Risk Assessment Issue Paper for:
Evaluation of Subchronic Inhalation Systemic Toxicity
for Vinyl Chloride (CASRN 75-01-4)

METABOLISM

Absorption of vinyl chloride in humans after inhalation exposure is rapid. A study was conducted using five young adult male volunteers to measure percent retention and rate of elimination of vinyl chloride by the human lung (Krajewski et al., 1980). In this study, volunteers were exposed to 7.5, 15, 30, or 60 mg/m^3 vinyl chloride for 6 hours via gas mask, with GC measurement of vinyl chloride concentration in inspired and expired air. Retention of vinyl chloride was calculated as the difference between inspired and expired air concentrations. It was estimated that these subjects retained 42% of inhaled vinyl chloride in the lung, that maximum retention was reached within 15 minutes, and that the percent retention was independent of inspired vinyl chloride concentration. After cessation of exposure, the vinyl chloride concentration in expired air decreased rapidly within 30 minutes to 4% of the inhaled concentration. Again, this occurred independent of exposure concentration. This study was limited by the lack of information regarding accuracy of reproducibility of vinyl chloride assays, verification of chamber concentration measurement and if a steady state had been established, or information regarding the test subjects (body weight, physical condition, smoking status).

Human volunteers (5 males) were exposed to 2.9 to 23.5 ppm vinyl chloride for 6 hours. In the first 30 minutes after cessation of exposure, the mean expired air concentrations of vinyl chloride ranged from 0.20 to 1.11 ppm (3.6–4.73% of the inhaled concentration) (Krajewski et al., 1980). The authors suggest that exhalation of unmetabolized vinyl chloride was not an important pathway of elimination at low exposure concentrations, which is consistent with studies in animals.

In animal studies, the importance of the lungs as an excretion route for vinyl chloride varies according to the exposure concentration. This is a reflection of saturation of vinyl chloride metabolic processes (discussed above). In rats, the polar metabolites of vinyl chloride are excreted primarily via the urine; smaller amounts are excreted in the expired air as CO_2 and in the feces (Hefner et al., 1975). When metabolic pathways are saturated, substantial amounts of unmetabolized vinyl chloride are exhaled and appear to follow first-order kinetics regardless of exposure concentrations (ATSDR, 1991). Humans exposed to 7.5 to 60 mg/m^3 for 6 hours expired mean air concentrations from undetectable to 2.84 mg/m^3, representing up to 3.6 to 4.73% of the inhaled concentration (Krajewski et al., 1980), suggesting that exhalation of unmetabolized vinyl chloride is not an important route of elimination. In rats, it has been demonstrated that as the dose of vinyl chloride increases, a markedly greater proportion of vinyl chloride was expired unaltered while the percentage of

metabolites in the urine decreased substantially (Watanabe et al., 1976a). Rats exposed to 10 ppm for 6 hours eliminated 68% of the absorbed radioactivity in their urine and 2% in expired air, while 6 hour exposures to 1,000 ppm resulted in 56% of the dose appearing in the urine and 12% in expired air (Watanabe et al., 1976a). The urinary excretion of radioactivity was biphasic, with the second or slow phase accounting for less than 3% of the total urinary excretion (Watanabe et al., 1976a, 1978a).

Rats (number and strain unspecified) were exposed to 10,000 or 20,000 ppm radiolabeled vinyl chloride (25,561 or 51,122 mg/m^3) for 5 minutes, sacrificed, and frozen in liquid nitrogen, in order to establish the distribution pattern using whole-body autoradiography (Duprat et al., 1977). It was shown that vinyl chloride was rapidly absorbed through the lungs, and immediately accumulated in the liver. No quantitative information of percent absorption were provided in this general review.

Rat studies show that the distribution of vinyl chloride is rapid and widespread, but the storage of vinyl chloride in the body is limited by its rapid metabolism and excretion (Bolt et al., 1977). Male Wistar rats were pretreated with 50 mg/kg 6-nitro-1,2,3-benzothiadiazole i.p. to block cytochrome P-450-dependent metabolism, then were exposed to 25 to 10,000 ppm radiolabeled 14C-vinyl chloride for 5 hours (Buchter et al., 1977). The highest concentration of labeled vinyl chloride was in the fat (8.3 nMol vinyl chloride/g tissue), followed by a relatively uniform, 10- to 16-fold lower distribution to the blood, liver, spleen, kidneys, and muscle (average 0.52 nMol vinyl chloride/g tissue). Without pretreatment with the metabolic inhibitor, vinyl chloride metabolites were found preferentially in the liver and kidneys, with uniform lower distribution to the spleen, muscle, and fat.

Male Wistar rats (3/group) were exposed to 50 ppm vinyl chloride, with and without pretreatment with 6-nitro-1,2,3-benzothiadiazole (Bolt et al., 1976). As in the above experiment, when animals were not pretreated, distribution of the radiolabel to major organs immediately after the 5-hour exposure was highest in the kidney and liver, and was found in decreasing quantities in the spleen, muscle, fat, and brain.

Distribution of vinyl chloride in the rat has been observed autoradiographically to concentrate in the liver, bile duct, digestive lumen, and kidney within 10 minutes after a 5 minute inhalation exposure to high concentrations of vinyl chloride (20000 ppm, also discussed above). No quantitative analysis was made in this study (Duprat et al., 1977).

