

The Feron et al. (1981) study preceded the one reported by Til et al. (1983, 1991). Because effects were noted at the lowest concentration, the study was repeated by Til et al. using lower doses. Compound in the diet was administered to Wistar rats ($n = 80, 60, 60,$ and $80,$ respectively) as in Til et al. (1983, 1991) at bioavailable doses of $0, 1.7, 5.0,$ or $14.1 \text{ mg}/\text{kg}$ -day VC for a lifetime. All surviving animals were necropsied at week 135 (males) or week 144 (females). Significant clinical signs of toxicity in the 5.0 and $14.1 \text{ mg}/\text{kg}$ -day groups included lethargy, humpbacked posture, and emaciation. Significantly increased mortality was seen consistently in males at $14.1 \text{ mg}/\text{kg}$ -day and in females at 5.0 and $14.1 \text{ mg}/\text{kg}$ -day. Relative liver weight was significantly increased at $14.1 \text{ mg}/\text{kg}$ -day, but was not reported for the other dose groups. A variety of liver lesions were observed histologically to be dose-related and statistically significant in male and female rats. These included cellular foci (clear-cell, basophilic, and eosinophilic), neoplastic nodules, hepatocellular carcinoma, angiosarcoma, necrosis, cysts, liver-cell polymorphism, and necrosis. Several of these endpoints were significantly increased in the group exposed to $1.7 \text{ mg}/\text{kg}$ -day, including liver-cell polymorphism, cysts, and necrosis, all of which were observed in the principal study of Til et al. and are not considered preneoplastic. This oral study defines a NOAEL of $1.7 \text{ mg}/\text{kg}$ -day and a LOAEL of $5.0 \text{ mg}/\text{kg}$ -day for liver effects that are not thought to be preneoplastic. Using the PBPK model of Clewell et al. (1995b), a NOAEL(HEC) and LOAEL(HEC) of 33 and $97 \text{ mg}/\text{m}^3$, respectively, were calculated. Application of benchmark analysis and the PBPK model (for extensive liver necrosis because liver-cell polymorphism could not be modeled), using the internal dose metric from the PBPK model to get the BMC at a benchmark response of 10% extra risk, and then using the human PBPK model to get the human equivalent of the BMC as described for the Bi et al. (1985) study, resulted in a BMC(HEC) of $34 \text{ mg}/\text{m}^3$ for the effect in females and a BMC(HEC) of $59 \text{ mg}/\text{m}^3$ for males. This study corroborates the results reported in the principal study of Til et al. (1983, 1991), in that the same noncancer liver endpoints were observed.

Male Wistar rats (7-34/sex/group) were exposed via inhalation to $0, 50, 500,$ or $20,000 \text{ ppm}$ of VC for 5 hours/day, 5 days/week for 10 months (Sokal et al., 1980). Histopathology was conducted on all major organs, including the lungs, with groups sacrificed at 1.5, 3, 6, and 10 months of exposure. Ultrastructural examination of the liver was carried out at 3, 6, and 10 months. No adverse effects on the lung were reported. There was a statistically significant ($p < 0.05$) and biologically significant (e.g., $>10\%$ relative to concurrent controls) decrease in body weight at 10 months in the high-exposure group only. Relative liver weight was increased at 500 and $20,000 \text{ ppm}$ and absolute liver and testes weight were increased at $20,000 \text{ ppm}$. Treatment-related histological changes developed in the liver and testes. After 10 months,

significant increases in polymorphism of hepatocytes (2/28, 5/21, 18/34, and 10/17 in 0, 50, 500, and 20,000 ppm groups, respectively) and proliferation of reticulo-endothelial cells lining the sinusoids (3/28, 3/21, 13/34, and 8/17 in 0, 50, 500, and 20,000 ppm groups, respectively) were observed. These effects were also seen at 6 months in the 500 and 20,000 ppm groups (incidences not reported). Fatty degeneration was also observed and ultrastructural changes, including proliferation of smooth endoplasmic reticulum and lipid droplets, were reported, but no data were given. The report indicated that more detailed description of the histopathology and ultrastructure would be published separately, but no such record was found. Damage to the spermatogenic epithelium was significantly greater than in controls following exposure to 500 ppm (3/28, 3/21, 13/34, and 5/17 in the 0, 50, 500, and 20,000 ppm groups, respectively). A NOAEL of 50 ppm was identified for hepatocellular and testicular histopathology. Using the PBPK model of Clewell et al. (1995b), the NOAEL of 50 ppm corresponds to a duration-adjusted NOAEL(HEC) of 93 mg/m³ for liver effects and a NOAEL(HEC) of 145 mg/m³ for testicular effects. Applying benchmark modeling using the dosimetry provided by the PBPK model in the same manner as described for the principal study, the BMC(HEC) values are 59-169 mg/m³ for liver effects (59 mg/m³ for nuclear proliferation of hepatocytes, 92 mg/m³ for liver cell polymorphism, and 169 mg/m³ for the continuous endpoint of increased relative liver weight), and 122 mg/m³ for testicular effects.

In a related study, male Wistar rats (7-10/group) were exposed under dynamic conditions to nominal concentrations of 50, 500, or 20,000 ppm VC or to air only, 5 hours/day, 5 days/week (duration adjusted to 19, 190, or 7607 mg/m³, respectively) for 10 months with interim sacrifices at 1, 3, and 6 months (Wisniewska-Knypl et al., 1980). This study appears to be a different experiment from that reported by Sokal et al. (1980) because of different initial animal weights and chemical purity, although this is not entirely clear. Body weight was significantly affected only in the 20,000 ppm group exposed for 10 months. Tissue examinations were limited to the liver. Relative liver weight was increased at all sacrifice times at 500 and 20,000 ppm. Examination of liver tissue from exposed animals showed ultrastructural changes at all exposure levels, with the intensity of the effects increased in a dose-response manner, although no quantitative information was provided. This study identifies a minimal LOAEL of 50 ppm for minor liver histopathology and a NOAEL of 50 ppm for liver weight effects. Based on the PBPK model of Clewell et al. (1995a,b), this corresponds to a LOAEL(HEC) of 80 mg/m³. Because the exposure conditions and number of animals tested in this study were the same as in the Sokal et al. (1980) study, and the response data were the same as those in the Sokal study, although rounded off, the BMC(HEC) value of 169 mg/m³ identified in the Sokal study also applies here. The liver ultrastructural data are not amenable to benchmark analysis because only descriptive information was presented.

Several species of animals were exposed to 0, 50, 100, 200, or 500 ppm VC via inhalation for up to 6 months (Torkelson et al., 1961). Hematologic determinations, urinalysis, clinical

biochemistry, organ weight measurement, and histopathology examination were conducted. Rats (24/sex/group), guinea pigs (12/sex/group), rabbits (3/sex/group), and dogs (1/sex/group) exposed to 50 ppm (128 mg/m³), 7 hours/day, for 130 of 189 days did not exhibit toxicity as judged by appearance, mortality, growth, hematology, liver weight, and pathology. At an exposure concentration of 100 ppm administered 138-144 times in 204 days, a statistically significant increase in the relative liver weight of male and female rats was noted. Exposure to 200 ppm (138-144 times in 204 days) for 6 months resulted in increased relative liver weight in male and female rats, but there was no biochemical or microscopic evidence of liver damage. Rabbits exposed under the same conditions exhibited histological changes (characterized as granular degeneration and necrosis with some vacuolization and cellular infiltration) in the centrilobular area of the liver. There was no effect at this level in guinea pigs or dogs. Histopathological lesions of the liver (centrilobular granular degeneration) and increased organ weight occurred in rats exposed to 500 ppm. Although relative liver weights were slightly elevated in male rats (n = 5) exposed to 100 or 200 ppm for 2-4 hours/day (duration adjusted to 15-30 and 30-60 mg/m³, respectively), the increases were not statistically significant. A NOAEL for liver effects of 50 ppm (duration adjusted to 25.6 mg/m³) is identified in this study. Based on the PBPK model of Clewell et al. (1995b), this corresponds to a duration-adjusted NOAEL(HEC) of 93 mg/m³. These data were not amenable to benchmark analysis because standard deviations on the weight measurements were not reported.

Maltoni et al. (1980, 1981) exposed Sprague-Dawley or Wistar rats to 1-30,000 ppm 4 hours/day, 5 days/week for 52 weeks, and mice and hamsters to 50-30,000 ppm for 30 weeks, followed by an observation period. A statistically significant increase in tumor incidence, including liver angiosarcoma, was observed in all three species at 50 ppm (duration adjusted to 15.2 mg/m³). This study primarily investigated the development of tumors. However, the incidence of neoplastic and preneoplastic lesions including hepatomas, neoplastic liver nodules, nodular hyperplasia of the liver, and diffuse hyperplasia of the liver was presented. Using the combined results for two experiments in SD rats (one exposing 60 male and 60 female rats to 1-25 ppm and the second using exposure concentrations of 250-10,000 ppm with 120 male and 120 female rats), the incidence for diffuse hyperplasia at 0, 1, 5, 10, 25, 50, 250, 500, 2500, 6000, and 10,000 ppm for combined males and females was 1.9%, 0.8%, 0%, 8.3%, 7.5%, 3.0%, 1.7%, 10%, 1.7%, 3.3%, and 5.0%, respectively. Diffuse hyperplasia was increased significantly in most exposure groups, but did not appear to be concentration related. Likewise, the results for nodular hyperplasia, neoplastic nodules, and hepatomas in SD rats, and for these lesions in Wistar rats, showed significant increases but did not appear to be concentration related.

Several epidemiology and case studies have associated chronic occupational exposure with impaired liver function and/or biochemical or histological evidence of liver damage, notably

subcapsular, portal, and perisinusoidal fibrosis; hyperplasia of hepatocytes and sinusoidal cells; and portal hypertension (Buchancova et al., 1985; Doss et al., 1984; Gedigk et al., 1975; Lilis et al., 1975; Marsteller et al., 1975; Popper and Thomas, 1975; Tamburro et al., 1984). Focal hepatocellular hyperplasia and focal mixed (hepatocytes and sinusoidal cells) hyperplasia are early histological alterations indicative of VC exposure (Popper and Thomas, 1975), and are the principal anatomic lesions in VC-associated liver disease (Berk et al., 1976). Doss et al. (1984) reported coproporphyrinuria in 46 males occupationally exposed to VC for 18 months to 21 years. Gedigk et al. (1975) correlated liver damage manifested as parenchymal damage, fibrosis, and proliferation of the sinusoidal cells with duration of exposure to VC in 51 patients. The severity of degenerative lesions increased with increasing duration of exposure, and appeared to be reversible upon exposure cessation. Another study reported the progressive nature of the liver changes that resulted in "chronic hepatitis" (Lilis et al. 1975). Thresholds for hepatotoxicity cannot be identified because data regarding exposure concentrations and duration were not available. The symptoms and signs of liver disease associated with occupational exposure to VC include pain or discomfort in the right upper quadrant of the abdomen, hepatomegaly, splenomegaly, and thrombocytopenia, in addition to fibrosis, cirrhosis, and portal hypertension; however, these observations are not pathognomonic for VC-induced liver disease (Lilis et al., 1975; Marsteller et al., 1975; Popper and Thomas, 1975). Fibrosis frequently occurs in the elderly and patients with diabetes mellitus (Popper and Thomas, 1975).

Ho et al. (1991) reported VC-related liver dysfunction in 12 of 271 workers who were exposed to environmental levels of 1-20 ppm, with a geometric mean of 6 ppm (15 mg/m³). The affected workers were identified as a result of a medical surveillance program of biochemical liver function tests. Although results suggested effects at very low levels, the exposure estimates may well be flawed, and other problems exist with using this study (see Toxicological Review Section 4.1.2). Prior to 1983, concentrations of VC were reported to range from 2000 to 5000 ppm during tank washing and as high as 10,000 ppm near reactors. Du et al. (1995) found that serum levels of gamma-glutamyl transferase (GGT), but not other indicators of liver function, correlated with exposure in a group of 224 VC workers with time-weighted average (TWA) exposure ranging from 0.36 to 74 ppm (0.92-189 mg/m³). Such tests, however, are not specific for VC. Hepatomegaly, altered liver function as shown by biochemical tests, and Raynaud's phenomenon (cold sensitivity and numbness of fingers) were reported in chemical plant workers exposed to 25-250 ppm VC (64-639 mg/m³) (Occidental Chemical Corporation, 1975).

An occupational study attempted to correlate the effects of VC on the liver function of exposed workers (77 total), as measured by the plasma clearance of the ^{99m}Tc-N-(2,4-dimethylacetanilido)iminodiacetate (HEPIDA) complex (Studniarek et al., 1989). The duration of exposure varied from 3 to 17 years. Personal air samplers were used to determine

the mean VC concentrations in 1982 at various regions of the plant. Polymerization operators ($n = 13$) had the highest mean exposure to VC, 30 mg/m^3 , with a mean duration of employment of 10 years. Autoclave cleaners ($n = 9$) and auxiliary personnel ($n = 12$) in polymerization rooms were exposed to mean concentrations of 9 mg/m^3 for a mean duration of 8 and 12 years, respectively, whereas technical supervisors ($n = 6$) had the lowest mean VC exposure of 6 mg/m^3 for a mean duration of 13 years. The investigators found a significant correlation between degree of exposure to VC and frequency of low clearance values; however, no concentration-response relationship was detected among the groups with respect to plasma clearance of $^{99\text{m}}\text{Tc-HEPIDA}$. This study is of limited value because personal air sampling was conducted for only 1 year. The yearly geometric means of VC atmospheric concentrations in various departments of the plant were provided, but these concentrations fluctuated dramatically between 0.1 and 600 mg/m^3 from 1974 to 1982.

There was no evidence of decrements in pulmonary function over the course of a work shift in a group of 53 chemical, plastics, and rubber workers exposed to higher VC levels (up to 250 ppm, 639 mg/m^3) (Occidental Chemical Corporation, 1975). In an analysis of causes of death in a cohort of 10,173 VC workers for up to 30 years after the onset of exposure, the only noncancer cause for which the SMR was significantly elevated was emphysema (Dow Chemical Company, 1986). There was no correlation with exposure duration or latency. There was also no control for smoking, although there was no excess of lung cancer.

