

## 2. RELEVANCE TO PUBLIC HEALTH

### 2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO VINYL CHLORIDE IN THE UNITED STATES

Vinyl chloride is one of the highest production volume chemicals in the world, with a current worldwide demand of roughly 16 billion pounds annually. Approximately 98% of all vinyl chloride produced is used to manufacture polyvinyl chloride (PVC). These PVC materials become end products in automotive parts, packaging products, pipes, construction materials, furniture, and a variety of other products. Other miscellaneous uses that account for about 2% of the vinyl chloride that is produced annually include the manufacture of 1,1,1-trichloroethane and copolymers with vinyl acetate, vinyl stearate, and vinylidene chloride.

Vinyl chloride's production and use results in its release to the environment in waste water streams and air emissions. The microbial degradation of trichloroethylene, tetrachloroethylene, and 1,1,1-trichloroethane also results in the formation of vinyl chloride. Most vinyl chloride released to the environment will eventually partition to air, where it is degraded by atmospheric oxidants such as hydroxyl radicals. The half-life for vinyl chloride in the atmosphere is about 1 day. In water and soil, vinyl chloride may slowly be degraded microbially or undergo hydrolysis, but the rate of these degradation reactions are slow in comparison to the rate of volatilization. Very low levels of vinyl chloride are usually present in ambient air with concentrations typically around  $1 \mu\text{g}/\text{m}^3$  (0.4 ppb) or less. In source dominated areas where vinyl chloride is being produced, higher levels are often observed. Elevated levels of vinyl chloride may also be found in the vicinity of hazardous waste sites and municipal landfills. For example, vinyl chloride was found in emissions from 85% of the landfills studied, and concentrations  $>2,600 \mu\text{g}/\text{m}^3$  (1 ppm) were detected in more than half of the landfill emissions. Vinyl chloride possesses high mobility in soil, and as a consequence, is occasionally detected in groundwater and drinking water in the United States at levels in the parts per billion (ppb) range, although the rapid rate of volatilization generally attenuates the potential for vinyl chloride to leach substantially into groundwater.

The general population is primarily exposed to vinyl chloride from inhalation of ambient air and the ingestion of foods or other items that may contain low levels of vinyl chloride that has leached from a PVC container. Vinyl chloride possesses high mobility in the plastic and can leach into the food, beverages, or water that is ultimately ingested by the consumer. Dietary exposure to vinyl chloride from

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PVC packages used for food has been calculated by several agencies and, based upon estimated average intakes in the United Kingdom and the United States, an exposure of  $<0.0004 \mu\text{g}/\text{kg}/\text{day}$  was estimated for the late 1970s and early 1980s. People who smoke may also be exposed to vinyl chloride since tobacco smoke has been shown to contain low levels of this compound. Much higher exposures are expected for persons that are employed in occupations where vinyl chloride is produced or used. Occupational exposure can arise from inhalation or dermal routes and may vary with specific job function (see Section 6.5).

## 2.2 SUMMARY OF HEALTH EFFECTS

The effects that have been reported to occur in humans in response to vinyl chloride exposure come almost exclusively from studies of workers exposed by inhalation in the workplace. Because women traditionally have not been employed in PVC-manufacturing positions in North America and Western Europe, most of the data on humans from these areas concerns effects in men. Also, virtually all of the epidemiological studies are limited by the absence of data on the actual levels to which workers were exposed. However, studies in animals by the inhalation and oral routes provide an indication of the doses of vinyl chloride that may be associated with similar effects.

Acute high-level exposure of humans to vinyl chloride ( $>8,000 \text{ ppm}$ ) is associated with the development of signs of intoxication such as dizziness, drowsiness, and/or headache. Reports from vinyl chloride workers and studies in animals indicate that loss of consciousness may also be associated with exposure to very high levels ( $>25,000 \text{ ppm}$ ). Two deaths connected with occupational exposure to vinyl chloride have been reported. Autopsy results from these men as well as autopsy results from animals dying from extremely high-level exposures indicate that levels of vinyl chloride producing death may produce lung and kidney irritation and inhibition of blood clotting. Cardiac arrhythmias have also been reported in animals as a result of acute exposure to very high levels of vinyl chloride ( $>100,000 \text{ ppm}$ ). At high concentrations ( $>30,000 \text{ ppm}$ ), vinyl chloride has been shown to sensitize the heart to epinephrine, resulting in cardiac arrhythmias in dogs. Cardiac sensitization by halogenated hydrocarbons generally occurs at very high air concentrations (0.5–90%). Therefore, it appears unlikely that persons exposed to low levels of vinyl chloride will experience these effects.