Male Sprague-Dawley rats (4/group) were exposed by inhalation to 10 or 1,000 ppm vinyl chloride for 6 hours and followed for 72 hours postexposure to determine vinyl chloride disposition (Watanabe et al., 1976a). The fate of ^{14}C-vinyl chloride was found to be concentration-dependent, with an increasing proportion eliminated by the lungs with higher exposure concentrations. After exposure to 10 or 1,000 ppm vinyl chloride, expired radiolabeled vinyl chloride was 2% and 12% of total recovered radioactivity, respectively. Radioactivity in the urine did not change significantly with inspired concentration (68% and 56% of total recovered radioactivity, respectively). After inhalation of 10 ppm, distribution

was as follows: liver (14%), kidney (8%), skin (7%), lung (7%), muscle, carcass, plasma (5%), and fat (3%). After 1,000 ppm exposure, distribution was to the liver (15%), skin (12%), kidney (6%), carcass, lung (5%), muscle (4%), plasma, and fat (not detectable). Finally, there were no differences in distribution or rate of excretion between repeated- versus single-dose exposure of rats to 5,000 ppm vinyl chloride (Watanabe et al., 1978b). The distribution of vinyl chloride in tissues after single vs. repeated exposures was as follows: liver (12%, 16%), kidney (6%, 7%), skin (5%, 8%), carcass (3%, 4%), fat (not detected, not detected).

Placental transfer of vinyl chloride occurred rapidly in rats. Female rats exposed to 0, 5,500, 18,000, 33,000 mg/m^3 vinyl chloride (0, 2,000, 7,000, or 13,000 ppm) for 2.5 hours on gestational day 18 had the highest concentration of vinyl chloride in maternal blood, followed by fetal blood, then amniotic fluid (Ungvary et al., 1978).

Single oral doses of 0.05, 1, or 100 mg/kg radiolabeled vinyl chloride in corn oil (95-96% purity) were administered to male Sprague-Dawley rats in a well-conducted study (Watanabe et al., 1976b). Concentration of ^{14}C-vinyl chloride and ^{14}C-CO_2 were measured in expired air, and urine and feces were collected in metabolism cages for measurement of labeled excretion products in 30 minute intervals for the first 4 hours, and in 12-hour intervals for the remainder of 72 hours. As the administered dose of vinyl chloride increased, the proportion of expired unchanged vinyl chloride increased dramatically in expired air (1.4% and 2.3% in the lower doses, 66.6% in the high dose), illustrating the dose-dependency of vinyl chloride metabolism and distribution. Distribution in major organs of the animals was measured after 72 hours. The liver contained the highest concentration of radioactive label after 72 hours post-dosing. Distribution of the radiolabel to the liver ranged from 2- to 5-fold higher in all groups compared to the concentration found in the fat, lung, muscle, plasma, or carcass of these animals. Coincident with the greater metabolism in the lower dose groups, the proportion of vinyl chloride in the tissues after 72 hours was much higher than in the 100 mg/kg dose group.

The metabolism of vinyl chloride was studied in male Sprague-Dawley rats exposed for 6 hours to concentrations of 1.4 to 4,600 ppm vinyl chloride (Gehring et al., 1978). Rats were sacrificed after exposure, and the total radioactive content of the carcass was determined in order to estimate the total amount of metabolized vinyl chloride (less the exhaled labelled compounds). In this study, metabolism was determined to be a concentration-dependent process characterized by Michaelis-Menten type kinetics. It was emphasized that the toxicity of vinyl chloride exposure is related to its concentration-dependent, saturable conversion to its toxic metabolites, and is not necessarily a function of the vinyl chloride exposure concentration. This study is flawed by lack of experimental validation.

Kinetic studies were performed on groups of male Sprague-Dawley rats exposed to 51 to 1,167 ppm vinyl chloride for durations of 53 to 356 minutes by a nose-only apparatus (Hefner et al., 1975). The inhalation chamber was monitored continuously using an in-line infrared analyzer, and the decline in vinyl chloride from the inhalation chamber was

determined for each concentration of vinyl chloride used. The rate of decline of vinyl chloride monomer concentration from the closed system occurred via metabolism of vinyl chloride by the rats after being corrected for background loss from the system. Additional groups of rats were treated with ethanol (for inhibition of alcohol dehydrogenase activity) or SKF 525-A (for inhibition of microsomal oxidase activity). Results of this study indicate that metabolism followed first-order kinetics at concentrations less than 100 ppm, with a $t_{1/2}$ of 86 minutes. At ≥220 ppm, metabolism was decreased to a $t_{1/2}$ of 261 minutes, suggesting saturation of the metabolic pathway at below this concentration. Pretreatment with ethanol depressed the rate of metabolism by approximately 83% at less than 100 ppm but by approximately 47% at greater than 1,000 ppm, suggesting that at lower concentrations, alcohol dehydrogenase-dependent metabolism occurs. Pretreatment with SKF 525-A, however, had no effect at less than 100 ppm but depressed metabolism by 19% at greater than 1,000 ppm. This implies that at higher concentrations of vinyl chloride, metabolism may occur via pathways other than that of alcohol dehydrogenase, such as by microsomal oxidases.

Saturation of metabolic pathways occurred at exposure concentrations of 250 ppm vinyl chloride 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). In male Wistar rats, the metabolic rate (V_{max}) of 110 mol/hour/kg was estimated (Bolt et al., 1977). In rhesus monkeys, a V_{max} of 50 mol/hour/kg was estimated, and was believed to be a close estimate of the theoretical V_{max} for humans. (Buchter et al., 1980). The metabolic rate in rats, mice, and gerbils is 5-12 times greater than that in humans.

Evidence was also provided that repeated inhalation exposures of rats to the range of 50 to 15,000 ppm vinyl chloride reduces the nonprotein sulfhydryl concentration of the liver (Hefner et al., 1975). This reduction was not dependent on exposure concentration. This is consistent with a saturable mechanism for vinyl chloride metabolism followed by conjugation of the vinyl chloride metabolites with glutathione and/or cysteine (Bolt et al., 1976; Jedrychowski et al., 1984; Watanabe et al., 1978b).