Insufficient data exist to evaluate the teratogenicity of VC in humans. Several epidemiology studies have investigated the effects of VC exposure on incidence of fetal loss and birth defects (Hatch et al., 1981; Infante et al., 1976; Waxweiler et al., 1977); however, no solid association has been found. Studies of communities near VC plants (Edmonds et al., 1978; Theriault et al., 1983) have found no clear association between parental residence in a region with a VC plant and the incidence of birth defects in the exposed community.

VC does not appear to be teratogenic in animals and is embryotoxic only at high levels. Inhalation experiments in animals have associated developmental toxicity only with concentrations at or above those associated with maternal toxicity. John et al. (1977) examined the effects of inhaled VC on the fetuses of mice, rats, and rabbits. Pregnant CF1 mice (30-40/group) were exposed to 0, 50, or 500 ppm VC on gestational days 6-15. Sprague-Dawley rats (20-35/group) and New Zealand white rabbits (15-20/group) were administered 0, 500, or 2500 ppm VC, 7 hours/day on gestational days 6-15 for rats and 6-18 for rabbits. Parameters of maternal and developmental toxicity were evaluated; both the fetuses and litters were evaluated. Mice were more sensitive to the toxic effects of VC than either rats or rabbits. In mice, concentrations of 500 ppm induced maternal effects that included increased mortality, reduced body weight, and reduced absolute, but not relative, liver weight. Fetotoxicity also occurred in mice at 500 ppm, and was manifested as significantly increased fetal resorption,

decreased fetal body weight, reduced litter size, and retarded cranial and sternebral ossification. However, there was no evidence of a teratogenic effect in mice at either concentration. In rats exposed to 500 ppm, but not to 2500 ppm, maternal effects were restricted to reduced body weight. Maternal effects in rats at 2500 ppm were death of one rat, elevated absolute and relative liver weights, and reduced food consumption. A significant reduction in fetal body weight and an increase in the incidence of lumbar spurs were observed among rats exposed to 500 ppm but not 2500 ppm, and are not considered signs of VC-induced fetotoxicity. At 2500 ppm, increased incidence of dilated ureters was observed, which may represent a chemical-induced effect. No signs of maternal or developmental toxicity were observed in rabbits at either dose. This study identifies a NOAEL of 50 ppm (130 mg/m³) for maternal and fetotoxicity in mice and a NOAEL of 2500 ppm (6500 mg/m³) for rabbits.

Ungvary et al. (1978) exposed groups of pregnant CFY rats continuously to 1500 ppm (4000 mg/m³) on gestational days 1-9, 8-14, or 14-21 and demonstrated that VC is not teratogenic and has no embryotoxic effects when administered during the second or last third of pregnancy. During the first third of pregnancy, maternal toxicity was manifested by increased relative liver weight; increased fetal mortality and embryo toxic effects were evident. Slightly reduced body weight gain was noted in dams exposed on days 14-21.

VC does not appear to produce germinal mutations as manifested by a dominant lethal effect in male rats. In a dominant lethal study, Short et al. (1977) exposed male CD rats to 0, 50, 250, or 1000 ppm VC 6 hours/day, 5 days/week for 11 weeks. At the end of the exposure period, the exposed males were mated with untreated females, and there was no evidence of either preimplantation or postimplantation loss in pregnant females. However, reduced fertility was observed in male rats exposed to 250 and 1000 ppm (650 and 2600 mg/m³) VC.

Absorption of VC in humans after inhalation exposure is rapid. A study conducted in five young adult male volunteers showed that 42% of inhaled VC in the lung was retained, that maximum retention was reached within 15 minutes, and that the percent retention was independent of inspired VC concentration at least to the maximum used in the experiment, 60 mg/m³. After cessation of exposure, the VC concentration in expired air decreased rapidly within 30 minutes to 4% of the inhaled concentration (Krajewski et al., 1980). Animal inhalation studies also showed that VC is rapidly absorbed. Exposure of male Wistar rats (number/group unspecified) to 1000, 3000, or 7000 ppm VC (99.9% pure) for 5 hours using a head-only apparatus resulted in rapid uptake into the blood, as measured by gas-liquid chromatography (GLC) (Withey, 1976). Equilibrium blood levels were achieved within 30 minutes for all exposures. Upon cessation of exposure, blood levels declined to a barely detectable level after 2 hours. Rat studies show that the distribution of VC is rapid and widespread, but the storage of VC in the body is limited by its rapid metabolism and excretion (Bolt et al., 1977).

The primary route of VC metabolism is by the action of cytochrome P450 isozymes, primarily CYP 3A4, to form a highly reactive epoxide intermediate, CEO, which spontaneously rearranges to form CAA. These intermediates are detoxified mainly through conjugation with glutathione catalyzed by glutathione S-transferase (Hefner et al., 1975; Bolt et al., 1976; Jedrychowski et al., 1984; Watanabe et al., 1978a). The conjugated products are excreted in urine as substituted cysteine derivatives (Bolt et al., 1980; Hefner et al., 1975). Although VC has often been cited as a chemical for which saturable metabolism should be considered in the risk assessment, saturation appears to become important only at very high exposure levels (greater than 250 ppm by inhalation or 25 mg/kg-day orally) compared with those associated with the most sensitive noncancer effects or tumorigenic levels, and thus has little impact on the risk estimates.

Based on the elimination of VC observed following administration by various routes of exposure, the metabolism of VC appears to be a dose-dependent, saturable process in animals (Green and Hathway, 1975; Hefner et al., 1975; Gehring et al., 1978) and in humans (Krajewski et al., 1980). Saturation of metabolic pathways occurred at exposure concentrations of 250 ppm VC in male Wistar rats and 200 ppm in Rhesus monkeys; at concentrations below this, a straight, first-order decline in radioactivity was observed (Bolt et al., 1977; Buchter et al., 1980; Filser and Bolt, 1979). Studies have demonstrated the binding of metabolites of ¹⁴C-VC to liver macromolecules in vitro, and in rats exposed by inhalation (Guengerich and Watanabe, 1979; Guengerich et al., 1979, 1981; Kappus et al., 1976; Watanabe et al., 1978a,b). In single-exposure experiments at concentrations ranging from 1 to 5000 ppm ¹⁴C-VC, the binding to macromolecules increased proportionately with increasing metabolites of VC, and disproportionately with VC exposure concentration (Watanabe et al., 1978b).

The observation of Watanabe et al. (1978b) of a disproportionate relationship between effects (e.g., binding to macromolecules, liver effects, tumors) and exposure concentrations of unmetabolized VC is a principal reason for using PBPK modeling. The important contribution of PBPK modeling is to provide a more biologically plausible estimate of the effective dose, that is, the total production of reactive metabolites at the target tissue. The ratio of this biologically effective dose to exposure concentration or administered dose is not uniform across routes and species. Therefore, any estimate of administered dose is less adequate for performing route-to-route and interspecies extrapolation of risk.

Several different PBPK models for VC have been described in the literature. These models are described in detail and compared in the accompanying Toxicological Review Appendix A. The PBPK model used in this assessment was developed to support a cancer risk assessment based on the pharmacokinetic and metabolic data available in the literature for VC (Clewell et al., 1995a,b). The initial metabolism of VC was hypothesized to occur via two saturable

pathways, one representing low capacity-high affinity oxidation by cytochrome P450 IIE1 and the other representing higher capacity-lower affinity oxidation by other isozymes of P450, producing in both cases CEO as an intermediate product. The parameter values for the two metabolic pathways describing the initial step in VC metabolism were determined by simulation of gas uptake data from mice, rats, hamsters, monkeys, and controlled human inhalation exposures, as well as from data on total metabolism and glutathione depletion in both oral and inhalation exposures. Successful simulation of pharmacokinetic data from a large number of studies over a wide range of concentrations using primarily inhalation exposure and different measures of effect (decreased chamber concentration of VC, decreased serum levels of GSH) served as evidence that the PBPK model was valid over the exposure range of interest, especially for inhalation exposure scenarios. One limitation of the model is the lack of pharmacokinetic data via the oral route available for simulation and model validation. Model parameters for deriving dose metrics via the oral route have therefore been established such that the dose metrics generated would be "conservative," that is, predictive of higher human risk from animal results. This model, including the parameters and the rationale for their choice, pharmacokinetic data and model fit to these data, the sensitivity analysis of the model, and the actual dose metrics derived, is also presented in the appendices of the Toxicological Review.

For more detail on Susceptible Populations, exit to [the toxicological review, Section 4.7 \(PDF\)](#).

I.B.5. Confidence in the Inhalation RfC

Study — High

Database — Medium to High

RfC — Medium

The overall confidence in this RfC assessment is medium. Confidence in the study of Til et al. (1983, 1991) is high because it used adequate numbers of animals, was well controlled, and reported in detail on the histological effects on the liver. Bi et al. (1985) and Sokal et al. (1981) both give corroborative information on liver effects following inhalation exposure. Because of the close similarity of the pharmacokinetics via the inhalation and oral routes and the use of a PBPK model, inhalation data can be used to fill gaps in the inhalation database and vice versa.

Confidence in the database is medium to high. The two-generation reproductive study of CMA (1998) showed no indication of reproductive effects while demonstrating liver effects corroborative of results from other studies, both oral and inhalation. The repeated exposure dominant lethal study of Short et al. (1977) showed reduced fertility, but only at

concentrations well above those producing effects in the target organ (liver). Two developmental inhalation studies were located that reported embryotoxic effects only at levels much higher than those causing maternal toxicity in mice, rats, or rabbits (John et al., 1977; Ungvary et al., 1978). Several other inhalation studies report on other endpoints and support the use of the liver effects. Concern for the confidence of dose metrics derived by the PBPK model from the oral study of Til et al. is also offset by procedures instituted within the model when calculating oral dose metrics, including assumption of a maximum rate of VC uptake (i.e., designating it a zero-order process) and spreading the applied dose over a 24-hour period, which would minimize the concentration and maximize the likelihood that the parent VC would be metabolized to reactive species (i.e., the basis of this assessment, mg VC metabolized).

The high degree of confidence in the principal study of Til et al. (1983, 1991), combined with the medium to high assessment of the database and less than high confidence in the qualitative aspects of the PBPK model, is considered to result in an overall medium confidence in the RfC.

For more detail on Characterization of Hazard and Dose Response, exit to [the toxicological review, Section 6 \(PDF\)](#)

I.B.6. EPA Documentation and Review of the Inhalation RfC

Source Document — U.S. EPA, 2000

This assessment was peer reviewed by external scientists. Their comments have been evaluated carefully and incorporated in finalization of this IRIS Summary. A record of these comments is included as an appendix to the Toxicological Review of Vinyl Chloride in support of Summary Information on the Integrated Risk Information System (IRIS) (U.S. EPA, 2000). [To review this appendix, exit to the toxicological review, Appendix E, Summary of and Response to External Peer Review Comments \(PDF\)](#)

Agency Consensus Date - 07/20/2000

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfC for vinyl chloride conducted in August 2003 did not identify any critical new studies. IRIS users who know of important new studies may provide that information to the IRIS Hotline at hotline.iris@epa.gov or 202-566-1676.

I.B.7. EPA Contacts (Inhalation RfC)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (fax), or hotline.iris@epa.gov (Internet address).

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Vinyl chloride

CASRN — 75-01-4

Last Revised — 08/07/2000

Section II provides information on three aspects of the carcinogenic assessment for the substance in question, the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral exposure and from inhalation exposure. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per $\mu\text{g/L}$ drinking water or risk per $\mu\text{g/m}^3$ air breathed. The third form in which risk is presented is a concentration of the chemical in drinking water or air providing cancer risks of 1 in 10,000, 1 in 100,000, or 1 in 1,000,000. The rationale and methods used to develop the carcinogenicity information in IRIS are described in The Risk Assessment Guidelines of 1986 (EPA/600/8-87/045) and in the IRIS Background Document. IRIS summaries developed since the publication of EPA's more recent Proposed Guidelines for Carcinogen Risk Assessment also utilize those Guidelines where indicated (Federal Register 61(79):17960-18011, April 23, 1996). Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

II.A. Evidence for Human Carcinogenicity

II.A.1. Weight-of-Evidence Characterization

On the basis of sufficient evidence for carcinogenicity in human epidemiology studies, VC is considered to best fit the weight-of-evidence Category "A," according to current EPA Risk Assessment Guidelines (U.S. EPA, 1986). Agents classified into this category are considered known human carcinogens. This classification is supported by positive evidence for carcinogenicity in animal bioassays including several species and strains, and strong evidence for genotoxicity.

Under the Proposed Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1996), it is concluded that VC *is a known human carcinogen by the inhalation route of exposure*, based on human epidemiological data, and by analogy *the oral route* because of positive animal bioassay data as well as pharmacokinetic data allowing dose extrapolation across routes. VC *is also considered highly likely to be carcinogenic by the dermal route* because it is well absorbed and acts systemically. The weight-of-evidence for human carcinogenicity is based on (1) consistent epidemiologic evidence of a causal association between occupational exposure to VC via inhalation and the development of angiosarcoma, an extremely rare tumor; (2) consistent evidence of carcinogenicity in rats, mice, and hamsters by both the oral and inhalation routes; (3) mutagenicity and DNA adduct formation by VC and its metabolites in numerous in vivo and in vitro test systems; and (4) efficient VC absorption via all routes of exposure tested, followed by rapid distribution throughout the body. In light of the very high percentage of angiosarcomas worldwide that are associated with VC exposure, the evidence for VC carcinogenicity is considered strong.

The International Agency for Research on Cancer (IARC) has also concluded that sufficient evidence for carcinogenicity in humans exists and has placed VC in carcinogenicity category 1, that is, carcinogenic to humans (IARC, 1979).