Longer-term exposure of humans in occupational settings has been associated with the development of a number of other toxic effects. However, exposure levels in these studies are generally not quantified, and thresholds for the effects have not been identified. Histopathological changes characteristic of vinyl

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chloride exposure have been reported to take place in the liver. These changes include extensive fibrosis of the portal tracts and septa, and intralobular perisinusoidal regions, hepatocellular degeneration, sinusoidal dilation, and hypertrophy and hyperplasia of both hepatocytes and sinusoidal cells. These changes in liver structure in exposed workers develop in the absence of a measurable effect on liver function as determined by standard biochemical tests. Recent studies demonstrate morbidity and mortality related to fibrosis, portal hypertension, and cirrhosis among vinyl chloride workers. Reports indicate that peripheral neuropathy may also develop in some workers occupationally exposed to vinyl chloride. In addition, toxic effects on male reproductive function may occur. Studies in animals indicate that vinyl chloride may induce fetal resorptions, delayed development, and an increased incidence of the soft tissue anomaly, dilated ureter. When animals were exposed *in utero*, some changes in liver function were observed during adolescence. However, similar results have not been confirmed in humans.

A syndrome referred to as vinyl chloride disease has been observed in a small percentage of vinyl chloride workers, many of whom were employed as polymerization tank cleaners. This job exposed workers to high levels of vinyl chloride (>1,000 ppm). Vinyl chloride disease is very similar to systemic sclerosis and includes some or all of the following symptoms: Raynaud's phenomenon (fingers blanch and numbness and discomfort are experienced upon exposure to the cold), acroosteolysis (resorption of the terminal bones of the fingers and/or toes), joint and muscle pain, enhanced collagen deposition, decreased elasticity, and scleroderma-like skin changes. A few studies showed that Raynaud's phenomenon may gradually disappear upon removal from exposure. Bone resorption has continued after cessation of exposure in some cases, but not in all cases. Studies in animals support the findings observed in humans (i.e., blood vessel thickening, skin and skeletal changes). In addition, renal nephrosis has been reported to occur in animals exposed to vinyl chloride, but similar results have not been confirmed in humans.

Studies in both humans and animals indicate that vinyl chloride is carcinogenic. Hepatic angiosarcoma has been identified in workers exposed to vinyl chloride by the inhalation route. Other liver tumors, including hepatocellular carcinoma and cholangiocellular carcinoma, have also been associated with occupational exposure to vinyl chloride. Previous studies have also suggested that cancers of the central nervous system, and lymphatic and hematopoietic systems may occur in humans following occupational inhalation exposure. More recent studies, however, have not demonstrated an association between vinyl chloride exposure and brain, lung, or lymphatic/hematopoietic system cancers. Studies in a variety of animal species exposed by both the inhalation and oral routes show an increased incidence of hepatic

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angiosarcoma. Therefore, it is appropriate to consider that vinyl chloride is carcinogenic by the oral route as well.

The National Toxicology Program of the Department of Health and Human Services has determined vinyl chloride to be a known human carcinogen. In addition, the International Agency for Research on Cancer (IARC) has concluded that sufficient evidence for carcinogenicity in humans and animals exists and has placed vinyl chloride in carcinogenicity category 1 (i.e., carcinogenic to humans). EPA also considers vinyl chloride to be a known human carcinogen. EPA's cancer risk assessment for vinyl chloride is discussed below in Section 2.3.

**Death.** Vinyl chloride, at sufficiently high levels, may be fatal to humans following inhalation exposure. The autopsy report regarding the deaths of two vinyl chloride workers showed congestion of the internal organs, particularly the kidneys and lungs, and failure of the blood to clot, but did not estimate the levels to which these workers had been exposed. Inhalation exposure of animals for as brief a period as 30 minutes to concentrations of vinyl chloride ranging from 100,000 to 400,000 ppm have been reported to be lethal to rats, mice, and guinea pigs. The cause of death was attributed to respiratory failure secondary to central nervous system depression in one study. However, reports of cardiac arrhythmicity in dogs at similar levels (>100,000 ppm) suggest that cardiac arrest may have contributed to the deaths. The levels of vinyl chloride found to cause death in animals are extremely high and are unlikely to exist under most environmental conditions (with the exception of concentrated emissions from a large point source). However, increased mortality was observed in pregnant mice when they were exposed to 500 ppm for 7 hours/day for 10 days during gestation. Therefore, it is possible that pregnancy might increase the susceptibility to the effects of vinyl chloride. Because of the limited solubility of vinyl chloride in water, acute ingestion of a lethal dose of vinyl chloride in contaminated water is improbable. Thus, it is unlikely that acute exposure to low levels of vinyl chloride in the air or water near hazardous waste sites will result in sudden death from cardiovascular effects.

No change in mortality rate was noted in a prospective cohort study of 1,100 workers exposed to vinyl chloride compared to the controls. Longer term, low-level exposures have been associated with decreased survival in a number of animal inhalation exposure studies and oral exposure studies. Decreased survival in the number of rats and mice was observed at inhalation exposures as low as 50 ppm for 6 hours/day, 5 days/week, for up to 10 months and oral exposures as low as 1.7 mg/kg/day over the course of a lifetime. The decreased survival rate noted in these studies may be a reflection of the increased mortality rate due to cancer induction by vinyl chloride.