Three alternative pathways for vinyl chloride metabolism have been postulated (Bolt et al., 1980; Hefner et al., 1975). At low concentrations (i.e. ≤100 ppm), vinyl chloride is primarily metabolized by sequential oxidation to 2-chloroethanol, 2-chloroacetaldehyde, and 2-chloroacetic acid by the alcohol dehydrogenase pathway (inhibited by pretreatment with ethanol). Little 2-chloroacetic acid was formed, however, probably because 2-chloroacetaldehyde conjugates rapidly with ubiquitous sulfhydryl groups (such as glutathione and cysteine). When the alcohol dehydrogenase pathway becomes saturated, 2-chloroethanol can be oxidized by catalase in the presence of hydrogen peroxide (H_2O_2) to a peroxide (2-chloroethylhydroperoxide), which undergoes subsequent dehydration to form 2-chloroacetaldehyde. An alternative pathway involves oxidation by mixed-function oxidase to form a highly reactive epoxide intermediate, 2-chloroethylene oxide, which spontaneously rearranges to form 2-chloroacetaldehyde. These intermediates are detoxified mainly through conjugation with glutathione catalyzed by glutathione S-transferase. The conjugated products are excreted in urine as substituted cysteine derivatives and include thiodiglycolic acid, S-

formyl-methylcysteine, and N-acetyl-S-(2-hydroxyethyl)cysteine (Bolt et al., 1980; Hefner et al., 1975). Urinary metabolites identified in rats exposed by inhalation include polar compounds at low exposure concentrations (Hefner et al., 1975; Watanabe et al., 1976a) and 2-chloroacetic acid at high exposure concentrations (Hefner et al., 1975).

Studies have demonstrated the binding of metabolites of ^{14}C-vinyl chloride 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, 1978b). In single-exposure experiments at concentrations ranging from 1 to 5,000 ppm ^{14}C-vinyl chloride, the binding to macromolecules increased proportionately with increasing metabolites of vinyl chloride, and disproportionately with vinyl chloride exposure concentration (Watanabe et al., 1978a). The extent of macromolecular binding increased with repeated exposures to 5,000 ppm vinyl chloride (Watanabe et al., 1978b), and by phenobarbital pretreatment (Guengerich and Watanabe, 1979). Macromolecular binding is attributed to the reactive epoxide intermediate, 2-chloroethylene oxide, which has been shown to bind to DNA and RNA, and to its product 2-chloroacetaldehyde, which has been shown to bind to protein molecules (Guengerich and Watanabe, 1979; Guengerich et al., 1979, 1981; Kappus et al., 1976; Watanabe et al., 1978a, 1978b). These epoxide intermediates have been hypothesized to alkylate liver macromolecules, and thus be responsible for the carcinogenicity and toxicity associated with vinyl chloride (Bolt, 1986).

Urinary metabolites, in particular 2-chloroethylene oxide and 2-chloroacetaldehyde, have been identified after oral exposure to ^{14}C-labeled vinyl chloride (Green and Hathaway, 1975, 1977; Watanabe and Gehring, 1976; Watanabe et al., 1976b). These metabolites were not different than those produced after inhalation exposure. The Watanabe et al. (1976b) study has been discussed previously, therefore only conclusions will be mentioned. The proportions of the above metabolites in the urine were not dependent on the dose, however expiration of vinyl chloride was clearly dose-dependent, increasing dramatically with the highest dose administered (0.05 to 100 mg/kg). It was concluded that vinyl chloride metabolism is a dose-dependent, saturable process, and that metabolic saturation occurred between the doses of 1 and 100 mg/kg vinyl chloride (Watanabe et al., 1976b).

Urinary metabolites identified in rats exposed by inhalation include polar compounds resulting from conjugation with sulfhydryl groups at low exposure concentrations (Hefner et al., 1975; Watanabe et al., 1976a) and 2-chloroacetic acid at high exposure concentrations (Hefner et al., 1975). The urinary metabolites identified from rats orally exposed to ^{14}C-vinyl chloride are consistent with the metabolic pathways postulated for inhalation exposure, in particular with the formation of 2-chloroethylene oxide and 2-chloroacetaldehyde (Watanabe et al., 1976b). Metabolic saturation appears to occur with a single gavage dose in excess of 1 and less than 100 mg/kg-day (Watanabe et al., 1976b). In rats, urinary metabolites include N-acetyl-S-(2-hydroxyethylcysteine) and thiodiglycolic acid (Watanabe et al., 1976a).

In the Watanabe study discussed above (1976b), within 72 hours of dosing, a total of 10.3%, 15.4%, and 69.1% of the radioactivity administered was detected in expired air (as

unchanged vinyl chloride or CO_2) for the 0.05, 1, and 100 mg/kg dose groups, respectively. Pulmonary excretion of vinyl chloride was estimated to be a monophasic process at doses ≤ 1 mg/kg, and biphasic at the higher doses. Urinary excretion was predominant after administration of 0.05 mg/kg (68%), and was of similar magnitude after 1 mg/kg (59%), but decreased to 11% with administration of 100 mg/kg due to the disproportionately high amount of exhaled vinyl chloride at this dose level. This indicated that there was metabolic saturation above 1 mg/kg. Total recovery of radioactivity was rather low in this study (82 to 91% if total dose), and may be partly explained by the lack of special precautions for measuring volatile compounds in the urine and feces. Administration of single oral doses of ^{14}C-vinyl chloride in corn oil (0.05, 0.25, 1, 20, 100, and 450 mg/kg) gave similar large increases in the exhalation of unchanged vinyl chloride at doses ≥ 20 mg/kg in other oral studies, suggesting again metabolic saturation at this approximate dose (Green and Hathaway, 1975; Watanabe and Gehring, 1976). In these studies, there was also a compensatory decrease in urinary and fecal excretion of radioactive label. At concentrations lower than 1 mg/kg, urinary excretion of polar metabolites predominated. Urinary excretion was judged to be biphasic in nature, having half-lives of approximately 4.5 hours for doses of 0.05 to 100 mg/kg-day.