VC carcinogenicity occurs via a genotoxic pathway and is understood in some detail. VC is metabolized to a reactive metabolite, probably chloroethylene oxide (CEO), which is believed to be the ultimate carcinogenic metabolite of VC. The reactive metabolite then binds to DNA, forming DNA adducts that, if not repaired, ultimately lead to mutations and tumor formation. Therefore, a *linear* extrapolation was used in the dose-response assessment. Because of uncertainty regarding exposure levels in the occupationally exposed cohorts, recommended potency estimates are based on animal bioassay data.

For more detail on Characterization of Hazard and Dose Response, exit to [the toxicological review, Section 6](#) (PDF).

For more detail on Susceptible Populations, exit to [the toxicological review, Section 4.7](#) (PDF).

II.A.2. Human Carcinogenicity Data

Sufficient: Several independent retrospective and prospective cohort studies demonstrate a statistically significant elevated risk of liver cancer, specifically angiosarcomas, from exposure to VC monomer (Monson et al., 1974; Tabershaw and Gaffey, 1974; Byren et al., 1976; Waxweiler et al., 1976; Fox and Collier, 1977; Cooper, 1981; Weber et al., 1981; Jones et al., 1988; Wu et al., 1989; Pirastu et al., 1990; Simonato et al., 1991; Wong et al., 1991; Du and

Wang, 1998; Pirastu et al., 1998; CMA, 1998). The possible association of brain, soft tissue, and nervous system cancer with VC exposure was also reported (Monson et al., 1975; Waxweiler et al., 1976; Cooper, 1981; Wong et al., 1991; CMA et al., 1998). The evidence supporting a causal link between brain cancer and VC exposure is limited by the fact that most of the positive studies utilized the same CMA cohort, or workers from the same plants, and according to Doll (1988) contain certain weaknesses in the data. Some studies have found an association between VC exposure and cancer of the hematopoietic and lymphatic systems (Simonato et al., 1991; Weber et al., 1981); observed increases in other studies fell below statistical significance due to the small numbers of these types of cancers (Tabershaw and Gaffey, 1974). VC exposure has also been associated with lung cancer (Buffler et al., 1979; Monson et al., 1975; Waxweiler et al., 1976, 1981), but this response was considered more likely due to PVC particles than to VC. An excess of melanoma was reported in one study (Heldaas et al., 1984), but other studies have not substantiated this report.

In 1974, Creech and Johnson reported for the first time an association between exposure to VC and cancer in humans: three cases of liver angiosarcoma were reported in men employed in a PVC plant. Angiosarcoma of the liver is considered to be a very rare type of cancer, with only 20-30 cases per year reported in the United States (Gehring et al., 1978; ATSDR, 1995). As described in the following paragraphs, greater than expected incidences of angiosarcoma of the liver have since been reported in a number of other cohorts of workers occupationally exposed to VC.

In a proportionate mortality study analyzing the causes of death of 142 workers exposed to VC monomer or VC/PVC, Monson et al. (1974) found an excess incidence of liver cancer (8 observed versus 0.7 expected). Five of these were angiosarcomas. The study also found an excess of brain cancer (5 observed versus 1.2 expected) and lung cancer (13 observed versus 7.9 expected). No statistical analysis was conducted by tumor target.

Byren et al. (1976) reported a significantly elevated risk of pancreas/liver cancer (4 observed versus 0.97 expected) in a cohort of 750 Swedish workers exposed to VC. They also found a small excess of brain cancer (2 observed versus 0.33 expected).

Waxweiler et al. (1976) found a significantly elevated risk (7 observed versus 0.6 expected) of liver cancer in a cohort of 1294 workers who were exposed to VC monomer for a minimum of 5 years and followed for 10 or more years. In a separate phase of the study, the authors identified 14 cases of liver and biliary cancer, 11 of which were angiosarcomas. Several of the identified subjects were not included in the main study because they were still alive, or because they did not meet the minimum criteria for inclusion in the cohort. Brain cancer incidence was significantly increased in workers observed for 15 years or more after initial exposure (3 observed versus 0.6 expected); a nonsignificant increase was observed for a 10-

year latency. The cohort study also found a slight excess risk of lymphatic and hematopoietic system cancer (4 observed versus 2.5 expected). Of the 14 cases of primary lung cancer identified, 5 were large-cell undifferentiated, three were adenocarcinomas, and there were no squamous cell or small cell bronchiogenic carcinomas, suggesting that these cancers were not associated with smoking. In a study of 4806 workers at the same plants, an elevated risk of lung cancer was found in those exposed to PVC and chemicals other than VC. PVC appeared to be the most likely etiologic agent (Waxweiler et al., 1981).

A large number of occupational studies reported an association between VC and liver angiosarcoma or hepatocellular carcinoma, but quantitative exposure information is available for only a few studies. Fox and Collier (1977) reported 4 cases of liver cancer, 2 of which were angiosarcomas, in a cohort of 7717 British VC workers. The study authors grouped the subjects by estimated exposure levels and exposure duration. From these data, average exposure levels have been estimated as 12.5, 70, and 300 ppm (Clement Associates, 1987) or 11, 71, and 316 ppm (Chen and Blancato, 1989). Because workers were classified on the basis of the maximum exposure for each worker, cumulative exposure is overestimated, leading to a probable underestimation of risk using these data. Both angiosarcoma cases were considered to have had high exposure to VC monomer, at the level of 200 ppm and above TWA. There was no effect on other cancers, in comparison with cancer rates in England and Wales. In a followup study, Jones et al. (1988) analyzed mortality in 5498 male VC workers. This study found a significant excess of primary liver tumors, with 11 deaths, 7 of which were angiosarcomas. The median latency for angiosarcomas was 25 years.

Weber et al. (1981) examined mortality patterns in 7021 German and Austrian VC monomer/PVC workers and 4007 German PVC processing workers. Comparisons were with West German population death rates. A significantly elevated risk of liver cancer (12 observed versus 0.79 expected) was observed in the VC monomer/PVC cohort, but a significant increase (4 observed versus 1 expected) was also observed in an unexposed reference group. However, the risk in the VC monomer cohort increased with exposure duration. The study authors implied that four cases of angiosarcoma were identified in the study cohort, although it was not clear if all of the cases belonged to this cohort. A significant excess risk of brain cancer (Obs = 5, SMR = 535, $p < 0.05$) was also observed in the PVC processing workers, but not in VC monomer/PVC workers. Risk of lymphatic and hematopoietic cancer (Obs = 15, SMR = 214) was significantly increased in VC monomer/PVC production workers, and there was a tendency for increased risk at longer exposure durations.

In a preliminary mortality followup study of 464 workers at an Italian VC monomer production facility, a significant excess of respiratory cancers was observed (Obs = 5, SMR = 289, $p < 0.03$) (Belli et al., 1987). The excess remained after correction for smoking and was associated with longer exposure durations and higher exposure levels. They also found a

significant excess of lung cancer in a preliminary report of a cohort of 437 VC monomer/PVC workers.

Smulevich et al. (1988) investigated a cohort of 3232 workers (2195 men, 1037 women) in a Soviet VC/PVC chemical plant. No cases of angiosarcoma or other liver tumors were reported. Workers who were highly exposed to VC ($> 300 \text{ mg/m}^3$) had a significantly elevated risk of lymphomas and leukemias (apparently 7 observed versus about 1.1 expected for combined men and women, but there are inconsistencies in the reported numbers). The risk of brain cancer was elevated in women (Obs = 2, SMR = 500), but the effect was not statistically significant and the incidence in men was unaffected. Although mammary tumor incidence was increased in some of the animal studies reported in the following section, no cases of breast cancer were reported in the workers. This is the only study having a significant number of females in the cohort.

Wu et al. (1989) investigated a cohort of 2767 VC monomer workers, most of whom had been employed for fewer than 5 years. There was a significant excess risk of liver cancer (14 observed versus 4.2 expected). The incidence of angiosarcomas was not reported, but 12/18 liver cancers were angiosarcomas in a larger cohort of 3620 workers that included workers exposed to PVC, as well as the VC monomer workers. In a case-control study with the controls taken from a NIOSH database, angiosarcomas were related to higher cumulative exposure to VC monomer, but other liver cancers were not. Brain and lung cancer were not elevated for the VC monomer workers, but were elevated for the combined cohort.

Pirastu et al. (1990) evaluated clinical, pathological, and death certificate data for 63 deaths in 3 VC monomer/PVC manufacturing or PVC extruding plants in Italy. Fourteen deaths from primary liver cancer were found, of which seven were identified as angiosarcoma and two as hepatocellular carcinoma. No comparison with a control population was conducted. However, the authors stated that this study indicated a relationship between VC exposure and primary liver cancer, as well as with angiosarcoma. Pirastu et al. (1998) updated the cohort through 1996 for one of the plants and 1997 for the other two. The combined SMR for liver cancer at the three plants equaled 364 ($p < 0.05$).

Simonato et al. (1991) reported on the results of a large multicentric cohort study of 12,706 European VC/PVC workers. A significant increase in liver cancer deaths was observed (Obs = 24, SMR = 286). Workers were classified on the basis of maximum exposure level into ranges of $< 50 \text{ ppm}$, $50\text{-}499 \text{ ppm}$, and $\geq 500 \text{ ppm}$. Estimating an average exposure duration of 9 years, average exposure levels for these groups can be estimated at 25, 158, and 600 ppm. Histopathology was available for 17 of the liver cancers; 16 were confirmed as angiosarcoma and one was a nonangiosarcoma primary liver cancer. Excess risk from liver cancer was related to the time since first exposure, duration of exposure, and estimated total exposure. An

increased risk of lymphosarcoma was observed (SMR = 661, 95% CI = 136-1931), but there was no relationship to duration of employment. Brain cancer had an elevated risk in certain analyses, but there was no clear relationship to exposure duration. There was no excess risk of lung cancer.

Du and Wang (1998) studied 2224 workers employed at 5 factories in Taiwan during the period 1989-1995. A significantly increased risk of hospital admission among VCM workers due to primary liver cancer was reported, resulting in a morbidity odds ratio (MOR) of 4.5-6.5. Of the 12 cases of liver cancer found, 6 were diagnosed as hepatocellular carcinoma. The other 6 appeared to be the same, although angiosarcoma could not be ruled out without pathological confirmation. Ten of 11 cases of liver cancer for which detailed information was available were carriers of hepatitis B virus.

In a preliminary report with only 85% followup completed, Tabershaw and Gaffey (1974) compared mortality in a cohort of 8384 men occupationally exposed to VC with death rates among U.S. males. Each VC plant classified workers as exposed to high, medium, or low levels of VC, but no quantitative estimate of exposure was provided, and no attempt was made to establish consistent gradations of exposure between plants or exposure periods. No significant increases in any general cancer classification were found. However, six cases of angiosarcoma of the liver identified by other investigators occurred in the study population; only two of these were identified as angiosarcomas on the death certificate. The study authors also noted that 6 of 17 (40%) deaths in the category "other malignancies" were due to brain cancer. They stated that only 22% of the deaths in this category would be expected to be due to this cause, but they did not provide any supporting documentation. This preliminary report also noted a slight excess risk of lymphomas (5 observed versus 2.54 expected) in the group with the higher exposure index.

Cooper (1981) enlarged the Tabershaw and Gaffey (1974) study to include 10,173 VC workers; vital status was ascertained for 9677 men. Cooper noted that, of the nine angiosarcomas identified in the United States workers during the study period (prior to 1/93), eight were included in the study cohort. Statistical analyses were conducted for broad categories of tumors; a significant increase (Obs = 12, SMR = 203, $p < 0.05$) was observed for brain and central nervous system malignancies.

An update on this cohort (Wong et al., 1991) also found an association between VC exposure and angiosarcoma. Fifteen deaths from angiosarcoma were identified, a clear excess over the incidence in the general population, although no statistical analysis was conducted for this malignancy. This study also attempted to determine whether other cancers are associated with VC exposure. Excluding the 15 angiosarcomas identified from death certificates, a significant increase was observed in liver and biliary tract cancers alone (Obs = 22, SMR = 386, $p <$

0.02). However, the study authors suggested that these 22 cancers probably included some cases of angiosarcoma that were misdiagnosed. Based on a comparison of death certificates and pathology records in 14 cases, they estimated that the correct number of primary liver/biliary tract cancers (excluding angiosarcomas) is 14, which is still significantly increased over background (SMR = 243, $p < 0.01$). This study also found a significantly increased risk of cancer of the brain and central nervous systems (Obs = 23, SMR = 180, $p < 0.05$). There was no excess in cancer of the respiratory system or the lymphatic and hematopoietic system. Expected deaths were based on U.S. mortality rates, standardized for age, race, and calendar time.

CMA (1998) updated the Wong et al. (1991) study through 1995. This study was also designed to evaluate possible induction of cancer at a larger number of target sites than the Wong et al. study. In this study, all liver and biliary cancers were included in a single category. Mortality rate for these cancers, based on 80 deaths, was again significantly increased (SMR = 359; 95% CI = 284-446). The SMRs increased with duration of exposure from 83 (95% CI = 33-171), to 215 (95% CI = 103-396) to 679 (95% CI = 483-929), to 688 (95% CI = 440-1023) for workers exposed from 1 to 4 years, 5 to 9 years, 10 to 19 years, and 20 years or more, respectively. Mortality from brain and CNS cancer showed an excess based on 36 deaths (SMR = 142; 95% CI = 100-197). The elevation was statistically significant for those exposed 5- 9 years (SMR = 193; 95% CI = 96-346) and for those exposed 20 years or more (SMR = 290; 95% CI = 132-551). Finally, mortality from connective and other soft tissue cancers, based on 12 deaths, was also increased significantly (SMR = 270; 95% CI = 129-472). The increases were significant for those exposed 10-19 years (SMR = 477; 95% CI = 155-1113) and 20 or more years (SMR = 725; 95% CI = 197-1856). This cause of death category had not been evaluated in the Wong et al. (1991) study. Deaths were based upon regional (State-weighted) mortality rates for white males.