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The significance of a shortened lifespan in animals following low-level chronic exposure with regard to potential adverse effects in humans is unknown.

**Hepatic Effects.** Changes in the liver have been observed in humans exposed to vinyl chloride via inhalation. The characteristic pattern of changes consists of hypertrophy and hyperplasia of hepatocytes and sinusoidal cells; sinusoidal dilation associated with damage to the cells lining the sinusoids and/or sinusoidal occlusion associated with crowding due to cellular hypertrophy and hyperplasia; focal areas of hepatocellular degeneration due to disruption of hepatic circulation; and fibrosis of portal tracts, septa, and intralobular perisinusoidal regions. These findings are supported by studies in animals. The primary difference between effects observed in animals and humans was the greater degree of fibrosis (reticulin and collagen deposition) in human liver tissue. Structural changes occurred in the livers of humans and animals with little or no change in serum hepatic enzyme activities. The lack of change in serum biochemistry may have been due to the limited scope of the necrotic changes. Acute degenerative changes were seen in the livers of animals that inhaled extremely high levels of vinyl chloride. Areas of cellular alteration and necrosis were also observed in the livers of rats chronically exposed to vinyl chloride in the diet.

A recent IARC update of a multi-center cohort study demonstrated an increase in mortality from liver cirrhosis in workers exposed to moderate to high concentrations of vinyl chloride. The critical confounding factor of alcohol consumption was not considered in this study. Morbidity associated with liver cirrhosis was also reported to be elevated among vinyl chloride workers. Liver ultrasonography illustrated an increase in the incidence of periportal fibrosis in vinyl chloride workers. Portal fibrosis and portal hypertension were considered to contribute to mortality in several cases. Abnormal liver function was demonstrated in workers exposed to low concentrations of both vinyl chloride and ethylene dichloride.

**Immunological and Lymphoreticular Effects.** Increased levels of circulating immune complexes and immunoglobulins have been observed in vinyl chloride workers, indicating a stimulatory effect of vinyl chloride on the immune system. Increased percentages of lymphocytes have also been noted in exposed workers.

When workers with vinyl chloride disease were examined, a correlation between the severity of the symptoms of vinyl chloride disease (Raynaud's phenomenon, acroosteolysis, joint and muscle pain,

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enhanced collagen deposition, stiffness of the hands, scleroderma-like skin changes) and the magnitude of the immune response was observed. The most frequent immunologic findings in workers with vinyl chloride disease were an increase in circulating immune complexes and cryoglobulinemia. As the severity of the clinical signs of vinyl chloride disease increased, there was an increase in B-cell proliferation, hyperimmunoglobulinemia, and complement activation.

Because of the similarity of vinyl chloride disease with the proposed autoimmune disease, systemic sclerosis, and the association of many autoimmune diseases with certain inherited genetic characteristics, the human lymphocyte antigen (HLA) phenotypes of vinyl chloride workers both with and without vinyl chloride disease were examined. The study authors determined that susceptibility to vinyl chloride disease was increased in the presence of the HLA-DR5 allele or a gene in linkage disequilibrium with it, and progression of the disease to its more severe forms was favored by HLA-DR3 and HLA-B8 phenotypes. Stimulation of the immune response has been observed in mice exposed to low-to-moderate levels of vinyl chloride via inhalation for several weeks.

**Musculoskeletal Effects.** Another characteristic of vinyl chloride disease is acroosteolysis, in which the terminal phalanges of the fingers are resorbed. Acroosteolysis in vinyl chloride workers was observed to be preceded by Raynaud's phenomenon in most instances. It is unclear whether the resorptive bone changes are due to activation of osteoclasts secondary to vascular insufficiency in the finger tips.

**Cardiovascular Effects.** A small percentage of workers exposed to vinyl chloride develop vinyl chloride disease. One of the symptoms of this disease is a condition referred to as Raynaud's phenomenon, in which the fingers blanch and feel numb and uncomfortable upon exposure to the cold. Arteriography and biopsy material from afflicted workers indicate that exposure to vinyl chloride may produce blockage of the blood vessels supplying the hand, hypervascularity, and a thickening of the blood vessel walls.

Vinyl chloride disease has been reported to be an autoimmune response similar to systemic sclerosis. Proposed mechanisms for the vascular effects elate the vascular response to the immunologic changes observed in these workers. According to these mechanisms, a reactive vinyl chloride intermediate metabolite, such as 2-chloroethylene oxide or 2-chloroacetaldehyde, binds to a protein such as IgG. The altered protein initiates an immune response, with deposition of immune products along the vascular endothelium. Circulating immune complexes are proposed to precipitate in response to exposure to the cold, and these precipitates are proposed to produce blockage of the small vessels.

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Studies in rodents exposed by inhalation to high levels of vinyl chloride have reproduced these symptoms to some extent. Thickening of the arterial vessel walls has been observed in rats exposed to high concentrations of vinyl chloride (>5,000 ppm) for a year.