Green and Hathaway (1975) also performed longer-term oral studies that showed that although exhalation of unchanged vinyl chloride was complete within hours, excretion of metabolites in the urine continued for days. These metabolites have been identified as thiodiglycolic acid and N-acetyl-S-(2-hydroxyethylcysteine) (Watanabe et al., 1976b).

HUMAN TOXICITY

Vihko et al. (1984) attempted to assess the early hepatotoxicity of vinyl chloride-exposed workers by measuring liver enzymatic activities, and quantitating serum primary bile acids by radioimmunoassay. A total of 76 workers were exposed to vinyl chloride air concentrations varying up to 2.6 mg/m^3 for a mean duration of 3 years. All subjects were fasted overnight and refrained from alcohol consumption for at least 1 week prior to blood analysis. A statistically significant increase in serum chenodeoxycholic acid was noted; however, all other parameters examined were normal in comparison to the healthy reference population. This study is limited because the exposure concentrations were not well characterized, and the methodology for estimating the vinyl chloride air concentration was not reported. The investigators suggest that determination of serum bile acid concentrations might be useful indicators of early hepatotoxicity.

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 vinyl chloride exposure

(Popper and Thomas, 1975), and are the principal anatomic lesion in vinyl chloride-associated liver disease (Berk et al., 1976). Doss et al. (1984) reported coproporphyinuria in 46 males occupationally exposed to vinyl chloride 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 vinyl chloride 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 which 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 vinyl chloride include pain or discomfort in the right upper quadrant of the abdomen, hepatomegaly, splenomegaly, thrombocytopenia, in addition to fibrosis, cirrhosis and portal hypertension; however, these observations are not pathognomonic for vinyl chloride-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).

An occupational study attempted to correlate the effects of vinyl chloride 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 vinyl chloride concentrations in 1982 at various regions of the plant. Polymerization operators (n=13) had the highest mean exposure to vinyl chloride, 30 mg/m^3, with a mean duration of employment of 10 years. Autoclave cleaners (n=9), and auxillary 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, while technical supervisors (n=6) had the lowest mean vinyl chloride exposure of 6 mg/m^3 for a mean duration of 13 years. The investigators found a significant correlation between degree of exposure to vinyl chloride and the frequency of low clearance values; however, no concentration-response relationship was detected among the groups with respect to plasma clearance of ^{99m}Tc-HEPIDA. This study is of limited value since personal air sampling was conducted for only one year. The yearly geometric means of vinyl chloride atmospheric concentrations in various departments of the plant were provided, but these concentrations dramatically fluctuated between 0.1 to 600 mg/m^3 from 1974 to 1982.

ANIMAL TOXICITY

SUBCHRONIC EXPOSURE

Hong et al. (1981) exposed groups of CD rats (4-16/sex/group) and CD-1 mice (8-28/sex/group) by inhalation to 0, 50, 250, or 1000 ppm vinyl chloride 6 hour/day, 5 day/week for 1, 3, 6, or 10 months (rats only). Animals were sacrificed 12 months after termination of exposure. Clinical signs, biweekly body weight and weekly food consumption measurements, hematological (RBC, reticulocyte, platelet, and WBC counts, hemoglobin,

hematocrit, methemoglobin, and Heinz bodies) and clinical chemistry [SGPT and BUN (both species), prothrombin time, SGOT, alkaline phosphatase, bilirubin, creatinine, LDH, immunoglobulin IgA, IgB-A, IgB-B, and IgM, total protein, albumin, globulin, and collagen contents of liver and lungs (rats only)] parameters, gross examination of major tissues and organs, and histopathological examination of mammary gland, lung, liver, spleen, kidney and tissues with gross pathological changes were used to assess toxicity. During the recovery period for rats, significant ($p<0.05$, Fisher exact test performed by EPA) increases in mortality were observed in rats exposed to 1000 ppm for 6 months and all groups of rats exposed to vinyl chloride for 10 months. Increased incidence of neoplastic nodules (mid-concentration group exposed for 6 or 10 months), hemangiosarcomas in the liver (mid-concentration group exposed for 10 months), fibroadenoma (low-concentration group exposed for 6 or 10 months), and bronchioloalveolar tumor and hemangiosarcomas in the lungs (mid- and high-concentration groups) were observed. During the recovery phase for mice, significant ($p<0.05$, Fisher exact test performed by EPA) dose- and duration-related increases in mortality were observed. Increased mortality was observed in mice exposed to 1000 ppm for 1 month, in the 250 and 1000 ppm groups exposed for 3 months, and all vinyl chloride exposed groups exposed for 6 months. Rough coat hair, lethargy, and the appearance of external tumor masses were observed in animals dying early. Increased incidence of bronchioloalveolar tumors (mid- and high-concentration groups exposed for 1 month; all vinyl chloride exposed groups after 3 and 6 months of exposure), hemangiosarcoma in the liver (mid- and high-concentration groups after 3 and 6 months of exposure), and adenocarcinoma/carcinoma in mammary gland (low-, mid- and high-concentration females after 3 months of exposure and mid-and high-concentration females after 6 months of exposure) were observed.