In conclusion, strong evidence exists for a causal relationship between exposure to VC in humans and a significantly excessive risk of liver angiosarcoma; the highest relative risk is associated with this cancer type. There is also highly suggestive evidence of a causal relationship with other liver cancers. Brain cancer and cancer of the lymphopoietic system, connective tissue, and soft tissue have been associated with VC exposure in some studies, but not others, suggesting a possible relationship. Lung cancer has also been associated with VC exposure, but, based on the data of Waxweiler et al. (1981), the increased risk of lung cancer observed in some cohorts may be due to exposure to PVC dust, rather than VC monomer. In reviewing the effects of exposure to VC, both Doll (1988) and Storm and Rozman (1997) concluded that evidence for induction of nonliver tumors is weak. Because of the consistent evidence for liver cancer in all the studies, knowledge that VC is metabolized primarily by the liver, and the weaker association for other sites, it is concluded that the liver is the most

sensitive site, and protection against liver cancer will protect against possible cancer induction in other tissues.

II.A.3. Animal Carcinogenicity Data

Sufficient: VC is carcinogenic in rodents by both oral and inhalation routes, and some data indicate that it produces tumors when given i.p., s.c., and transplacentally.

Feron et al. (1981) conducted lifespan oral bioassays of VC in Wistar rats. In order to incorporate VC into the diet of Wistar rats, Feron et al. (1981) administered diets containing 10% PVC with varying proportions of VC monomer. Diets were available to experimental animals for 4 hours per day and food consumption and VC concentrations were measured several times during the feeding period to account for loss of VC from the diet due to volatilization. This information was used to calculate the ingested dose. Evaporative loss averaged 20% over 4 hours. The ingested dose was adjusted downward by the amount of VC measured in the feces to arrive at the bioavailable doses of 0, 1.7, 5.0, or 14.1 mg VC/kg-day, which were fed to Wistar rats (n = 80, 60, 60, and 80, respectively) for a lifetime. The amount actually absorbed was used in estimating risk because, although VC absorption is near 100% under most conditions, in the present case a small amount of VC was attached to or encapsulated in the PVC present in the feed and not taken up. Animals were sacrificed at 135 weeks (males) or 144 weeks (females). An additional group of 80/sex were administered 300 mg/kg bw/day by gavage in oil 5 days/week for 83 weeks. Increased mortality was noted in all treated groups, as was increased tumor incidence. Almost exclusively angiosarcomas were observed in the groups administered 300 mg/kg-day by gavage, whereas a mixture of angiosarcomas, hepatocellular carcinomas, and neoplastic nodules was observed at the middle and high dietary doses. Only hepatocellular carcinomas and neoplastic nodules were reported at the low dose. Several other rare tumors were identified as possibly associated with VC exposure. With one exception, animals with pulmonary angiosarcomas (significant at $p < 0.05$) also had liver angiosarcoma, suggesting metastases from the liver. A few Zymbal gland tumors, a rare tumor type, were noted, although the increases were not statistically significant. These neoplasms occurred at and above doses of 5 mg/kg bw/day. Abdominal mesotheliomas were elevated over controls in all dosed groups, but there was no clear dose response. Significant increases in preneoplastic proliferative lesions (clear-cell foci, basophilic foci, and eosinophilic foci) were observed in all dose groups. These foci are hepatocyte-derived, whereas angiosarcomas are derived from sinusoidal cells, indicating that the foci are precursors of hepatocellular carcinomas, not angiosarcomas.

Til et al. (1983, 1991) extended the study of Feron et al. (1981) to lower doses. The oral doses were delivered in the same way except that the diets contained a final concentration of 1% PVC, rather than 10%. Groups of 50 or 100 male and female Wistar rats were administered

lifetime dietary doses of VC at 0, 0.014, 0.13, or 1.3 mg/kg bw/day (149 weeks for males and 150 weeks for females). An additional control group of 100 males and 100 females was held in a separate room. Mortality differences were not remarkable for males, but were slightly increased for females receiving 1.3 mg/kg-day. Angiosarcomas were observed in one high-dose male and two high-dose females. Although this incidence did not achieve statistical significance, angiosarcomas are rare in rats. Other significant increases in tumors were limited to neoplastic nodules in females and hepatocellular carcinomas in males. No Zymbal gland tumors or abdominal mesotheliomas were observed. In this study, VC at 0.13 mg/kg-day did not induce tumors, whereas at 1.3 mg/kg-day, neoplastic and nonneoplastic lesions in the liver were clearly increased by comparison to controls. Significant increases in foci of cell proliferation were observed in males and females at the high dose, with significant increases in basophilic foci extending down to 0.014 mg/kg-day.

Male and female Sprague-Dawley rats (40/sex/group) were administered 0, 3.33, 16.65, or 60 mg/kg VC in olive oil, by gavage, 5 days/week beginning at 13 weeks of age and continuing for 52 weeks (Maltoni et al., 1981, 1984). Animals were observed for their lifetime (136 weeks). In a separate phase of testing, groups of 75 Sprague-Dawley rats received 0, 0.03, 0.3, or 1.0 mg/kg-day VC using the same dosing protocol. During the second year of the study, all three groups of treated males showed a lower rate of survival than controls. The rate of survival in controls was very low in terms of adequate number surviving for development of neoplasms appearing late in life. Nonetheless, angiosarcomas of the liver appeared with a dose-related incidence, down to a dose of 0.3 mg/kg-day. Nephroblastomas, a rare tumor type in rats, were also reported at 16.65 and 60 mg/kg-day. There was no effect on mammary tumors.

Male and female Sprague-Dawley rats (30/sex/group) were exposed to 0, 1, 5, 10, 25, 50, 100, 150, 200, 250, 500, 2500, 6000, or 10,000 ppm VC by inhalation for 4 hours/day, 5 days/week for 52 weeks (Maltoni et al., 1981, 1984). Animals were observed throughout their lifetime (135 weeks). Tumor incidence (including liver angiosarcomas) and latency were concentration dependent. Additional tumor types seen included liver hepatoma, nephroblastoma, neuroblastoma of the brain, Zymbal gland tumors, and mammary carcinomas. The study authors particularly noted the rarity of angiosarcoma, hepatoma, nephroblastoma, and neuroblastoma in their animal colony.

These results in rats are confirmed in similar experiments in other species. Maltoni et al. (1984) also exposed male and female Swiss mice and male Syrian golden hamsters (approximately 40-80/sex/species/group) to 0, 50, 250, 500, 2500, 6000, or 10,000 ppm VC by inhalation for 4 hours/day, 5 days/week for 30 weeks. Animals were observed for life. The following types of tumors were increased in exposed mice: mammary, liver (including

angiosarcomas), forestomach, lung, and epithelial. Tumor types in hamsters were liver (including angiosarcomas), forestomach, and epithelial.

Other inhalation experiments support the carcinogenicity of VC. Rats and mice exposed to 0, 50, 250, or 1000 ppm for 6 hours per day, 5 days per week for up to 6 months (mice) or 10 months (rats) (Hong et al., 1981) or up to 12 months (mice and rats) (Lee et al., 1978) had a significantly increased incidence of hemangiosarcoma of the liver at ≥ 250 ppm. Animals were sacrificed 12 months after the end of exposure. Mice in this study exposed to ≥ 250 ppm also had an increase in bronchoalveolar adenoma of the lung and mammary gland tumors in females (adenocarcinomas, squamous and anaplastic cell carcinomas). Male rats exposed to concentrations as low as 100 ppm for 6 hours per day, 6 days per week, for 12 months and sacrificed at 18 months (6 months after the end of exposure) had significantly increased incidences of angiosarcoma of the liver (Bi et al., 1985). Rats exposed to 3% VC (30,000 ppm) for 4 hours per day, 6 days per week, for 12 months had significantly increased incidences of epidermoid carcinoma of the skin, adenocarcinoma of the lungs, and osteochondroma in the bones (Viola et al., 1971), and rats exposed to 0-5000 ppm for 52 weeks had primary tumors in the brain, lung, Zymbal gland, and nasal cavity (Feron and Kroes, 1979). Keplinger et al. (1975) provided a preliminary report of a concentration-dependent increase in tumor formation (alveogenic adenomas of the lung, angiosarcomas of the liver, and adenosquamous carcinoma of the mammary gland) in mice exposed to 0, 50, 200, or 2500 ppm VC.

Suzuki (1978, 1983) investigated the effect of VC on lung tumor formation. In a preliminary study conducted with a limited number of animals, alveogenic lung tumors developed in 26 of 27 mice exposed to 2500 or 6000 ppm for 5-6 months (Suzuki, 1978). A concentration-related increase in the incidence of alveogenic tumors was observed in a study in which 30-40 mice/group were exposed to 1-660 ppm or filtered air for 4 weeks and then observed for up to 41 weeks postexposure (Suzuki, 1983). An increase in bronchoalveolar adenoma was observed in a lifetime study of mice exposed to 50 ppm for 100 1-hour exposures, and 5000 or 50,000 ppm for a single 1-hour exposure (Hehir et al., 1981). The statistical significance of these observations was not presented.

The available evidence from either inhalation or oral studies in animals supports the findings in humans that VC is carcinogenic. Additional evidence for cancer induction by intraperitoneal, subcutaneous, and transplacental administration of VC was presented by Maltoni et al. (1984). IARC reached similar conclusions (IARC, 1979).

Several studies have compared the carcinogenic effects of VC in newborn animals and adults. Newborn rats treated with VC respond with both angiosarcoma and hepatocellular carcinoma, in contrast with adult animals, in which angiosarcomas generally predominate (Maltoni et al.,

1981). Consistent with this observation, VC was found to induce preneoplastic foci in newborn rats, but not in adults (Laib et al., 1979). Interestingly, in the same study it was found that VC did induce preneoplastic foci in adult rats after partial hepatectomy, indicating that the appearance of foci, and presumably of hepatocellular carcinoma, in neonatal animals was a consequence of the increased rate of cell proliferation at that age. Similarly, Laib et al. (1989) found that inhaled radiolabeled VC was incorporated into physiological purines of 11-day-old Wistar rats at eightfold higher levels than in similarly treated adult rats (presumably reflecting the DNA replication activity), and roughly fivefold higher levels of the DNA adduct 7-(2-oxoethyl) guanine (OEG) were found in the livers of young animals, reflecting an increased alkylation rate. In a similar study, roughly fourfold greater concentrations of both OEG and N2,3-ethenoguanine (EG) were also seen in preweanling rats exposed to VC (Fedtke et al., 1990). The higher cell proliferation rates found in newborn animals suggest that VC, or any other DNA-reactive carcinogen, could be more potent in newborns than in adults. Nevertheless, increased cell proliferation and DNA adduct formation are not in themselves adequate to demonstrate a quantitative potency difference for tumor formation between infants and adults.

Additional evidence indicating that young animals are more sensitive than adults to VC carcinogenicity is provided by Maltoni et al. (1981). Pregnant rats were exposed from gestation day 12 through 18 to 6000 or 10,000 ppm VC for 4 hours/day, and tumors were ascertained at 143 weeks postexposure. Nephroblastomas, forestomach tumors, epithelial tumors, and mammary gland carcinomas were observed only in the offspring, and the incidence of Zymbal gland carcinomas was higher in transplacentally exposed animals than in maternal animals. Because the dams and offspring were followed for the same period, latency is not an issue for this experiment. However, it is important to note that the offspring were exposed during organogenesis, a period of rapid cell division, and any genotoxic carcinogen would be expected to have a higher potency during this period.

Drew et al. (1983) studied the effects of age and exposure duration on cancer induction by VC in rats, mice, and hamsters. Female golden Syrian hamsters, F344 rats, Swiss CD-1 mice, and B6C3F1 mice were exposed for 6 hours/day, 5 days/week to VC (50, 100, or 200 ppm for mice, rats, and hamsters, respectively) for 6, 12, 18, or 24 months, with the exception of mice, which were exposed only up to 18 months. All animals were sacrificed at month 24 or 18 (mice), and about 50 animals/species/group were tested. Other groups of rodents were held 6-12 months, and then exposed for 6 or 12 months, and also sacrificed at month 24. Unfortunately, time-to-tumor data were not reported in this study, making it impossible to deconvolute the impact of survival on the observation of tumors from later exposure periods. Because both mice and hamsters showed significant survival effects (life-shortening) from the VC exposures, only the data on exposures of rats during the first 12 months of life are appropriate for analysis. In the rats, exposure from 0 to 6 months showed an overall similar

potency to exposure from 6 to 12 months of life. In particular, the incidence of hepatocellular carcinoma combined with neoplastic nodules and hemangiosarcoma was 24% and 5%, respectively, in rats exposed from 0 to 6 months, whereas for exposure from 6 to 12 months, the incidence was 31% and 4%, respectively. In this study, however, even the 0- to 6-month animals were 8-9 weeks old at the start of exposure and thus approaching maturity.

II.A.4. Supporting Data for Carcinogenicity

Several lines of evidence indicate that VC metabolites are genotoxic, interacting directly with DNA. Occupational exposure to VC has resulted in chromosome aberrations, micronuclei, and sister chromatid exchanges (SCEs); response levels were correlated with exposure levels (Hansteen et al., 1978; Purchase et al., 1978; Sinues et al., 1991). VC is mutagenic in the *Salmonella typhimurium* reverse mutation assay, with the mutagenic activity decreased or eliminated in the absence of exogenous metabolic activation (Bartsch et al., 1975; Rannug et al., 1974). The VC metabolites CEO and CAA are both mutagenic in the *Salmonella* assay (Bartsch et al., 1975; Rannug et al., 1976). The highly reactive metabolite CEO was much more mutagenic than CAA, suggesting that this is the metabolite responsible for VC carcinogenicity. DNA adducts formed by VC have also been identified (Swenberg et al., 1992, 1999).