Limited data are available regarding cardiovascular-related deaths in humans; however, cardiac arrhythmias have been produced in dogs exposed by inhalation to extremely high levels of vinyl chloride (>100,000 ppm). It is unlikely that persons exposed to low levels of vinyl chloride in the air or water near hazardous waste sites will develop cardiac rhythm abnormalities due to vinyl chloride.

**Neurological Effects.** Central nervous system depression is the earliest symptom associated with acute high-level vinyl chloride exposure in humans and animals. Concentrations as low as 8,000 ppm may produce dizziness in humans exposed by inhalation. Workers exposed to vinyl chloride before occupational standards were made more rigorous, complained of dizziness, drowsiness, euphoria, nausea, headache, and occasional loss of consciousness. These symptoms were most frequently experienced by those employed in positions with the greatest exposure to vinyl chloride (cleaners of the autoclaves used to synthesize PVC).

A state of unconsciousness was produced in animals acutely exposed via inhalation to concentrations of approximately 100,000 ppm. It is unlikely that exposure to low levels of vinyl chloride in air or water near hazardous waste sites would produce central nervous system depression.

Reports suggest that peripheral nerve damage may occur in occupationally exposed workers. Chronic inhalation exposure of animals to high levels of vinyl chloride produce peripheral nerve damage and cerebellar degeneration.

**Respiratory Effects.** Both autopsy reports from workers with vinyl chloride-related deaths and animal studies with exposure to extremely high levels of vinyl chloride (100,000 ppm and above) indicate that such levels of vinyl chloride produce respiratory irritation.

Studies of workers who have been occupationally exposed to vinyl chloride give mixed results regarding the chronic adverse respiratory effects of vinyl chloride. Some studies reported no adverse respiratory effects associated with occupational vinyl chloride exposure. However, other investigators found increased incidences of emphysema, decreased respiratory volume and vital capacity, respiratory

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insufficiency, decreased respiratory oxygen and carbon dioxide transfer, pulmonary fibrosis, and abnormal chest x-rays. Factors that may confound the interpretation of these results include a smoking history and exposure to PVC resin dust or to other chemicals.

Histopathologic examination of rats and mice exposed to vinyl chloride for periods of 6 months or a year provides some supportive evidence for the respiratory pathology associated with high-level exposure (2,500, 5,000, or 30,000 ppm). These studies identified changes such as proliferation and hypertrophy of the bronchiolar epithelium, hypersecretion of mucin, hyperplasia of the alveolar epithelium, mobilization of alveolar macrophages, increased pulmonary hemorrhages, and interstitial pneumonia.

**Renal Effects.** No evidence of human renal disease has been reported in studies of workers occupationally exposed to vinyl chloride. However, increased severity of tubular nephrosis and increased kidney-to-body-weight ratios were observed in rats exposed to concentrations of vinyl chloride ranging from 100 to 5,000 ppm for periods of up to a year. It is unclear whether the effects observed in rats represent an increase in severity of naturally occurring tubular nephrosis in rats, or whether these effects represent a lesion attributable to the toxic effects of vinyl chloride on the kidney.

**Gastrointestinal Effects.** Although adverse gastrointestinal effects such as gastritis and ulcers were reported in vinyl chloride workers, the significance of these effects is not known because no unexposed workers were used as controls. Other effects that have been reported, such as nausea, were found in workers who had been selected based upon liver dysfunction.

**Hematological Effects.** The blood of both humans and animals that died as a result of acute exposure to extremely high levels of vinyl chloride did not clot. Slight-to-severe thrombocytopenia has been observed in vinyl chloride workers in several, but not all, studies. However, studies in animals using nonlethal concentrations of vinyl chloride have indicated that such levels result in a decreased clotting time. In one study, a decrease was observed in the time necessary for blood to clot in rats exposed to 5,000 ppm for 1 year. However, the statistical significance of these effects was not reported. A decreased clotting time was observed in rats whose oral intake of vinyl chloride in the diet was 17 mg/kg/day for 2 years. Mean prothrombin time was significantly decreased after either 26 or 52 weeks. The contrast between the acute human studies and the chronic animal data suggest that the hematological effects of vinyl chloride are highly dose-dependent.

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**Endocrine Effects.** One study of workers exposed to vinyl chloride found a thyroid insufficiency in most of those with scleroderma. Thyroid changes, including colloid goiter and increased perifollicular cells, were also noted in rats exposed to high levels of vinyl chloride for 1 year. In guinea pigs, no histopathological changes in the adrenal glands were reported after a 30-minute exposure to 400,000 ppm.

**Dermal Effects.** The third most common characteristic of vinyl chloride disease that was identified in persons with exposure to very high levels of vinyl chloride (such as polymerization tank cleaners) is thickening of the subepidermal layer of the skin. The changes in the skin may appear as thickening above the joints of the fingers or rope-like bundles on the hands and forearms. Analysis of biopsied tissue indicates that the thickening is due to increased synthesis and deposition of collagen. In most cases, the skin changes are also preceded by Raynaud's phenomenon. Thickening of the skin and increased collagen content have been reproduced to some extent in rats administered high concentrations of vinyl chloride by gavage.