Bi et al. (1985) reported a concentration-related elevation in relative liver weight and testicular degeneration in Wistar rats (8-30/sex/concentration) exposed to 0, 10, 100, or 3,000 ppm vinyl chloride (99.99% pure), 6 hours/day, 6 days/week (duration adjusted to 0, 5.5, 55, 1,643 mg/m^3, respectively) for up to 12 months. The dynamic exposure chambers were controlled for temperature and relative humidity. Gross and histopathological examinations were performed on the testes, lungs, liver, heart, kidneys, spleen and brain. After 6 months, rats exposed to 10 ppm (duration adjusted to 5.5 mg/m^3) had significantly elevated relative liver, spleen and heart weights ($p<0.01$). The magnitude of these changes were 14%, 8%, and 12% above controls, respectively. The results of histopathology were not reported for any organ except the testes (including the lung). Kidney-to-body weight ratios were significantly increased after 3 months exposure to 3,000 ppm (duration adjusted to 1,643 mg/m^3). The incidence of damage to the testicular seminiferous tubules in rats ($n=74$) exposed to 0, 10, 100 and 3,000 ppm groups were 18.9, 29.7, 36.5 and 56%, respectively. The incidence was statistically elevated at 100 and 3,000 ppm (duration adjusted to 55 and 1,643 mg/m^3, respectively) ($p<0.05$ and $p<0.001$, respectively) compared to controls and appeared to be concentration-related. This damage consisted of cellular alterations, degeneration and necrosis. The testes-to-body weight ratio was also significantly elevated at 100 ppm (duration adjusted to 55 mg/m^3); measurement of this organ weight was limited to 6 months exposure. Thus, 10 ppm (duration adjusted to 5.5 mg/m^3;

HEC=5.5 mg/m^3) is considered a LOAEL for liver, kidney and heart organ weight changes, and for biologically significant testicular degeneration.

Several species of animals were exposed to either 0, 50, 100, 200 or 500 ppm vinyl chloride via inhalation for up to 6 months (Torkelson et al., 1961). Hematologic determinations, urinalysis, 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 (127.8 mg/m^3), 7 hours/day for 130 days in 189 days (duration adjusted to 26.6 mg/m^3) did not exhibit toxicity as judged by appearance, mortality, growth, hematology, liver weight and pathology. At concentrations of 100 ppm administered 138-144 times in 204 days (duration adjusted to 53.25 mg/m^3), a statistically significant increase in the liver weight of female rats was noted (approximately 12% above controls). Repeated exposure (138-144 times in 204 days) for 6 months to 200 ppm (duration adjusted to 106.5 mg/m^3) resulted in histological changes (characterized as granular degeneration and necrosis with some vacuolization and cellular infiltration) in the centrilobular area of the liver of rabbits, but not in rats, guinea pigs or dogs. The liver weight of rats (both sexes) were also significantly increased at this level (7-13% above controls). Histopathological lesions of the liver (centrilobular granular degeneration) and increased organ weight occurred in rats exposed to 500 ppm (duration adjusted to 266 mg/m^3), although biochemical parameters of liver status were within normal limits at all exposure concentrations. Slightly elevated relative liver weights appeared to be the most sensitive indicator of hepatotoxicity and were observed in both sexes of rats (n=5) at 100 and 200 ppm, exposed for 2-4 hours/day (duration adjusted to 15 to 30 and 30 to 60 mg/m^3, respectively). The small sample size made these findings statistically insignificant in the 100 ppm males, however female rats had significantly higher relative liver weight. The highest concentration without any detectable effect on any species was 50 ppm (duration adjusted to 26.2 mg/m^3), therefore this dose is designated as a NOAEL for liver effects.

Another subchronic inhalation study exposed male Wistar rats (7-10/group) under dynamic conditions to nominal concentrations of 50, 500, and 20,000 ppm vinyl chloride (99.99% pure) or to air only, 5 hours/day, 5 days/week (duration adjusted to 127.8, 190, 7,607 mg/m^3, respectively) for 10 months (Wisniewska-Knypl et al., 1980). Examinations were limited to the liver. Concentrations of 50 ppm (duration adjusted to 127.8 mg/m^3) for 10 months resulted in hepatocellular changes characterized by proliferation of smooth endoplasmic reticulum. Rats exposed to 500 ppm (duration adjusted to 190 mg/m^3) for 3 months exhibited hypertrophy of the smooth endoplasmic reticulum, distension of canals of rough-surfaced membranes, swelling of mitochondria and an increased number of lipid droplets in cytoplasm; these changes were more intensive in the 20,000 ppm (duration adjusted to 7,607 mg/m^3) exposure group. Pathological alterations in liver did not occur earlier than after 6-month exposure to 500 and 20,000 ppm (duration adjusted to 190 and 7,607 mg/m^3, respectively), and not before 10-month exposure to 50 ppm (duration adjusted to 127.8 mg/m^3). This study identifies a LOAEL of 50 ppm (duration adjusted to 127.8 mg/m^3) for liver effects.