II.B. Quantitative Estimate of Carcinogenic Risk from Oral Exposure

II.B.1. Summary of Risk Estimates

II.B.1.1. Oral Slope Factor	(a) LMS method (per mg/kg-day)	(b) LED 10/linear method (per mg/kg-day)
Continuous lifetime exposure during adulthood	7.2E-1	7.5E-1
Continuous lifetime exposure from birth	1.4	1.5
II.B.1.2. Drinking Water Unit Risk	(a) LMS	(b) LED 10/linear

II.B.1.1. Oral Slope Factor	(a) LMS method (per mg/kg-day)	(b) LED 10/linear method (per mg/kg-day)
	method (per µg/L)	method (per µg/L)
Continuous lifetime exposure during adulthood	2.1E-5	2.1E-5
Continuous lifetime exposure from birth	4.2E-5	4.2E-5

II.B.1.3. Extrapolation Method: (a) Linearized multistage (b) LED 10/linear method

The oral slope factor of 7.2E-1 per mg/kg-day to account for continuous lifetime exposure during adulthood, based on use of the linearized multistage model is recommended. A twofold increase to 1.4 per mg/kg-day to account for continuous lifetime exposure from birth is also recommended. According to the EPA Cancer Risk Assessment Guidelines of 1986 (U.S. EPA, 1987) "in the absence of adequate evidence to the contrary, a linearized multistage procedure will be employed." The 1996 proposed guidelines (U.S. EPA, 1996) recommend employment of the LED 10/linear method in similar situations. This approach is to draw a straight line between the point of departure from observed data, generally as a default the LED₁₀. The LED₁₀ is the lower 95% limit on a dose that is estimated to cause a 10% response. As can be seen, the derived values using either approach are virtually identical.

Drinking Water Concentrations at Specified Risk Levels:

Risk Level	Concentration (µg/L)	
	Adult exposure	Exposure from birth
E-4 (1 in 10,000)	4.8	2.4
E-5 (1 in 100,000)	4.8E-1	2.4E-1

Risk Level	Concentration (µg/L)	
E-6 (1 in 1,000,000)	4.8E-2	2.4E-2

II.B.2. Dose-Response Data (Carcinogenicity, Oral Exposure)

Tumor Type — Total of liver angiosarcoma, hepatocellular carcinoma, and neoplastic nodules

Test animals — Female Wistar rats

Route — Oral, diet

Reference — Feron et al., 1981

Admin. Dose (mg/kg/-day)	mg Metabolite/ L liver ^a	HED ^b	Tumor Incidence
0	0	0	2/57
1.7	38.6	1.07	28/58
5.0	113.2	3.13	49/59
14.1	316.6	8.77	56/57

^aDose metric (lifetime average delivered dose in rats) calculated from PBPK modeling of administered animal dose.

^bLifetime daily human oral dose required to produce an equivalent liver concentration.

II.B.3. Additional Comments (Carcinogenicity, Oral Exposure)

The slope factor is the 95% upper confidence limit on risk for female Wistar rats. Human equivalent doses were calculated using the PBPK model of Clewell et al. (1995), based on a dose metric of the daily metabolite generated, divided by the volume of the tissue in which the metabolite is produced, that is, mg metabolites/L liver (Andersen et al., 1987). The initial VC metabolism was hypothesized to occur via two saturable pathways, one representing low-capacity, high-affinity oxidation by cytochrome P450 IIE1, and the other representing higher

capacity, lower affinity oxidation by other isozymes of P450, both of which were addressed by the PBPK model in calculation of the dose metric described above.

Modeling of risk was conducted on the basis of the animal dose metric (mg metabolites/L liver) generated by the PBPK model from input of the administered dose. PBPK analysis showed that when generated with the pathway operative at low concentrations (low-capacity, high-affinity), the dose metric was linear with concentration. At high concentrations used in rodent bioassays, the second pathway becomes more involved, causing the metric-concentration relationship to become nonlinear. The PBPK model addressed both pathways. Then, consistent with the statement that "tissues experiencing equal average concentrations of the carcinogenic moiety over a full lifetime should be presumed to have equal lifetime cancer risk" (U.S. EPA, 1992), the calculated risk values based on the animal dose metric were assumed to correspond to the same risk for the same human dose metric. It was further assumed that the linear relationship between the dose metric and concentrations of interest (i.e., low) demonstrated by PBPK modeling was valid (see Appendix B of the Toxicological Review).

In order to convert the human dose metric to a human dose, the model was run for a sample human continuous oral exposure (1 mg/L in drinking water) to determine the dose of metabolites to the human liver corresponding to a given ingested dose. Because VC metabolism is linear in the human dose range of interest, this equivalence factor could be used to convert the risk based on the dose metric (now in humans) into the human oral dose. Calculation of a slope factor is appropriate in this case, in spite of the use of a pharmacokinetic model, because VC metabolism is linear in the human exposure range. Risk was based on results from the species and sex with the greatest response if differences between sexes were significant. In this case female rats are the most sensitive. This is in accordance with EPA guidelines (U.S. EPA, 1986).

Because statistically significant increases in liver angiosarcomas, neoplastic nodules, and hepatocellular carcinomas were reported in the oral studies of Feron et al. (1981), risk was calculated based on animals exhibiting any of these endpoints. This is in agreement with EPA policy to combine data from animals with any tumor that is statistically significantly increased. Although nodules may not progress to malignancy in every case, a conservative approach avoids possible underestimation of total cancer risk. Lung angiosarcoma incidences were significantly increased, but these animals also had liver tumors, so they were included in the counts.

HECs were derived using a PBPK model, an approach considered to be more accurate than a scaling factor, because it accounts for many more interspecies variables. Although the model does not account for possible pharmacodynamic differences, no adjustment was made for this

variable because available evidence suggests that humans are considered unlikely to be more susceptible to cancer induction by VC than laboratory species. A number of published cancer risk estimates based on epidemiologic data provided no evidence for greater carcinogenic sensitivity to VC in humans than in rats or mice, and some evidence for less sensitivity (see Section 5.3.3 of the Toxicological Review of Vinyl Chloride).

Confidence is high that the steady-state concentration of the active metabolite in the liver is accurately modeled, although the possibility of cancer induction at sites other than the liver is of some concern. Increases in nonliver tumors have been detected in some of the animal studies. They were generally sporadic in nature, however, with little evidence of a positive dose response. Although increases in nonliver tumors were noted in some of the epidemiology studies, the increase in relative risk was generally less than for liver tumors, and the evidence is considered to be fairly weak. Because VC is activated in the liver and because both human and animal data indicate that the liver is the most sensitive site for cancer induction, it is concluded that adequate protection against liver cancer will be protective against cancers at other sites. For a discussion of possible cancer induction at nonliver sites, see Section 5.3.5 of the Toxicological Review of Vinyl Chloride.

Animal evidence indications of age-dependent sensitivity warrant concern for young children potentially exposed to VC. This is based on several observations in animals regarding early-life studies. Exposure periods in the early-life studies do not overlap those of the chronic studies from which chronic slope factors and unit risk are derived. The angiosarcoma incidence after short-term, early-life exposure is approximately equal to that of long-term exposure starting after maturity. Based on these observations, continuous lifetime exposure from birth would about double cancer risk. Although there is some uncertainty regarding differences in sensitivity during early exposure, and although a portion of the increased responsiveness may be due to greater air or liquid intake per unit body weight, nevertheless the recommendation put forth is considered prudent. For further discussion on the basis for recommending adjustment to account for early-life sensitivity, as well as methodology to adjust for partial lifetime exposure, see Section 5.3.5.1 of the Toxicological Review of Vinyl Chloride.

In general, the potential for added risk from early-life exposure to VC is accounted for in the quantitative cancer risk estimates by a twofold uncertainty factor. If exposure occurs only during adult life, the twofold factor need not be applied.

Although increases in mammary tumors were reported in several inhalation bioassays, the increases were sporadic, with little evidence of a positive dose response. Because of the uncertainty in the animal data, the lack of reported breast cancer in occupationally exposed males or in one small cohort of females, and the knowledge that VC is primarily activated in

the liver, it is concluded that the liver is the most sensitive organ and no adjustment is necessary for possible breast cancer induction. For further discussion see section 5.3.5 of the Toxicological Review of Vinyl Chloride.

In summary, extrapolation of dose was based on equivalent concentration of the active metabolite per unit of liver volume. Because individual animal data, including time-to-tumor data, were available, a time-to-tumor model was used. In accordance with the 1986 Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1987), a linearized low-dose extrapolation was conducted for this genotoxic carcinogen. In accordance with the proposed cancer guidelines (U.S. EPA, 1996) a linear approach was also utilized by drawing a straight line between the LED₁₀ and the origin (zero dose). The results are nearly identical to those derived using the linearized multistage model. The values derived are recommended for lifetime exposure beginning at adulthood. For exposures beginning at birth an additional twofold safety factor is recommended.

The unit risk should not be used if the water concentration exceeds 10⁵ µg/L, because above this concentration the slope factor may differ from that stated.

II.B.4. Discussion of Confidence (Carcinogenicity, Oral Exposure)

The study was well conducted, used an adequate number of rats, and is supported by results of a followup study by Til et al. (1991) as well as those reported by Maltoni et al. (1981, 1984). Although inclusion of neoplastic nodules may represent a conservative approach, it should be noted that low body weights in the Feron et al. (1981) study, due to restriction of food intake to 4 hours per day, are likely to decrease tumorigenesis.

Use of a pharmacokinetic model reduces the uncertainty in extrapolating from animals to humans. A sensitivity analysis conducted on the parameters for the model found no amplification of error from inputs to outputs (Clewel et al., 1995). This is the desired result in a model used for risk assessment. A Monte Carlo uncertainty/variability analysis (2 realizations, 500 simulations/realization) was conducted to evaluate the impact of parameter uncertainty and variability on the risk prediction. The 95th percentile of the distribution of UCL risks was within 50% of the mean UCL risk. It should be noted that the slope factor was not based on the Monte Carlo analysis.

II.C. Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure

II.C.1. Summary of Risk Estimates

II.C.1.1. Inhalation Unit Risk:	(a) LMS method (Risk per $\mu\text{g}/\text{m}^3$)	(b) LED 10/linear method (Risk per $\mu\text{g}/\text{m}^3$)
Continuous lifetime exposure during adulthood	4.4E-6	4.4E-6
Continuous lifetime exposure from birth	8.8E-6	8.8E-6

The unit risk estimate of 4.4 E-6/ ($\mu\text{g}/\text{m}^3$)³ to account for continuous, lifetime exposure during adulthood, based on use of the linearized multistage model is recommended. A twofold increase to 8.8 E-6/ ($\mu\text{g}/\text{m}^3$)³, to account for continuous lifetime exposure from birth, is also recommended (see Toxicological Review Section 5.3.5.1). According to the EPA Cancer Risk Assessment Guidelines of 1986 (U.S. EPA, 1986) "in the absence of adequate evidence to the contrary, a linearized multistage procedure will be employed." The 1996 proposed guidelines (U.S. EPA, 1996) recommend employment of the LED 10/linear method in similar situations. This approach is to draw a straight line between the point of departure from the observed data, generally as a default the LED₁₀. The LED₁₀ is the lower 95% limit on a dose that is estimated to cause a 10% response. As can be seen, the derived values using either approach are virtually identical.

II.C.1.2. Extrapolation Method: (a) Linearized multistage (b) LED 10/linear method

Air Concentrations at Specified Risk Levels for continuous lifetime exposure during adulthood (based on female rats using the linearized multistage method):

Risk Level	Concentration
E-4 (1 in 10,000)	23 $\mu\text{g}/\text{m}^3$
E-5 (1 in 100,000)	2.3 $\mu\text{g}/\text{m}^3$
E-6 (1 in 1,000,000)	2.3E-1 $\mu\text{g}/\text{m}^3$

II.C.2. Dose-Response Data for Carcinogenicity, Inhalation Exposure

Tumor Type — Liver angiosarcomas, angiomas, hepatomas, and neoplastic nodules

Test animals — Female Sprague-Dawley rats

Route — Inhalation

Reference — Maltoni et al. (1981, 1984)

Admin. conc.(ppm)^a	Metabolite mg/L liver^b	HEC (ppm)^c	Tumors^d
0	0	0	0/141
1	0.59	0.20	0/55
5	2.96	1.0	0/47
10	5.90	2.0	1/46
25	14.61	4.6	5/40
50	31.27	10.1	1/29
100	55.95	19	1/43
150	76.67	26	5/46
200	90.00	31	10/44
250	103.45	35	3/26
500	116.94	40	11/28

Admin. conc.(ppm)^a	Metabolite mg/L liver^b	HEC (ppm)^c	Tumors^d
2500	134.37	48	10/24
6000	143.72	51	13/25

^a Animals exposed 4 hours/day, 5 days/week for 52 weeks.

^b Dose metric (lifetime average delivered dose in female rats) calculated from PBPK modeling of the administered animal concentration.

^c Continuous human exposure concentration over a lifetime required to produce an equivalent mg metabolite/L of liver.

^d Based on number of animals alive after detection of first liver tumor.

HEDs were calculated with the aid of the PBPK model of Clewell et al. (1995), using a dose metric of the daily metabolite generated, divided by the volume of the tissue in which the metabolite is produced (Andersen et al., 1987). The initial VC metabolism was hypothesized to occur via two saturable pathways, one representing low-capacity, high-affinity oxidation by cytochrome P450 IIE1, and the other representing higher capacity, lower affinity oxidation by other isozymes of P450. In order to convert the human dose metric to a human dose, the model was run for a sample human continuous inhalation exposure (1 mg/m³) to determine the dose of metabolites to the human liver corresponding to a given inhalation dose. As described for the oral slope factor, the risk modeling was conducted based on the animal dose metric, and the resulting risk was converted to a human risk value based on an equivalence factor. The equivalence factor for inhalation exposure was calculated by determining the human dose metric for continuous human inhalation exposure to a range of exposure concentrations (1 µg/m³ to 10,000 mg/m³). This calculation showed that the model was linear up to nearly 100 mg/m³, and the calculated equivalence factor was used to convert the risk from the inhalation experiments conducted in animals (in the units of the dose metric) to human risk values. The slope factor is based on the 95% upper confidence on risk in female rats. Calculation of a slope factor is appropriate in this case, in spite of the use of a pharmacokinetic model, because VC metabolism is linear in humans in this exposure range.