**Body Weight Effects.** Workers who had been intoxicated by vinyl chloride were reported to have experienced anorexia, but no consistent changes in body weight were reported in rats exposed to up to 50,000 ppm for acute durations. No changes in body weight were reported in rats, mice, or rabbits exposed to 200 or 1,000 ppm vinyl chloride for up to 6 months. Body weight changes were noted in rats exposed to either 50 ppm vinyl chloride (10 months, 5 days/week, 5 hours/day) or 5,000 ppm vinyl chloride (4–52 weeks, 5 days/week, 7 hours/day). Maternal body weight gain was significantly decreased in mice exposed to 500 ppm for 7 hours/day during gestation days 6–15.

**Reproductive Effects.** Studies in humans indicate that the male reproductive function may be adversely affected by exposure to vinyl chloride. Decreased androgen levels have been found in workers occupationally exposed to vinyl chloride. Also, workers have complained of impotency and decreased libido. These findings are supported by histopathological evidence of testicular damage and decreased male fertility in rats exposed by inhalation.

Fewer studies have reported the effects of vinyl chloride on the reproductive function in females. Reduced hemoglobin levels during pregnancy and an increased incidence of elevated blood pressure and edema during pregnancy (preeclampsia) have been observed. Studies designed to examine these effects in animals were not located.

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No adverse effects were noted in reproductive capability in a 2-generation study in rats exposed to vinyl chloride. Male and female Sprague-Dawley rats were exposed to 0, 10, 100, or 1,100 ppm vinyl chloride 6 hours/day for a 10-week pre-mating period and a 3-week mating period. No exposure-related effects were seen in body weight, feed consumption, ability to reproduce, gestation index or length, or pre- and postweaning developmental landmarks. Sperm counts, motility, and morphology were also unaffected by vinyl chloride exposure.

**Developmental Effects.** Although a statistically significant increase in congenital abnormalities has been observed in members of some communities located near a vinyl chloride processing facility, reports have failed to establish a statistically significant association between developmental toxicity and either parental occupation or proximity to the facility. There are also inconsistencies in the developmental toxicity data for vinyl chloride in laboratory animals. In general, vinyl chloride produced minor developmental effects only at concentrations that were significantly toxic to maternal animals. Concentrations of 500 ppm for 7 hours/day were observed to produce delayed ossification in the fetus and decreased food consumption, body weight gain, and an increase in mortality rate in maternal mice. In contrast, no adverse effects were reported in an embryo-fetal developmental toxicity study conducted in rats exposed to vinyl chloride concentrations as high as 1,100 ppm for 6 hours/day. Embryo-fetal developmental parameters including uterine implantation, fetal gender distribution, fetal body weight, and fetal malformations and variations were not affected by vinyl chloride exposure. Vinyl chloride produced a decrease in maternal body weight gain; however, no changes were observed in feed consumption, clinical signs, or postmortem gross findings. Maternal liver and kidney weights were increased relative to body weight.

**Cancer.** A large number of studies have reported a greater than expected incidence of a rare type of cancer, angiosarcoma of the liver, among workers exposed to vinyl chloride. Other liver tumors, including hepatocellular carcinoma and cholangiocellular carcinoma, have also been associated with occupational exposure to vinyl chloride. Other types of cancer that have shown a statistically significant increase in incidence among vinyl chloride workers, in at least some studies, include cancer of the brain and central nervous system, the lung and respiratory tract, and the lymphatic/hematopoietic system. However, more recent studies have not confirmed an association between vinyl chloride exposure and brain, lung, or lymphatic/hematopoietic system cancers. A significant increase in cancers of connective and other soft tissues was observed in a recent follow-up mortality study and in a meta-analysis of eight independent studies. Rhomberg also suggests that vinyl chloride can induce soft tissue sarcoma outside of the liver; however, an IARC update of a multi-center cohort study was negative for soft tissue sarcoma.

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A recent review pooled the analyses of worker cohort from 56 vinyl chloride plants in North America and Europe. This analysis includes over 22,000 workers and represents the most comprehensive data on occupational risks of vinyl chloride exposure. An elevated risk of liver cancer mortality was observed. Deaths from lung and laryngeal cancer were lower than expected and no excess cancer risk was observed for soft tissue sarcoma, brain, lymphoid, and hematopoietic system cancers. Lewis reports the continuing occurrence of angiosarcoma of the liver in retirees from a PVC production plant in Louisville, Kentucky. This ongoing incidence is reported primarily for those workers employed prior to 1960, suggesting that those exposed to the highest concentrations of vinyl chloride remain at risk for developing cancer for the remainder of their lives. The reported latency period for workers diagnosed prior to 1975 was 12–28 years, while those diagnosed after 1975 showed a latency of 27–47 years. Because women traditionally have not been employed in PVC-manufacturing positions in North America and Western Europe, virtually all of the information available from occupational studies in these areas is based on the responses of males to vinyl chloride. One study by Smulevich et al. reporting on Soviet males and females occupationally exposed to vinyl chloride indicates that females may have higher incidences of stomach cancer, leukemias, and lymphomas than males.