Lee et al. (1977) observed no adverse effects on clinical chemistry parameters of rats or mice exposed to less than 250 ppm (duration adjusted to 114 mg/m^3), and failed to identify a NOAEL for hepatotoxicity. Albino CD-1 mice (36/sex/group) and CD rats (36/sex/group) were exposed to concentrations of 0, 50, 250, or 1,000 ppm vinyl chloride 6 hours/day, 5 days/week (duration adjusted to 22.6, 114, 456 mg/m^3, respectively) for up to 12 months. Parameters of toxicity evaluated included general appearance, food consumption, body weight, hematology, clinical chemistry, macrophage counts of pulmonary washings, cytogenic examination of bone marrow cultures, senographic radiography of the long bones of the limbs, gross necropsy on all tissues including the respiratory tract, selected organ weights and histopathologic examination of a comprehensive set of organs and tissues. Several mitotic figures, indicating increased rate of cell division, were observed in the livers of mice exposed to 50 or 1,000 ppm (duration adjusted to 22.67 or 456 mg/m^3, respectively) at 8 to 9 months, and increased rate of DNA synthesis was observed at 50 ppm (duration adjusted to 22.67 mg/m^3) in male mice. Since the liver is a known target organ for the toxicity of vinyl chloride, 50 ppm (duration adjusted to 22.67 mg/m^3) is considered an (LOAEL) effect level in this study. No persistent changes were noted in mice of either sex compared to controls with respect to hematology, clinical blood chemistry, cytogenic analysis of bone marrow cultures, x-ray examination of extremities, and serum alpha-fetoprotein. No significant changes were noted in rats for the same parameters, and in addition for: macrophage count, collagen contents in liver and lung, serum ALA synthetase, and urinary ALA level. Abnormalities observed in the mice included body weight loss at 1,000 ppm (duration adjusted to 456 mg/m^3) after 8 months, and elevated pulmonary macrophage count in mice from all exposure groups that had bronchioloalveolar adenoma; however, because of its association with lung tumors, this in not considered a noncarcinogenic toxic effect. Only a few mice exposed to 50 ppm (duration adjusted to 22.67 mg/m^3) survived for 12 months, no mice survived after 9 months in the 250 or 1,000 ppm (duration adjusted to 114 and 456 mg/m^3, respectively) exposure groups. Due to the high mortality among mice, 50 ppm (duration adjusted to 22.67 mg/m3) is considered a FEL. Histopathology of 5 unscheduled deaths of mice exposed to 1,000 ppm (duration adjusted to 456 mg/m^3) for 3-9 days revealed acute toxic hepatitis, and marked tubular necrosis. After the 7th month, the general health of mice exposed to vinyl chloride deteriorated. Rats were more resistant to the toxic effects of vinyl chloride. Rats exposed to 1,000 ppm (duration adjusted to 456 mg/m^3) had reduced body weights compared with controls, but no other non-neoplastic effects. Exposure to 1,000 ppm (duration adjusted to 456 mg/m^3) also resulted in the death or sacrifice of 21/36 rats during 8-12 months; of those exposed to 250 ppm (duration adjusted to 114 mg/m^3), 14/35 died or were terminated.

CHRONIC EXPOSURE

Male Wistar rats (7-34/sex/group) (2-months old) were exposed to vinyl chloride in dynamic inhalation chambers at concentrations of 50, 500 and 20,000 ppm for 5 hours/day, 5 days/week (duration adjusted to 19, 190, 7,607 mg/m^3, respectively) for 10 months (Sokal et al., 1980). Control animals received ambient air only. The animals were examined for hematological indices, and urinalysis, and histopathology was conducted on all major organs,

including the lungs. Treatment-related histological changes developed in the liver and testes; however, the liver appeared to be the more sensitive target organ. After 10 months, the rats exposed to 500 and 20,000 ppm (duration adjusted to 190 and 7,607 mg/m^3, respectively) exhibited a significant increase in scanty histological changes in the liver, characterized as increased polymorphism of hepatocytes and proliferation of reticulo-endothelial cells lining the sinusoids. In addition, damage to the spermatogenic epithelium was significant ($p<0.05$) following exposure to 500 ppm (duration adjusted to 190 mg/m^3) compared to controls, but these effects were not clearly concentration-related. At 50 ppm (duration adjusted to 19 mg/m^3), relative spleen and heart weights were significantly elevated (9% and 4% above control, respectively). In addition, body weight gain was significantly decreased at concentrations $\geq$50 ppm. At 500 ppm and 20,000 ppm (duration adjusted to 190 and 7,607 mg/m^3, respectively) relative spleen, kidney and liver weights were significantly elevated; relative testis and heart weights were also significantly increased at 20,000 ppm (duration adjusted to 7,607 mg/m^3). Increased relative spleen and kidney weights were not accompanied by any histopathological changes and the indices of kidney function disorders were negative. The increased relative heart weight was not concentration-dependent. No statistically differences were observed for urinalysis, hematological or biochemical indices. The incidence of histopathological changes in the liver and testes did not correlate with the exposure level. No adverse effects on the lung were reported. The authors postulate that the enzymatic pathways become saturated at 20,000 ppm (duration adjusted to 7,607 mg/m^3), resulting in reduced vinyl chloride metabolism, and thus less active metabolite formation. A LOAEL of 50 ppm (duration adjusted to 19 mg/m^3) has been identified for decreased body weight gain, and increased relative weights of the spleen and heart. A NOAEL of 50 ppm (duration adjusted to 19 mg/m^3) has been identified for hepatocellular changes.

Maltoni et al. (1980, 1981) exposed Wistar rats intermittently to 1 to 30,000 ppm 4 hours/day, 5 days/week (duration adjusted to 0.3 to 9,129 mg/m^3) for 52 weeks, and mice and hamsters to 50 to 30,000 ppm (duration adjusted to 127.8 to 9,129 mg/m^3) 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/m^3). This study primarily investigated the development of tumors. However, the incidence of preneoplastic lesions including hepatomas, neoplastic liver nodules, nodular hyperplasia of the liver, and diffuse hyperplasia of the liver were presented. Diffuse hyperplasia was the most significant observation which was evident in most exposure groups but did not appear to be concentration-related. The incidence for diffuse hyperplasia among controls, 1, 50, 250, 500, 2,500, 6,000 and 10,000 ppm (duration adjusted to 0.3, 15.2, 76, 152, 760, 1,826, 3,043 mg/m^3, respectively) exposure groups were 2.3%, 4.2%, 10%, 16.7%, 3.3%, 6.7%, 6.7%, and not reported, respectively. Statistical significance and non-neoplastic results were not reported for the other organs examined, including the lung. Thus, 50 ppm (duration adjusted to 15.2 mg/m^3) was designated as a LOAEL for diffuse hyperplasia. This endpoint was not recommended for calculation of the RfC, however, due to the pre-neoplastic nature of the lesion.