HECs were derived using a PBPK model, an approach considered to be more accurate than a scaling factor, because it accounts for many more interspecies variables. While the model does not account for possible pharmacodynamic differences, no adjustment was made for this variable because available evidence suggests that humans are considered unlikely to be more susceptible to cancer induction by VC than laboratory species (see Section 5.3.3 of the

Toxicological Review of Vinyl Chloride as well as the following section for additional details).

II.C.3. Additional Comments (Carcinogenicity, Inhalation Exposure)

Although human studies are preferable for deriving human cancer risk estimates, exposure data from most of the epidemiology studies are inadequate to derive risk estimates. For those that do provide exposure information, cumulative exposure (e.g., ppm-years) can be calculated. Because VC metabolism becomes nonlinear at high exposure concentrations, however, cumulative exposure is not sufficient for quantitating risk.

Hepatomas, angiomas, and neoplastic nodules were not statistically significantly increased in the Maltoni et al. (1981, 1984) studies. However, because hepatocellular tumors were significantly increased in the Feron et al. study, it was concluded that all liver tumors in the Maltoni et al. studies are likely the result of exposure to VC as well, and should be included as a conservative approach. The additional numbers of tumors were quite small and only minimally influenced the quantitative estimates.

A twofold adjustment is recommended to account for greater responsiveness to VC exposure during early life. Although there is some uncertainty regarding differences in sensitivity during early exposure, and although a portion of the increased responsiveness may be due to increased minute-volume ventilation, nevertheless the recommendation put forth is considered prudent. For a more detailed discussion regarding application of this adjustment, see Section 5.3.5.2 of the Toxicological Review.

Although increases in mammary tumors were reported in several inhalation bioassays, the increases were sporadic, with little evidence of a positive dose response. Because of the uncertainty in the animal data, the lack of reported breast cancer in occupationally exposed males or in one small cohort of females, and the knowledge that VC is primarily activated in the liver, it is concluded that the liver is the most sensitive organ and no adjustment is necessary for possible breast cancer induction. For further discussion see section 5.3.5 of the Toxicological Review of Vinyl Chloride.

The unit risk estimate, even with the addition of adjustments for early exposure, is about 10-fold lower than the previous EPA "HEAST" value of 8.4E-5 (U.S. EPA, 1994). There are several reasons for this. First, in the earlier estimate, absorption was assumed to equal 50% in the rat versus 100% in humans. Such an assumption is invalid in that virtually all VC is absorbed in both species until a blood concentration determined by the inspired concentration and the blood-to-air partition coefficient is reached. Because the partition coefficient is about twice as large in rats as in humans, arterial blood concentration will be greater in rats than

humans, rather than less. Metabolic activation of VC (V_{max}/K_m) is about 10 times faster in rats than humans. Blood flow to the liver is more rapid. After accounting for these and other pharmacokinetic differences, the model predicts that rats will have a considerably greater steady-state concentration of the active metabolite of VC than humans and thereby greater risk. Use of administered dose and standard defaults, on the other hand, would result in a prediction of lower risk in rats than in humans.

The unit risks can be compared with those derived from human epidemiology data. Risk estimates have been derived from four epidemiology studies (Fox and Collier, 1977; Jones et al., 1988; Simonato et al., 1991; Wong et al., 1991). Uncertainties associated with use of these studies are described in greater detail in the Toxicological Review. The primary weakness of the Fox and Collier (1977) study is the relatively small cohort associated with only two liver cancer cases. The Jones et al. (1978) study is an update of the Fox and Collier study. Workers were categorized according to cumulative exposure, which was considered to vary with duration, but not concentration. The Simonato et al. (1991) study was the largest, but the data were collected from many different workplaces in different countries, resulting in considerable uncertainty regarding exposures.

Chen and Blancato, using one pathway model, derived a unit risk estimate of $1.5E-6$ per $\mu\text{g}/\text{m}^3$ based on the Fox and Collier study. Clewell et al. (1995) developed risk estimates, using the two-pathway model, based on epidemiology studies reported by Fox and Collier (1977), Jones et al. (1988), and Simonato et al. (1991) ranging from $1.6 E-7$ to $1.5E-6$ per $\mu\text{g}/\text{m}^3$. Reitz et al. (1996) also assessed risk based on the Simonato et al. (1991) study. Although they did not develop a formal unit risk estimate using this study, they did report that a unit risk estimate of $5.7E-7$ per $\mu\text{g}/\text{m}^3$ derived using the Maltoni et al. (1981, 1984) animal inhalation studies overpredicted tumor counts from the Simonato et al. (1991) study by 10- to 35-fold.

The epidemiology-based estimates thus vary over about an order of magnitude, with the upper end of this range still somewhat lower than the animal inhalation-based estimates. Although each of these estimates contains a considerable degree of uncertainty, collectively they indicate that the animal data-based unit risk estimates are unlikely to underestimate true risk, despite being considerably lower than an earlier EPA estimate (ATSDR, 1997).

As discussed for the oral slope factor, a linear extrapolation from the 95% lower bound on the ED10 (LED10) was also considered for this genotoxic carcinogen. The maximum likelihood estimates (MLEs) and risk based on the MLEs were also derived. The LED10s were slightly less conservative than those risk estimates derived using the linearized multistage approach.

The unit risk should not be used if the air concentration exceeds $10^4 \mu\text{g}/\text{m}^3$, because above this concentration the slope factor may differ from that stated.

II.C.4. Discussion of Confidence (Carcinogenicity, Inhalation Exposure)

Maltoni et al. (1981, 1984) conducted a series of experiments in which rats were exposed to varying concentrations of VC, resulting in a broad, well-characterized concentration-response curve based on experiments conducted with an adequate number of animals.

Use of a pharmacokinetic model reduces the uncertainty in extrapolating from animals to humans. A sensitivity analysis conducted on the parameters for the model found no amplification of error from inputs to outputs (Clewel et al., 1995). This is the desired result in a model used for risk assessment. A Monte Carlo uncertainty/variability analysis (4 realizations, 500 simulations/realization) was conducted to evaluate the impact of parameter uncertainty and variability on the risk prediction. The 95th percentile of the distribution of UCL risks was within approximately a factor of 2 of the mean UCL risk.

II.D. EPA Documentation, Review, and Contacts (Carcinogenicity Assessment)

II.D.1. EPA Documentation

Source Documents --

U.S. Environmental Protection Agency (U.S. EPA). (2000) Toxicological review of vinyl chloride in support of summary information on the Integrated Risk Information System (IRIS). Available online from National Center for Environmental Assessment, <http://www.epa.gov/iris>.

U.S. Environmental Protection Agency. (1985) Health and environmental effects profile for chloroethene. EPA/600/85/374.

U.S. Environmental Protection Agency. (1984) Health effects assessment for vinyl chloride. Prepared by the Environmental Criteria and Assessment Office, Cincinnati, OH, for the Office of Solid Waste. EPA 540/1-86-036.

U.S. Environmental Protection Agency. (1984) Examination of recent information concerning cancer risk associated with vinyl chloride. Memorandum. Carcinogen Assessment Group.

This assessment was peer reviewed by external scientists. Their comments have been evaluated carefully and incorporated in finalization of this IRIS Summary. A record of these

comments is included as an appendix to the Toxicological Review of Vinyl Chloride in Support of Summary Information on the Integrated Risk Information System (IRIS) (U.S. EPA, 2000). [*To review this appendix, exit to the toxicological review, Appendix E, Summary of and Response to External Peer Review Comments \(PDF\).*](#)

II.D.2. EPA Review (Carcinogenicity Assessment)

Agency Consensus Date — 07/20/2000

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the cancer assessment for vinyl chloride conducted in August 2003 did not identify any critical new studies. IRIS users who know of important new studies may provide that information to the IRIS Hotline at hotline.iris@epa.gov or 202-566-1676.

II.D.3. EPA Contacts (Carcinogenicity Assessment)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (fax), or hotline.iris@epa.gov (Internet address).

III. [reserved]

IV. [reserved]

V. [reserved]

VI. Bibliography

Substance Name — Vinyl chloride
CASRN — 75-01-4

VI.A. Oral RfD References

Andersen, M; Clewell, H; Gargas, M; et al. (1987) Physiologically based pharmacokinetics and the risk assessment process for methylene chloride. *Toxicol Appl Pharmacol* 87:185-205.

Bi, WF; Wang, YS; Huang, MY; et al. (1985) Effect of vinyl chloride on testis in rats. *Ecotoxicol Environ Saf* 10(3):281-289.

Bolt, HM; Filser, JG; Laib, RJ; et al. (1980) Binding kinetics of vinyl chloride and vinyl bromide at very low doses. Quantitative aspects of risk assessment in chemical carcinogenesis. *Arch Toxicol Suppl* 3:129-142.

Bolt, HM; Kappus, H; Buchter, A; et al. (1976) Disposition of [1,2-¹⁴C] vinyl chloride in the rat. *Arch Toxicol* 35:153-162.

Buchancova, J; Reznak, I; Horak, V; et al. (1985) Scintigraphic pictures of the liver in workers after a long-term exposure to vinyl chloride. *Pracov Lek* 37:190-194.

Chemical Manufacturers Association (CMA). (1998) Vinyl chloride combined inhalation two-generation reproduction and developmental toxicity study in CD rats. Final Report: CMA, Arlington, VA.

Clewell, HJ; Gentry, PR; Gearhart, JM; et al. (1995a) The development and validation of a physiologically based pharmacokinetic model for vinyl chloride and its application in a carcinogenic risk assessment for vinyl chloride. ICF Kaiser report prepared for EPA/OHEA and OSHA/DHSP.

Clewell, HJ; Covington, TR; Crump, KS; et al. (1995b) The application of a physiologically based pharmacokinetic model for vinyl chloride in a noncancer risk assessment. ICF/Clement report prepared for EPA/NCEA under contract number 68-D2-0129.

Doss, M; Lange, CE; Veltman, G. (1984) Vinyl chloride-induced hepatic coproporphyrinuria with transition to chronic hepatic porphyria. *Klin Wochenschr* 62(4):175-178.

Drew, RT; Boorman, GA; Haseman, JK; et al. (1983) The effect of age and exposure duration on cancer induction by a known carcinogen in rats, mice and hamsters. *Toxicol Appl Pharmacol* 68:120-130.

Edmonds, LD; Anderson, CE; Flynt, Jr, JW; et al. (1978) Congenital central nervous system malformations and vinyl chloride monomer exposure: a community study. *Teratology* 17(2):137-142.

Feron, VJ; Hendriksen, CFM; Speek, AJ; et al. (1981) Lifespan oral toxicity study of vinyl-chloride in rats. *Food Cosmet Toxicol* 19(3):317-333.

Gedigk, P; Muller, R; Bechtelsheimer, H. (1975) Morphology of liver damage among polyvinyl chloride production workers. A report on 51 cases. *Ann NY Acad Sci* 246:279-285.

Hatch, M; Kline, J; Stein, Z. (1981) Power considerations in studies of reproductive effects of vinyl chloride and some structural analogs. *Environ Health Perspect* 41:195-201.

Hefner, RE, Jr; Watanabe, PG; Gehring, PJ. (1975) Preliminary studies of the fate of inhaled vinyl chloride monomer in rats. *Ann NY Acad Sci* 246:135-148.

Ho, SF; Phoon, WH; Gan, SL; et al. (1991) Persistent liver dysfunction among workers at a vinyl chloride monomer polymerization plant. *J Soc Occup Med* 41:10-16.

Infante, PF; Wagoner, JK; Waxweiler, RJ. (1976) Carcinogenic, mutagenic, and teratogenic risks associated with vinyl chloride. *Mutat Res* 41:131-142.

Jedrychowski, RA; Sokal, JA; Chmielnicka, J. (1984) Influence of exposure mode on vinyl chloride action. *Arch Toxicol* 55:195-198.

John, JA; Smith, FA; Leong, BKJ; et al. (1977) The effects of maternally inhaled vinyl chloride on embryonal and fetal development in mice, rats, and rabbits. *Toxicol Appl Pharmacol* 39:497-513.

Lilis, R; Anderson, H; Nicholoso, WJ; et al. (1975) Prevalence of disease among vinyl chloride and polyvinyl chloride workers. *Ann NY Acad Sci* 246:22-41.

Maltoni, C; Lefemine, G; Ciliberti, A; et al. (1981) Carcinogenicity bioassays of vinyl chloride monomer: a model or risk assessment on an experimental basis. *Environ Health Perspect* 41:3-29.

Marsteller, HJ; Lebach, WK; Muller, R; et al. (1975) Unusual splenomegalic liver disease as evidenced by peritoneoscopy and guided liver biopsy among polyvinyl chloride production workers. *Ann NY Acad Sci* 246:95-134.

Popper H; Thomas LB. (1975) Alterations of liver and spleen among workers exposed to vinyl chloride. *Ann NY Acad Sci* 246:172-194.

Schoental, R; Magee, PN. (1957) Chronic liver changes in rats after a single dose of Lasiocarpine, a pyrrolizidine (Senecio) alkaloid. *J Pathol Bacteriol* 74:305-319.

Schoental, R; Magee, PN. (1959) Further observations on the subacute and chronic liver changes in rats after a single dose of various pyrrolizidine (Senecio) alkaloids. *J Pathol Bacteriol* 78:471-482.

Short, RD; Minor, JL; Winston, JM; et al. (1977) Dominant lethal study in male rats after repeated exposures to vinyl chloride or vinylidene chloride. *J Toxicol Environ Health* 3:965-968.

Sokal, JA; Baranski, B; Majka, J; et al. (1980) Experimental studies on the chronic toxic effects of vinyl chloride in rats. *J Hyg Epidemiol Microbiol Immunol* 24:285-294.