An increased incidence of angiosarcoma of the liver has been found after inhalation of vinyl chloride gas by a variety of animal species. Although no studies examining the incidence of carcinogenic effects in humans exposed to vinyl chloride by the oral route have been located, vinyl chloride incorporated into the diet of rats has been demonstrated to cause an increased incidence of hepatic angiosarcoma.

There are ample data on the genotoxicity of vinyl chloride in both humans and animals and information on the mechanisms by which this compound may exert its carcinogenic effects has been elucidated from both *in vitro* and *in vivo* studies (see Section 3.3).

**Genotoxic Effects.** Genotoxicity studies of vinyl chloride in humans include a large number of assays for chromosomal aberrations in the cultured lymphocytes of occupationally exposed workers. Workers exposed to vinyl chloride for an average of 15 years were shown to have elevated levels of micronuclei and chromosomal aberrations when compared to the unexposed controls. An increase in chromosome aberrations and micronuclei was correlated with exposure to vinyl chloride in the air at a plastics plant. Micronuclei counts were also significantly increased in a group of 52 workers exposed to vinyl chloride levels of 1.3–16.7 ppm compared to those of controls, but these increases were not observed in workers exposed to 0.3–7.3 ppm.

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Increased sister chromatid exchanges have also been reported in occupationally exposed workers. Sister chromatid exchange frequencies were significantly increased compared to those of the controls at 0.003–7.3 ppm vinyl chloride. A positive correlation was reported between frequency of chromosomal aberrations and length and history of exposure. DNA single strand breaks present in human lymphocytes from exposed workers were quickly repaired following cessation of exposure. DNA damage in lymphocytes of plastic industry workers was also demonstrated by a single-cell gel electrophoresis technique. A correlation was observed between the severity of DNA damage and the duration of exposure. Induction of single-strand breaks in liver DNA was also observed in mice after inhalation of vinyl chloride. The reversibility of chromosome damage has been reported for several populations of workers following a cessation or reduction of exposure to vinyl chloride.

Vinyl chloride has also been demonstrated to be mutagenic in bacteria and yeast. Vinyl chloride is mutagenic in *Salmonella typhimurium*, but only in strains reverted by base-pair substitution by alkylating agents rather than by frameshift mutations. Metabolic activation is necessary for any mutagenic activity in this system or for a maximal response. In addition, vinyl chloride is mutagenic in the gaseous phase, but not when it is dissolved in water. The negative findings for vinyl chloride dissolved in water are most likely due to methodological problems associated with rapid evaporation and therefore do not reflect a lack of mutagenic potential. There is evidence that in *Salmonella typhimurium* and *Escherichia coli*, it is the oxidation of vinyl chloride to the reactive intermediates 2-chloroethylene oxide and 2-chloroacetaldehyde that is responsible for the mutagenicity of vinyl chloride.

Vinyl chloride is metabolized by mixed function oxidases (MFO) to form an epoxide intermediate, 2-chloroethylene oxide, which spontaneously rearranges to form 2-chloroacetaldehyde. Reactive metabolites of vinyl chloride can be transported intercellularly from parenchymal cells to the non-parenchymal cells. Many studies have characterized the mutation profile associated with DNA adducts formed by the reactive metabolites of vinyl chloride. Four primary DNA adducts are formed by the reactive metabolites of vinyl chloride. These are cyclic etheno-adducts that include, 1,N<sup>6</sup>-ethenoadenine, 3,N<sup>4</sup>-ethenocytosine, N<sup>2</sup>,3-ethenoguanine, and 1,N<sup>2</sup>-ethenoguanine. These adducts can produce base-pair (i.e., purine-to-purine or pyrimidine-to-pyrimidine exchange) transitions during transcription. DNA crosslinks can also be formed because chloroacetaldehyde is bifunctional.

The role of etheno-adducts in the carcinogenesis of vinyl chloride has been recently reviewed. 2-Chloroethylene oxide and 2-chloroacetaldehyde can both react with DNA nucleotide bases; however, 2-chloro-

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ethylene oxide is a more potent mutagen and may be the ultimate carcinogenic metabolite of vinyl chloride. Etheno-adducts generate mainly base pair substitution mutations. Mutations in specific genes (i.e., *ras oncogenes*, p53 tumor suppressor gene) have been identified in vinyl chloride-induced liver tumors in rats and humans and are discussed in further detail in Section 3.3.

## 2.3 MINIMAL RISK LEVELS (MRLs)

### *Inhalation MRLs*

Studies in humans did not provide sufficient data regarding exposure levels and their correlation with observed effects. Therefore, animal studies were used for the derivation of inhalation MRLs.

- An MRL of 0.5 ppm has been derived for acute-duration inhalation exposure ( $\leq 14$  days) to vinyl chloride.