The liver appears to be the critical target organ for animals orally exposed to vinyl chloride (Feron et al., 1981; Til et al., 1983). Feron et al. (1981) administered Wistar rats (60-80/sex/group) dietary concentrations of 0, 1.7, 5.0, or 14.1 mg vinyl chloride/kg-day (99.97% pure) for a lifetime. A statistically significant increased incidence of several histopathologic lesions (foci of cellular alterations) were observed in the livers of rats exposed to 1.7, 5.0 and 14.1 mg/kg-day. Rats exposed to 1.7 mg/kg-day exhibited a series of changes in the hepatic parenchyma, characterized by an increased incidence of cellular alteration, liver polymorphism, cysts, neoplastic nodules and a few hepatocellular carcinomas. The liver lesions were most pronounced in the 14.1 mg/kg-day group. Liver-to-body weight ratios were higher in the 14.1 mg/kg-day dose group compared to controls. This study observed an increased incidence of neoplastic nodules of the liver and/or hepatocellular carcinoma in male rats administered 1.7 mg/kg-day, and in females exposed to 5.0 mg/kg-day.

In a lifetime dietary study, Wistar rats (100/sex/dose) were administered doses of 0, 0.014, 0.13 or 1.3 mg vinyl chloride/kg-day for 149 weeks (Til et al., 1983). Relative organ weights were not evaluated. An increased incidence of basophilic foci were observed in both sexes at 1.3 mg/kg-day and only in females in the two lower dosage groups. Since the basophilic foci lacked a dose-related increase, and histopathological alterations at 0.13 mg/kg-day, basophilic foci in the liver of rats of one sex may be considered a nonadverse, although a compound-related effect. Rats exposed to 1.3 mg/kg-day also had a significantly increased incidence of liver cell polymorphism, hepatic cysts, neoplastic nodules, and hepatocellular carcinoma.

DEVELOPMENTAL TOXICITY

Insufficient data exist to evaluate the teratogenicity of vinyl chloride in humans. Several epidemiology studies have investigated the effects of vinyl chloride exposure on the incidence of fetal loss and birth defects (Edmonds et al., 1978; Hatch et al., 1981; Infante et al., 1976; Theriault et al., 1983; Waxweiler et al., 1977), however no solid association has been found. Using a questionnaire, Infante et al. (1976) and Waxweiler et al. (1977) associated increased fetal loss and birth defects with paternal exposure to vinyl chloride. They studied the outcome of pregnancies of wives of 95 vinyl chloride polymerization workers, a control group of 158 unexposed rubber workers and polyvinyl chloride fabricators exposed to "very low" levels of vinyl chloride monomer. Data were obtained for the exposed cohort regarding pregnancies that occurred before and during employment in a vinyl chloride-contaminated atmosphere. Subsequent to the husband's exposure, the most significant observation was that "age adjusted" fetal loss occurred in 8.8% of the pregnancies of wives of controls and in 15.8% of the pregnancies of wives of exposed workers. The most significant difference occurred in wives of men under age 30, where fetal loss was 5.3% (7/131) for controls and 20% (14/70) for exposed workers. The exposure data were not quantified (Infante et al. 1976). A published evaluation by Hatch et al. (1981) severely criticized the conduct and statistical analysis of the Infante et al. (1976) study. Women with

multiple spontaneous abortions were included in the exposed group of this study. Since one spontaneous abortion is associated with a 66% increase in the risk of subsequent abortions, use of Chi-square for statistical analysis is incorrect because a woman's first pregnancy and her subsequent pregnancies can not be considered independent. Hatch et al. (1981) concluded that the study showed no association of paternal occupational exposure to vinyl chloride with increased fetal loss and that the study lacked statistical power to do so. It appears that the data of Infante et al. (1976) are suggestive of an effect, but additional studies are warranted.

This association was contradicted by other case-control studies (Edmonds et al., 1978; Theriault et al., 1983) which found no association between parental residence in a region with a vinyl chloride plant and the incidence of birth defects in the exposed community. Edmonds et al. (1978) compared the incidence rates of CNS defects in a West Virginia county in which a polyvinyl chloride polymerization plant was located with those for other regions in the United States with no exposure to vinyl chloride. The incidence rates of the index county exceeded those of control areas by a factor of 1.5 to 2. By comparing data from parents of deformed infants with randomly chosen matched controls living in the index county (46 matched pairs), no correlation was noted for parental occupation, for proximity to the polyvinyl chloride plant, or for patterns of wind direction and air pollution. Furthermore, one major and several smaller chemical plants were located in the area.

Vinyl chloride does not appear to be teratogenic in animals. Inhalation experiments in animals have not associated vinyl chloride with developmental toxicity at concentrations below those associated with maternal toxicity. John et al. (1977) examined the effects of inhaled vinyl chloride on the fetuses of mice, rats, and rabbits. Pregnant CF1 mice (30-40/group) were exposed to 0, 50 or 500 ppm vinyl chloride on gestational days 6 to 15. Sprague-Dawley rats (20-35/group) and New Zealand white rabbits (15-20/group) were administered 0, 500 or 2,500 ppm vinyl chloride, 7 hours/day on gestational days 6 through 15 for rats and 6 to 18 for rabbits. Parameters of maternal and developmental toxicity were evaluated; both the fetuses and litter were evaluated. Mice were more sensitive to the toxic effects of vinyl chloride than either rats or rabbits. In mice, concentrations of 500 ppm induced maternal effects which 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. Maternal effects restricted to reduced body weight gain were noted in rats exposed to 500 ppm but not to 2,500 ppm. Maternal effects in rats at 2,500 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 2,500 ppm and are not considered signs of vinyl chloride-induced fetotoxicity. At 2,500 ppm, an 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 for maternal and fetotoxicity in mice and a NOAEL of 2,500 ppm for rabbits.