Tamburro, CH; Makk, L; Popper, H. (1984) Early hepatic histologic alterations among chemical (vinyl monomer) workers. *Hepatology* 4(3):413-418.

Theriault, G; Iturra, H; Gingras, S. (1983) Evaluation of the association between birth-defects and exposure to ambient vinyl-chloride. *Teratology* 27(3):359-370.

Til, HP; Feron, VJ; Immel, HR (1991) Lifetime (149-week) oral carcinogenicity study of vinyl chloride in rats. *Food Chem Toxicol* 29:713-718.

Til, HP; Immel, HR; Feron, VJ. (1983) Lifespan oral carcinogenicity study of vinyl chloride in rats. Final report. Civo Institutes. TNO. Report No. V 83.285/291099, TSCATS Document FYI-AX-0184-0353, Fiche No. 0353.

Torkelson, TR; Oyen, F; Rowe, VK. (1961) The toxicity of vinyl chloride as determined by repeated exposure of laboratory animals. *Am Ind Hyg Assoc J* 22:354-361.

Ungvary, G; Hudak, A; Tatrai, E; et al. (1978) Effects of vinyl chloride exposure alone and in combination with trypan blue applied systematically during all thirds of pregnancy on the fetuses of CFY rats. *Toxicology* 11(1):45-54.

U.S. Environmental Protection Agency (U.S. EPA). (1987) The Risk Assessment Guidelines of 1986. EPA/600/8-87/045.

U.S. Environmental Protection Agency (U.S. EPA). (1996) Proposed Guidelines for Carcinogen Risk Assessment. Federal Register Vol. 61, No. 79, 4/23/1996. pp.17960-18011.

U.S. Environmental Protection Agency (U.S. EPA). (2000) Toxicological review of vinyl chloride in support of summary information on the Integrated Risk Information System (IRIS). Available online from National Center for Environmental Assessment, <http://www.epa.gov/iris>.

Watanabe, PG; Gehring, PJ. (1976) Dose-dependent fate of vinyl chloride and its possible relationship to oncogenicity in rats. Environ Health Perspect 17:145-152.

Watanabe, PG; McGowan, GR; Gehring, PJ. (1976) Fate of ¹⁴C-vinyl chloride after single oral administration in rats. Toxicol Appl Pharmacol 36(2):339-352.

Watanabe, PG; Zempel, JA; Gehring, PJ. (1978) Comparison of the fate of vinyl chloride following single and repeated exposure in rats. Toxicol Appl Pharmacol 44:391-399.

Waxweiler, RJ; Falk, H; McMichael, A; et al. (1977) A cross-sectional epidemiologic survey of vinyl chloride workers. NTIS PB274193.

Wisniewska-Knypl, JM; Klimczak, J; Kolakowski, J. (1980) Monooxygenase activity and ultrastructural changes of liver in the course of chronic exposure of rats to vinyl chloride. Int Arch Occup Environ Health 46(3):241-249.

Withey, JR. (1976) Pharmacodynamics and uptake of vinyl chloride monomer administered by various routes to rats. J Toxicol Environ Health 1:381-394.

VI.B. Inhalation RfC References

Andersen, M; Clewell, H; Gargas, M; et al. (1987) Physiologically based pharmacokinetics and the risk assessment process for methylene chloride. Toxicol Appl Pharmacol 87:185-205.

Berk, PD; Martin, JF; Young, RS; et al. (1976) Vinyl chloride-associated liver disease. Ann Intern Med 84(6):717-731.

Bi, WF; Wang, YS; Huang, MY; et al. (1985) Effect of vinyl chloride on testis in rats. Ecotoxicol Environ Saf 10(3):281-289.

Bolt, HM; Filser, JG; Laib, RJ; et al. (1980) Binding kinetics of vinyl chloride and vinyl bromide at very low doses. Quantitative aspects of risk assessment in chemical carcinogenesis. *Arch Toxicol Suppl* 3:129-142.

Bolt, HM; Kappus, H; Buchter, A; et al. (1976) Disposition of [1,2-¹⁴C] vinyl chloride in the rat. *Arch Toxicol* 35:153-162.

Bolt, HM; Laib, RJ; Kappus, H; et al. (1977) Pharmacokinetics of vinyl chloride in the rat. *Toxicology* 7:179-188.

Buchancova, J; Reznak, I; Horak, V; et al. (1985) Scintigraphic pictures of the liver in workers after a long-term exposure to vinyl chloride. *Pracov Lek* 37(6):190-194.

Buchter, A; Filser, JG; Peter, H; et al. (1980) Pharmacokinetics of vinyl chloride in the rhesus monkey. *Toxicol Lett* 6:33-36.

Chemical Manufacturers Association (CMA). (1998) Vinyl chloride combined inhalation two-generation reproduction and developmental toxicity study in CD rats. Final Report: CMA, Arlington, VA.

Chen, CW; Blancato, JN. (1989) Incorporation of biological information in cancer risk assessment: example-vinyl chloride. *Cell Biol Toxicol* 5:417-444.

Clewell, HJ; Covington, TR; Crump, KS; et al. (1995b) The application of a physiologically based pharmacokinetic model for vinyl chloride in a noncancer risk assessment. ICF/Clement report prepared for EPA/NCEA under contract number 68-D2-0129.

Clewell, HJ; Gentry, PR; Gearhart, JM; et al. (1995a) The development and validation of a physiologically based pharmacokinetic model for vinyl chloride and its application in a carcinogenic risk assessment for vinyl chloride. ICF Kaiser report prepared for EPA/OHEA and OSHA/DHSP.

Doss, M; Lange, CE; Veltman, G. (1984) Vinyl chloride-induced hepatic coproporphyrinuria with transition to chronic hepatic porphyria. *Klin Wochenschr* 62(4):175-178.

Dow Chemical Company. (1986) Co-initial submission: an update of an epidemiologic study with vinyl chloride workers, 1942-1982 (final report) with cover letter dated 072492 and attachments. Document Number: 88-920005649. Journal/Source: U.S. EPA/OTS public files. Fiche Number: 0544432 (1).

Drew, RT; Boorman, GA; Haseman, JK; et al. (1983) The effect of age and exposure duration on cancer induction by a known carcinogen in rats, mice and hamsters. *Toxicol Appl Pharmacol* 68:120-130.

Du, CL; Kuo, ML; Chang, HL; et al. (1995) Changes in lymphocyte single strand breakage and liver function of workers exposed to vinyl chloride monomer. *Toxicol Lett (Ireland)*. 77(1-3):379-385.

Edmonds, LD; Anderson, CE; Flynt, JW, Jr; et al. (1978) Congenital central nervous system malformations and vinyl chloride monomer exposure: a community study. *Teratology* 17(2):137-142.

Feron, VJ; Hendriksen, CFM; Speek, AJ; et al. (1981) Lifespan oral toxicity study of vinyl-chloride in rats. *Food Cosmetol Toxicol* 19(3):317-333.

Filser, JG; Bolt, HM. (1979) Pharmacokinetics of halogenated ethylenes in rats. *Arch Toxicol* 42:123-136.

Gedigk, P; Muller, R; Bechtelsheimer, H. (1975) Morphology of liver damage among polyvinyl chloride production workers. A report on 51 cases. *Ann NY Acad Sci* 246:279-285.

Gehring, PJ; Watanabe, PG; Park, CN. (1978) Resolution of dose-response toxicity data for chemicals requiring metabolic activation: Example-vinyl chloride. *Toxicol Appl Pharmacol* 44:581-591.

Green, T; Hathway, DE. (1975) The biological fate in rats of vinyl chloride in relation to its oncogenicity. *Chem Biol Interact* 11:545-562.

Guengerich, FP; Crawford, WM, Jr; Watanabe, PG. (1979) Activation of vinyl chloride to covalently bound metabolites: roles of 2-chloroethylene oxide and 2-chloroacetaldehyde. *Biochemistry* 18:5177-5182.

Guengerich, FP; Mason, PS; Stott, WT; et al. (1981) Roles of 2-haloethylene oxide and 2-haloacetaldehydes derived from vinyl bromide and vinyl chloride in irreversible binding to protein and DNA. *Cancer Res* 41:4391-4398.

Guengerich, FP; Watanabe, PG. (1979) Metabolism of (¹⁴C)- and (³⁶Cl)-labeled vinyl chloride in vivo and in vitro. *Biochem Pharmacol* 28:589-596.

Hatch, M; Kline, J; Stein, Z. (1981) Power considerations in studies of reproductive effects of vinyl chloride and some structural analogs. *Environ Health Perspect* 41:195-201.

Hefner, RE, Jr; Watanabe, PG; Gehring, PJ. (1975) Preliminary studies of the fate of inhaled vinyl chloride monomer in rats. *Ann NY Acad Sci* 246:135-148.

Ho, SF; Phoon, WH; Gan, SL; et al. (1991) Persistent liver dysfunction among workers at a vinyl chloride monomer polymerization plant. *J Soc Occup Med* 41(1):10-16.

Infante, PF; Wagoner, JK; Waxweiler, RJ. (1976) Carcinogenic, mutagenic, and teratogenic risks associated with vinyl chloride. *Mutat Res* 41:131-142.

Jedrychowski, RA; Sokal, JA; Chmielnicka, J. (1984) Influence of exposure mode on vinyl chloride action. *Arch Toxicol* 55:195-198.

John, JA; Smith, FA; Leong, BKJ; et al. (1977) The effects of maternally inhaled vinyl chloride on embryonal and fetal development in mice, rats, and rabbits. *Toxicol Appl Pharmacol* 39:497-513.

Kappus, H; Bolt, HM; Buchter, A; et al. (1976) Liver microsomal uptake of [¹⁴C] vinyl chloride and transformation to protein alkylating metabolites in vitro. *Toxicol Appl Pharmacol* 37:461-471.

Krajewski, J; Dobecki, M; Gromiec, J. (1980) Retention of vinyl chloride in the human lung. *Br J Ind Med* 37(4):373-374.

Lilis, R; Anderson, H; Nicholoso, WJ; et al. (1975) Prevalence of disease among vinyl chloride and polyvinyl chloride workers. *Ann NY Acad Sci* 246:22-41.

Maltoni, C; Lefemine, G; Ciliberti, A; et al. (1980) Vinyl chloride carcinogenicity bioassays (BT project) as an experimental model for risk identification and assessment in environmental and occupational carcinogenesis. *Epidemiol Anim Epidemiol Hum: Cas Chlorure Vinyle Monomer (Reun Club Carcerog Chim) 20th meeting, 1979, Publ Essent, Paris, France; pp. 11-112.*

Maltoni, C; Lefemine, G; Ciliberti, A; et al. (1981) Carcinogenicity bioassays of vinyl chloride monomer: a model or risk assessment on an experimental basis. *Environ Health Perspect* 41:3-29.

Marsteller, HJ; Lebach, WK; Muller, R; et al. (1975) Unusual splenomegalic liver disease as evidenced by peritoneoscopy and guided liver biopsy among polyvinyl chloride production workers. *Ann NY Acad Sci* 246:95-134.

Occidental Chemical Corporation. (1975) Initial submission: Pottstown vinyl chloride medical survey results (final report with attachments and cover letter dated 022192). U.S. EPA/OTS files (8eCP). Fiche number 0535773. Document number 88-920001077.

Popper, H; Thomas, LB. (1975) Alterations of liver and spleen among workers exposed to vinyl chloride. *Ann NY Acad Sci* 246:172-194.

Schoental, R; Magee, PN. (1957) Chronic liver changes in rats after a single dose of Lasiocarpine; a pyrrolizidine (Senecio) alkaloid. *J Pathol Bacteriol* 74:305-319.

Schoental, R; Magee, PN. (1959) Further observations on the subacute and chronic liver changes in rats after a single dose of various pyrrolizidine (Senecio) alkaloids. *J Pathol Bacteriol* 78:471-482.

Short, RD; Minor, JL; Winston, JM; et al. (1977) Dominant lethal study in male rats after repeated exposures to vinyl chloride or vinylidene chloride. *J Toxicol Environ Health* 3:965-968.

Sokal, JA; Baranski, B; Majka, J; et al. (1980) Experimental studies on the chronic toxic effects of vinyl chloride in rats. *J Hyg Epidemiol Microbiol Immunol* 24:285-294.

Studniarek, M; Durski, K; Liniecki, J; et al. (1989) Effects of vinyl chloride on liver function of exposed workers, evaluated by measurements of plasma clearance of the ^{99m}Tc-N-2,4-dimethylacetanilido-iminodiacetate complex. *J Appl Toxicol* 9(4):213-218.

Tamburro, CH; Makk, L; Popper, H. (1984) Early hepatic histologic alterations among chemical (vinyl monomer) workers. *Hepatology* 4(3):413-418.

Theriault, G; Iturra, H; Gingras, S. (1983) Evaluation of the association between birth-defects and exposure to ambient vinyl-chloride. *Teratology* 27(3):359-370.

Til, HP; Feron, VJ; Immel, HR. (1991) Lifetime (149-week) oral carcinogenicity study of vinyl chloride in rats. *Food Chem Toxicol* 29:713-718.

Til, HP; Immel, HR; Feron, VJ. (1983) Lifespan oral carcinogenicity study of vinyl chloride in rats. Final report. Civo Institutes. TNO. Report No. V 83.285/291099, TSCATS Document FYI-AX-0184-0353, Fiche No. 0353.

Torkelson, TR; Oyen, F; Rowe, VK. (1961) The toxicity of vinyl chloride as determined by repeated exposure of laboratory animals. *Am Ind Hyg Assoc J* 22:354-361.

Ungvary, G; Hudak, A; Tatrai, E; et al. (1978) Effects of vinyl chloride exposure alone and in combination with trypan blue applied systematically during all thirds of pregnancy on the fetuses of CFY rats. *Toxicology* 11(1):45-54.

U.S. EPA. (2000) Toxicological review of vinyl chloride in support of summary information on the Integrated Risk Information System (IRIS). Available online from National Center for Environmental Assessment, <http://www.epa.gov/iris>.