This MRL was derived from a no-observed-adverse-effect level (NOAEL) of 50 ppm for developmental effects in mice exposed 7 hours/day on gestational days 6–15 (John et al. 1977, 1981). No adverse maternal or fetal effects were noted at 50 ppm, with the exception of an increase in crown-rump length that was not observed at 500 ppm. The 50-ppm exposure level is considered to represent a NOAEL for maternal and developmental toxicity. At the lowest-observed-adverse-effect level (LOAEL) of 500 ppm, delayed ossification was observed. An increase in resorptions at 500 ppm was considered to have been within historical control limits. There was frank maternal toxicity at 500 ppm (17% death). The NOAEL of 50 ppm for intermittent exposure (7 hours/day) was converted to a continuous exposure ( $50 \text{ ppm} \times 7/24 = 15 \text{ ppm}$ ).

Following EPA (1994g) methodology, the human equivalent concentration ( $\text{NOAEL}_{\text{HEC}}$ ) for an extrarrespiratory effect produced by a category 3 gas, such as vinyl chloride, is calculated by multiplying the duration-adjusted animal NOAEL by the ratio of the blood:gas partition coefficients in animals and humans  $[(H_{\text{b/g}})_{\text{A}} / H_{\text{b/g}}]_{\text{H}}$ . Since the partition coefficient in mice is greater than that in humans, as seen in Table 3-3, a default value of 1 is used for the ratio and the duration-adjusted animal NOAEL (15 ppm) is equivalent to the  $\text{NOAEL}_{\text{HEC}}$  (15 ppm). A total uncertainty factor of 30 (3 for extrapolation from mice to humans using a dosimetric adjustment and 10 for human variability) was applied to the  $\text{NOAEL}_{\text{HEC}}$ .

Therefore, the acute-duration inhalation  $\text{MRL} = \text{NOAEL}_{\text{HEC}} (15 \text{ ppm}) \div 30 (\text{UF}) = 0.5 \text{ ppm}$ .

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- An MRL of 0.03 ppm has been derived for intermediate-duration inhalation exposure (15–364 days) to vinyl chloride.

An intermediate-duration inhalation MRL of 0.03 ppm was derived for vinyl chloride, based on a  $LEC_{10}$  value of 5 ppm for hepatic centrilobular hypertrophy in rats (Thornton et al. 2002). All dichotomous models in the Benchmark Dose Software (BMDS version 1.3.2) were fit to the incidence data for centrilobular hypertrophy in the rats exposed to vinyl chloride by inhalation (Thornton et al. 2002). The lower 95% confidence limit ( $LEC_{10}$ ) of a 10% extra risk (LEC) for hepatic centrilobular hypertrophy was selected as the benchmark response for the point of departure. Several models provided equivalent goodness-of-fit statistics. Therefore, the  $LEC_{10}$  value of 3 ppm, derived from the simplest model (Weibull), was selected as the point of departure for calculating an intermediate-duration inhalation MRL (see Appendix A for more detailed information on the application of Benchmark Dose Modeling in deriving the intermediate-duration inhalation MRL for vinyl chloride). The  $LEC_{10}$  of 3 ppm was duration-adjusted from intermittent (6 hours/day) to continuous exposure ( $3 \text{ ppm} \times 6/24 = 0.8 \text{ ppm}$ ). Following EPA (1994g) methodology, the human equivalent concentration ( $LEC_{10\text{HEC}}$ ) for an extrarrespiratory effect produced by a category 3 gas, such as vinyl chloride, is calculated by multiplying the duration-adjusted animal  $LEC_{10}$  by the ratio of the blood:gas partition coefficients in animals and humans [ $(H_{b/g})_A / H_{b/g})_H$ ]. Since the partition coefficient in mice is greater than that in humans, as seen in Table 3-3, a default value of 1 is used for the ratio and the duration-adjusted animal  $LEC_{10}$  (0.8 ppm) is equivalent to the  $LEC_{10\text{HEC}}$  (0.8 ppm). A total uncertainty factor of 30 (3 for extrapolation from mice to humans using a dosimetric adjustment and 10 for human variability) was applied to the  $NOAEL_{\text{HEC}}$ .

Therefore, the intermediate-duration inhalation  $MRL = LEC_{10\text{HEC}} (0.8 \text{ ppm}) \div 30 (UF) = 0.03 \text{ ppm}$ .

Increased relative liver weight (Bi et al. 1985; Sokal et al. 1980; Torkelson et al. 1961) and adverse histopathological changes (Lester et al. 1963; Schaffner 1978; Sokal et al. 1980; Wisniewska-Knypl et al. 1980) have been observed in several other intermediate-duration inhalation studies. Additional support for the selection of 10 ppm as the lowest LOAEL comes from another study demonstrating immunostimulation at 10 ppm (Sharma and Gehring 1979).