Ungvary et al. (1978) exposed groups of pregnant CFY rats continuously to 1,500 ppm (4,000 mg/m^3) on gestational days 1 to 9, 8 to 14 or 14 to 21 and demonstrated that vinyl chloride 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 to 21.

Vinyl chloride does not appear to produce germinial mutations as manifested by a dominant lethal effect in male rats. In an dominant lethal study, Short et al. (1977) exposed male CD rats to 0, 50, 250, or 1,000 ppm vinyl chloride 6 hours/day, 5 days/week. Eleven weeks later 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 1,000 ppm vinyl chloride.

CONCLUSION

The occupational study (Vihko et al., 1984) was a subchronic study and lacks experimental details related to measurement of the dosage concentration and other biochemical and clinical indices. The subchronic study by Bi et al. (1985) was conducted in one species (rats) in the appropriate numbers of animals, and measured several endpoints. There are several corroborative inhalation studies which observed effects on the liver and testes (Lee et al., 1977; Maltoni et al., 1980, 1981; Sokal et al., 1980; Torkelson et al., 1961; Wisniewska-Knypl et al., 1980) in rodents and rabbits following subchronic inhalation exposure. Numerous human occupational studies observed hepatotoxicity as the endpoint. Two developmental inhalation studies were located which did not observe teratogenicity in mice, rats or rabbits (John et al., 1977; Ungvary et al., 1978), and one reproductive study examining the dominant lethal effect of vinyl chloride was located (Short et al., 1977).

The Hong et al. (1981) study showed that significantly more mice exposed by inhalation to 50 ppm vinyl chloride 6 hour/day, 5 day/week for 6 months (equivalent oral dose of 19 mg/kg-day) died 6-12 months after exposure termination as compared to the control group. No significant increases in the incidence of neoplastic tumors were observed in this group of mice (Fisher exact test performed by EPA). Non-neoplastic effects were not reported, however, it is not known if the tissues were examined for neoplastic endpoints only. No deaths were reported during exposure. Similar effects were observed in rats. However, mice may be more sensitive than rats to the lethal effects of vinyl chloride. The Hong et al. (1981) study suggests that the data are not adequate for the derivation of a subchronic value for vinyl chloride because subchronic exposure to 300 mg/kg may result in increased mortality several months after exposure termination. Furthermore, data from chronic exposure studies should not be used to derive a subchronic value.

The health effects data for vinyl chloride were reviewed and determined to be inadequate for the derivation of a subchronic inhalation RfC. The status for this chemical is currently not verifiable.

Summary Table of the Toxicity Data for Vinyl Chloride

Study	Species	Effect	Reported dose or concentration	Dose (mg/kg/day)	UF/MF	RfD (mg/kg/day)
Subchronic oral toxicity						
Feron et al., 1975	rat		0 (mg/kg, 6 d/wk) 30 100 300	0 26 86 257		
Chronic oral toxicity						
Til et al., 1983	rat	decreased lifespan and liver damage at 1.3 mg/kg/day		0 0.014 0.13 1.3		
Feron et al., 1981	rat	decreased lifespan and liver damage at ≥1.7 mg/kg/day		0 1.7 5.0 14.1 214[a]		
Knight and Gibbons, 1987	rat	decreased lifespan and increased collagen in the skin at 30 mg/kg/day		0 3 30 300		
Subchronic inhalation toxicity studies						
Bi et al., 1985	rat	testicular damage	0 (ppm) 10 100 L 3000	0[b] 3 30 L 888		
Hong et al., 1981	rat	increased mortality; increased incidence of lung tumors	0 (ppm) 50 F 250 1000			
Lee et al., 1977, 1978;	rat	increased mortality	0 (ppm) 50 250 F 1000	0[c] 10 51 F 204		

Study	Species	Effect	Reported dose or concentration	Dose (mg/kg/day)	UF/MF	RfD (mg/kg/day)
Lee et al., 1977, 1978;	mouse	increased mortality	0 (ppm) 50 F 250 1000	0[d] 20 F 98 392		
Inhalation developmental toxicity						
John et al., 1981	rat	developmental toxicity	0 (ppm) 500 L 2500	0[e] 194 L 968		
John et al., 1981	mouse	developmental toxicity and maternal toxicity	0 (ppm) 50 500 L	0[f] 31 312 L		
John et al., 1981	rabbit	developmental toxicity	0 (ppm) 500 2500	0[g] 70 351		

[a] gavage dose of 300 mg/kg 5 day/week
[b] mg/kg/day doses were calculated by multiplying the duration expanded concentration (mg/m^3) by the inhalation rats of 0.2136 m^3/day (using allometric equation, U.S. EPA, 1987) and dividing by a TWA body weight of 0.200 kg. This mg/kg/day dose was multiplied by the ratio of the inhalation absorption rate of 0.42 (Krajewski et al., 1980) and oral absorption rate of 0.83 (Feron et al., 1981).
[c] mg/kg/day doses calculated same as in [b], inhalation rate of 0.5116 m^3/day and body weight of 0.580 kg
[d] mg/kg/day doses calculated same as in [b], inhalation rate of 0.0537 m^3/day and body weight of 0.032 kg
[e] mg/kg/day doses calculated same as in [b], inhalation rate of 0.2565 m^3/day and initial body weight of 0.250 kg
[f] mg/kg/day doses calculated same as in [b], inhalation rate of 0.0414 m^3/day and initial body weight of 0.025 kg
[g] mg/kg/day doses calculated same as in [b], inhalation rate of 1.303 m^3/day and initial body weight of 3.5 kg

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