Watanabe, PG; Zempel, JA; Gehring; PJ. (1978a) Comparison of the fate of vinyl chloride following single and repeated exposure in rats. *Toxicol Appl Pharmacol* 44:391-399.

Watanabe, PG; Zempel, JA; Pegg, DG; et al. (1978b) Hepatic macromolecular binding following exposure to vinyl chloride. *Toxicol Appl Pharmacol* 44:571-579.

Waxweiler, RJ; Falk, H; McMichael, A; et al. (1977) A cross-sectional epidemiologic survey of vinyl chloride workers. NTIS PB274193.

Wisniewska-Knypl, JM; Klimczak, J; Kolakowski, J. (1980) Monooxygenase activity and ultrastructural changes of liver in the course of chronic exposure of rats to vinyl chloride. *Int Arch Occup Environ Health* 46(3):241-249.

Withey, JR. (1976) Pharmacodynamics and uptake of vinyl chloride monomer administered by various routes to rats. *J Toxicol Environ Health* 1:381-394.

VI.C. Carcinogenicity Assessment References

Agency for Toxic Substances and Disease Registry (ATSDR). (1995) Toxicological profile for vinyl chloride. U.S. Department of Health and Human Services, Public Health Service. Agency for Toxic Substances and Disease Registry. Draft for public comment.

Bartsch, H; Malaveille, C; Montesano, R. (1975) Human, rat and mouse liver-mediated mutagenicity of vinyl chloride in *S. typhimurium* strains. *Int J Cancer* 15:429-437.

Belli, S; Bertazzi, PA; Comba, P; et al. (1987) A cohort study on vinyl chloride manufacturers in Italy: study design and preliminary results. *Cancer Lett* 35:253-261.

Bi, W; Wang, Y; Huang, M; et al. (1985) Effect of vinyl chloride on tests in rats. *Ecotoxicol Environ Safety* 10:281-289.

Buffler, PA; Word, S; Eifler, C; et al. (1979) Mortality experience of workers in a vinyl chloride monomer production plant. *J Occup Med* 21:195-203.

Byren, D; Engholm, G; Englund, A; et al. (1976) Mortality and cancer morbidity in a group of Swedish VCM and PVC production workers. *Environ Health Perspect* 17:167-170.

Chemical Manufacturers Association (CMA). (1998) Epidemiological study of men employed in the vinyl chloride industry between 1942 and 1972: I. Re-analysis of mortality through December 31, 1982. II. Update of Mortality through December 31, 1995. Final Report. CMA, Arlington, VA. pp. 1-178.

Chen, CW; Blancato, JN. (1989) Incorporation of biological information in cancer risk assessment: example-vinyl chloride. *Cell Biol Toxicol* 5:417-444.

Clement Associates. (1987) Investigation of cancer risk assessment methods. Final report. Vol. 1: introduction and epidemiology. Prepared for the U.S. Environmental Protection Agency, the Department of Defense, and the Electric Power Research Institute.

Clewell, HJ; Gentry, PR; Gearhart, JM; et al. (1995) The development and validation of a physiologically based pharmacokinetic model for vinyl chloride and its application in a carcinogenic risk assessment for vinyl chloride. ICF Kaiser report prepared for EPA/OHEA and OSHA/DHSP.

Cooper, WC. (1981) Epidemiologic study of vinyl chloride workers: mortality through December 31, 1972. *Environ Health Perspect* 41:101-106.

Creech, JL; Johnson, MN. (1974) Angiosarcoma of the liver in the manufacture of polyvinyl chloride. *J Occup Med* 16:150-151.

Doll, R. (1988) Effects of exposure to vinyl chloride. *Work Environ Health* 14:61-78.

Drew, RT; Boorman, GA; Haseman, JK; et al. (1983) The effect of age and exposure duration on cancer induction by a known carcinogen in rats, mice and hamsters. *Toxicol Appl Pharmacol* 68:120-130.

- Du, CL; Wang, JD. (1998) Increased mortality odds ratio of primary liver cancer and cirrhosis among vinyl chloride monomer workers. *Occup Environ Med* 55:528-532.
- Fedtke, N; Boucheron, JA; Walker, VE; et al. (1990) Vinyl chloride-induced DNA adducts. II: formation and persistence of 7-(2'-oxoethyl)guanine and N²,3-ethenoguanine in rat tissue DNA. *Carcinogenesis* 11:1287-1292.
- Feron, VJ; Kroes, R. (1979) One year time-sequence inhalation toxicity study of vinyl chloride in rats II: morphological changes in the respiratory tract, ceruminous glands, brain, kidneys, heart and spleen. *Toxicology* 13:131-141.
- Feron, V; Hendrikson, CFM; Speek, AJ; et al. (1981) Lifespan oral toxicity study of vinyl chloride in rats. *Food Cosmet Toxicol* 19:317-333.
- Fox, AJ; Collier, PF. (1977) Mortality experience of workers exposed to vinyl chloride monomer in the manufacture of polyvinyl chloride in Great Britain. *Br J Ind Med* 34:1-10.
- Gehring, PJ; Watanabe, PG; Park, CN. (1978) Resolution of dose-response toxicity data for chemicals requiring metabolic activation: example-vinyl chloride. *Toxicol Appl Pharmacol* 44:581-591.
- Hansteen, IL; Hillestad, L; Thiis-Evensen, E; et al. (1978) Effects of vinyl chloride in man: a cytogenetic follow-up study. *Mutat Res* 51:271-278.
- Hehir, RM; McNamara, BP; McLaughlin, J; et al. (1981) Cancer induction following single and multiple exposures to a constant amount of vinyl chloride monomer. *Environ Health Perspect* 41:63-72.
- Heldaas, SS; Langard, SL; Anderson, A. (1984) Incidence of cancer among vinyl chloride and polyvinyl chloride workers: further evidence for an association with malignant melanoma. *Br J Ind Med* 41:25-30.
- Hong, CB; Winston, JM; Thornburg, LP; et al. (1981) Follow-up study on the carcinogenicity of vinyl chloride and vinylidene chloride in rats and mice: tumor incidence and mortality subsequent to exposure. *J Toxicol Environ Health* 7:909-924.
- International Agency for Research on Cancer (IARC). (1979) Monographs on the evaluation of carcinogenic risk of chemicals in humans. Vinyl chloride, polyvinyl chloride and vinyl chloride-vinyl acetate copolymers. Lyon, France: World Health Organization, International Agency for Research on Cancer. WHO, IARC 19:377-401, 419-438.

Jones, RW; Smith, DM; Thomas, PG. (1988) A mortality study of vinyl chloride monomer workers employed in the United Kingdom in 1940-1974. *Scand J Work Environ Health* 14:153-160.

Keplinger, ML; Goode, JW; Gordon, DE; et al. (1975) Interim results of exposure of rats, hamsters, and mice to vinyl chloride. *Ann NY Acad Sci* 246:219-220.

Laib, RJ; Bolt, HM; Cartier, R; et al. (1989) Increased alkylation of liver DNA and cell turnover in young versus old rats exposed to vinyl chloride correlates with cancer susceptibility. *Toxicol Lett* 45:231-239.

Laib, RJ; Stoeckle, G; Bolt, HM; et al. (1979) Vinyl chloride and trichloroethylene. Comparison of alkylating effects of metabolites and induction of preneoplastic enzyme deficiencies in rat liver. *J Cancer Res Clin Oncol* 94:139-147.

Lee, CC; Bhandari, JC; Winston, JM; et al. (1978) Carcinogenicity of vinyl chloride and vinylidene chloride. *J Toxicol Environ Health* 4:15-30.

Maltoni, C; Lefemine, G; Ciliberti, A; et al. (1981) Carcinogenicity bioassays of vinyl chloride monomer, a model of risk assessment on an experimental basis. *Environ Health Perspect* 41:3-29.

Maltoni, C; Lefemine, G; Ciliberti, A; et al. (1984) Experimental research on vinyl chloride carcinogenesis, Vol. 1 and 2. In: *Archives of research on industrial carcinogenesis*. Princeton, NJ: Princeton Scientific Publishers, Inc.

Monson, RR; Peters, JM; Johnson, MN. (1975) Proportional mortality among vinyl chloride workers. *Environ Health Perspect* 11:75-77.

Pirastu, R; Bruno, C; De Santis, M; Comb, P. (1998) An epidemiological study of workers exposed to vinyl chloride in the plants of Ferrara, Rosignano and Ravenna. *Epidemiol Prev* 22:226-236.

Pirastu, R; Comba, P; Reggianai, A; et al. (1990) Mortality from liver disease among Italian vinyl chloride monomer/polyvinyl chloride manufacturers. *Am J Ind Med* 17:155-161.

Purchase, IFH; Richardson, CR; Anderson, D; et al. (1978) Chromosomal analysis in vinyl chloride exposed workers. *Mutat Res* 57:325-334.

Rannug, U; Gothe, R; Wachtmeister, CA. (1976) The mutagenicity of chloroethylene oxide, chloro-acetaldehyde, 2-chloroethanol and chloroacetic acid, conceivable metabolites of vinyl chloride. *Chem Biol Interact* 12:251-263.

Rannug, U; Johansson, A; Ramel, C; et al. (1974) The mutagenicity of vinyl chloride after metabolic activation. *Ambio* 3:194-197.

Reitz, RH; Gargas, ML; Anderson, ME; et al. (1996) Predicting cancer risk from vinyl chloride exposure with a physiologically based pharmacokinetic model. *Toxicol Appl Pharmacol* 137:253-267.

Simonato, L; L'Abbe, KA; Andersen, A; et al. (1991) A collaborative study of cancer incidence and mortality among vinyl chloride workers. *Scand J Work Environ Health* 17:159-169.

Sinues, B; Sanz, A; Bernal, ML. (1991) Sister chromatid exchanges, proliferating rate index, and micronuclei in biomonitoring of internal exposure to vinyl chloride monomer in plastic industry workers. *Toxicol Appl Pharmacol* 108:37-45.

Smulevich, VB; Fedotova, IV; Filatova, VS. (1988) Increasing evidence of the rise of cancer in workers exposed to vinyl chloride. *Br J Ind Med* 45:93-97.

Storm, JE; Rozman, KK. (1997) Evaluation of alternative methods for establishing safe levels of occupational exposure to vinyl halides. *Regul Tox Pharmacol* 24:240-255.

Suzuki, Y. (1978) Pulmonary tumors induced in mice by vinyl chloride monomer. *Environ Res* 16:285-301.

Suzuki, Y. (1983) Neoplastic effect of vinyl chloride in mouse lung-lower doses and short term exposure. *Environ Res* 32:91-103.

Swenberg, JA; Fedtke, N; Ciroussel, F; et al. (1992) Etheno adducts formed in DNA of vinyl chloride-exposed rats are highly persistent in liver. *Carcinogenesis* 13(4):727-729.

Swenberg, JA; Bogdanffy, MS; Ham, A.; et al. (1999) Formation and repair of DNA adducts in vinyl chloride- and vinyl fluoride-induced carcinogenesis. *IARC Sci Publ* 150:29-43.

Tabershaw, IR; Gaffey, WR. (1974) Mortality study of workers in the manufacture of vinyl chloride and its polymers. *J Occup Med* 16:509-518.

Til, HP; Feron, VJ; Immel, HR. (1991) Lifetime (149-week) oral carcinogenicity study of vinyl chloride in rats. *Food Chem Toxicol* 29:713-718.

Til, HP; Immel, HR; Feron, VJ. (1983) Lifespan oral carcinogenicity study of vinyl chloride in rats. Final report. The Netherlands: Civo Institutes. TNO. Report No. V 83.285/291099, TSCATS Document FYI-AX-0184-0353, Fiche No. 0353.

U.S. Environmental Protection Agency (U.S. EPA). (1986) Guidelines for carcinogen risk assessment. *Federal Register* 51(185):33992-43003.

U.S. Environmental Protection Agency (U.S. EPA). (1992) Request for comments on draft report of cross-species scaling factor for cancer risk assessment. *Federal Register* 57:24152.

U.S. Environmental Protection Agency (U.S. EPA). (1996) Proposed guidelines for carcinogen risk assessment. *Federal Register* 61(79):17960-18011.

U.S. Environmental Protection Agency (U.S. EPA). (2000) Toxicological review of vinyl chloride in support of summary information on the Integrated Risk Information System (IRIS). Available online from: National Center for Environmental Assessment; <http://www.epa.gov/iris>.

Viola, PL; Bigotti, A; Caputo, A. (1971) Oncogenic response of rats' skin, lungs, and bones to vinyl chloride. *Cancer Res* 31:516-522.

Waxweiler, RJ; Smith, AH; Falk, H; et al. (1981) Excess lung cancer risk in a synthetic chemicals plant. *Environ Health Perspect* 41:159-165.

Waxweiler, RJ; Stringer, W; Wagoner, JK; et al. (1976) Neoplastic risk among workers exposed to vinyl chloride. *Ann NY Acad Sci* 271:40-48.

Weber, H; Reinl, W; Geiser, E. (1981) German investigations on morbidity and mortality workers exposed to vinyl chloride. *Environ Health Perspect* 41:95-99.

Wong, O; Whorton, MD; Foliart, DE; et al. (1991) An industry-wide epidemiologic study of vinyl chloride workers, 1942-1982. *Am J Ind Med* 20:317-334.

Wu, W; Steenland, K; Brown, D; et al. (1989) Cohort and case-control analyses of workers exposed to vinyl chloride: an update. *J Occup Med* 31(6):618-523.

VII. Revision History

Substance Name — Vinyl chloride

CASRN — 75-01-4

Date	Section	Description
08/07/2000	I.-VIII.	RfD, RfC, Cancer assessment first on-line
10/28/2003	I.A.6, I.B.6, II.D.2	Screening-Level Literature Review Findings message has been added.

VIII. Synonyms

Substance Name — Vinyl chloride

CASRN — 75-01-4

Last Revised — 08/07/2000

- vinyl chloride
- vinyl chloride monomer
- chloroethylene
- chloroethene
- VC
- VCM