No chronic-duration inhalation MRL was derived for vinyl chloride because of the absence of a suitable LOAEL or NOAEL for derivation. A NOAEL (10 ppm) and a LOAEL (100 ppm) were identified for testicular effects (increases in the number of degenerative seminiferous tubule changes) in a chronic-duration inhalation study (Bi et al. 1985). However, these data were not used as the basis of a chronic-

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duration inhalation MRL because the LOAEL for these effects was higher than the LOAEL of 10 ppm for nonneoplastic liver lesions identified in the intermediate-duration rat inhalation study of Thornton et al. (2002). Bi et al. (1985) did not report the incidence of histopathological changes in the liver following chronic inhalation exposure; however, the results of the Thornton et al. (2002) study suggest that liver effects would occur at lower doses than the reported testicular effects. No other chronic-duration inhalation toxicity studies were located in which vinyl chloride-induced nonneoplastic lesions were described.

***Oral MRLs***

Studies in humans did not provide sufficient data regarding exposure levels and their correlation with observed effects. Therefore, animal studies were used for the derivation of MRLs.

No acute- or intermediate-duration oral MRLs were derived for vinyl chloride because of an absence of data on the effects of oral exposure to vinyl chloride for these duration categories.

- An MRL of 0.003 mg/kg/day has been derived for chronic-duration oral exposure ( $\geq 365$  days) to vinyl chloride.

This MRL of 0.003 mg/kg/day was based on a NOAEL of 0.17 mg/kg/day for noncancerous liver effects (i.e., liver cell polymorphism) in rats (Til et al. 1983, 1991) and application of the physiologically based pharmacokinetic (PBPK) model used to derive EPA's reference dose (RfD) (Clewell et al. 2001; EPA 2000). Source code and parameter values for running the rat and human models in Advance Continuous Simulation Language (ACSL) were transcribed from Appendix C of EPA (2000). Exposures in the Til et al. (1983, 1991) rat dietary study were simulated as 4-hour oral exposures with the NOAEL dose for liver effects of 0.17 mg/kg/day. A 4-hour feeding period was used in the study due to the rapid evaporative loss of vinyl chloride from the food. The total amount of vinyl chloride metabolized in 24 hours per liter of liver volume was the rat internal dose metric that was used in determining the human dose that would result in an equivalent human dose metric. One kilogram of liver was assumed to have an approximate volume of 1 L. Dose metrics reflect the cumulative amount of vinyl chloride metabolized over the 24-hour period. The human model was run iteratively, until the model converged with the internal dose estimate for the rat (3.16 mg/L liver). The human dose was assumed to be uniformly distributed over a 24-hour period with the resulting human equivalent dose of 0.09 mg/kg/day. Therefore, the human equivalent dose of 0.09 mg/kg/day, associated with the rat NOAEL of 0.17 mg/kg/day (Til et al. 1983, 1991), served as the basis for the chronic-duration oral MRL for vinyl chloride. A total uncertainty factor

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of 30 (3 for extrapolating from animals to humans using a dose metric conversion and 10 for human variability) was applied to the human equivalent NOAEL.

Therefore, the chronic-duration oral MRL =  $0.09 \text{ mg/kg/day (HED)} \div 30 = 0.003 \text{ mg/kg/day}$ .

More detailed information regarding the application of the PBPK modeling in deriving the chronic-duration oral MRL for vinyl chloride is provided in Appendix A.

EPA has concluded that sufficient evidence of carcinogenicity exists in humans and animals and has classified vinyl chloride according to its 1986 classification scheme as a Group A or known human carcinogen (EPA 1994c). EPA's current weight-of-evidence characterization for vinyl chloride concludes that vinyl chloride is a *known human carcinogen by the inhalation route of exposure*, based on human epidemiological data. By analogy, vinyl chloride is considered a *known human carcinogen by the oral route* because of positive animal bioassay data as well as pharmacokinetic data allowing dose extrapolation across routes. By inference, vinyl chloride is also considered highly *likely to be carcinogenic by the dermal route* because it acts systemically (EPA 2000). Because the epidemiological evidence does not provide sufficient exposure and incidence data to quantify risk based solely on human data, EPA cancer potency factors for inhalation and oral exposure have been calculated based on animal studies. An inhalation unit risk of  $8.8 \times 10^{-6}$  per  $\mu\text{g}/\text{m}^3$  for continuous lifetime exposure from birth was estimated by EPA (2000) based on the incidence of liver tumors observed in rats in the inhalation study by Maltoni et al. (1981). An inhalation unit risk of  $4.4 \times 10^{-6}$  per  $\mu\text{g}/\text{m}^3$  for continuous lifetime exposure during adulthood was also estimated by EPA (2000). An oral slope factor for continuous lifetime exposure from birth was estimated by EPA (2000) to be 1.5 per  $\text{mg}/\text{kg}/\text{day}$  based on the incidence of liver tumors in rats in the study by Feron et al. (1981). An oral slope factor of  $7.5 \times 10^{-1}$  per  $\text{mg}/\text{kg}/\text{day}$  for continuous lifetime exposure during adulthood was also estimated by EPA (2000).