2. RELEVANCE TO PUBLIC HEALTH

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

Vinyl chloride is a 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.

Most vinyl chloride released to the environment will eventually partition to air, where it is degraded by atmospheric oxidants such as hydroxyl radicals. Very low levels of vinyl chloride are usually present in ambient air with concentrations typically around 1 μg/m^3 (0.4 ppb) or less. In areas in close proximity to vinyl chloride production facilities, higher airborne levels are often observed. Elevated levels of vinyl chloride may also be found in the vicinity of hazardous waste sites and municipal landfills. This may be due to the presence of vinyl chloride or the microbial degradation of other chlorinated solvents to form vinyl chloride. Vinyl chloride is highly mobile 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 reduces 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 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 μg/kg/day was estimated for the late 1970s and early 1980s. People who smoke or work where vinyl chloride is produced or used may be exposed to higher levels of vinyl chloride.

2.2   SUMMARY OF HEALTH EFFECTS

The effects of vinyl chloride exposure have been studied in humans and animals, with similar results being exhibited in all species. Vinyl chloride exposure in humans is most likely to occur by inhalation or oral exposure routes. Effects from dermal exposures are unlikely, as vinyl chloride is not well absorbed across the skin. Chronic-duration, occupational exposures to high levels of vinyl chloride have resulted in a specific suite of effects in humans, including narcotic effects, Raynaud's phenomenon (blanching and numbness of fingers and discomfort experienced upon exposure to cold temperatures), acroosteolysis, scleroderma-like skin changes, hepatocellular alterations, and the development of hepatic angiosarcoma, a liver cancer that is quite rare in the general U.S. population. Laboratory animal exposure to vinyl chloride has resulted in neurological, liver, and cancer effects as well as respiratory, reproductive, developmental, and lymphoreticular effects. Though acute inhalation exposure of mice to vinyl chloride resulted in a developmental effect (on which the oral acute-duration Minimal Risk Level [MRL] is based), liver and neurological effects were observed consistently in vinyl chloride workers and several animal species across exposure durations, suggesting that these are the principal effects of vinyl chloride exposure.

The liver is the most sensitive target organ for vinyl chloride toxicity for both intermediate- and chronic-duration inhalation and chronic-duration oral exposures. The sensitivity of the liver to acute-duration effects is difficult to assess, since studies of acute-duration exposures either reported liver effects from high exposures of ≥20,000 ppm or focused on reproductive and developmental effects. The sensitivity of the liver to vinyl chloride exposure is consistent with the proposed mechanism of action in which metabolism of vinyl chloride via mixed function oxidases (MFO), specifically CYP2E1, results in the formation highly reactive metabolites. These metabolites have been shown to bind to DNA and hepatocellular proteins. Thus, the prevalence of MFO activity in the liver and resulting production of reactive metabolites results in the observed sensitivity of the liver to cancer and noncancer effects. Occupational studies have identified a consistent group of liver effects resulting from vinyl chloride exposure, including hypertrophy, hyperplasia of hepatocytes and sinusoidal cells, portal fibrosis, sinusoidal dilation, and focal cellular degeneration. Animal studies demonstrate that the intensity of effects increased with increasing dose, ranging from cellular hypertrophy and sinusoidal compression, to vacuolization, hepatic hyperplasia, fibrosis, and necrosis. Longer duration exposures resulted in manifestation of effects at lower doses. In animal studies, the lowest observed adverse noncancer effects in the liver included liver cell polymorphisms and development of hepatic cysts resulting from chronic oral exposures of 2 mg/kg/day; centrilobular hypertrophy and fatty liver changes resulted from intermediate-duration inhalation exposures of 10 and 50 ppm, respectively. In addition to noncancer

effects, the liver was sensitive to tumor development. For intermediate- and chronic-duration inhalation and chronic-duration oral exposures, the development of liver angiosarcoma resulted from exposures as low as 50 ppm and 0.2 mg/kg/day, respectively. The development of pre-neoplastic basophilic foci resulted from chronic oral exposures of 0.02 mg/kg/day.

Neurological effects of vinyl chloride have been observed following inhalation exposures. No data were available for neurological effects resulting from oral exposures. Inhalation-related neurological effects in humans include dizziness, drowsiness and fatigue, headache, euphoria and irritability, nervousness and sleep disturbances, nausea, visual and hearing disturbances, and loss of consciousness. Signs of pyramidal and cerebellar disturbances have also been observed. Dizziness has been reported by volunteers acutely exposed to 8,000 ppm, while nausea and subsequent headache resulted from exposures of 20,000 ppm. Peripheral neurological effects have been reported, including parasthesia, tingling or warmth in the extremities, numbness or pain in the fingers, and depressed reflexes. A variety of effects in animals from acute-duration inhalation exposures include ataxia, decreased coordination, twitching, tremors, and unconsciousness. Chronic-duration exposures resulted in damaged nerve tissue, including degeneration of brain tissue and fibrosis of peripheral nerve endings.

Human studies of reproductive and developmental effects from vinyl chloride exposure resulted in equivocal results. Studies examining parental employment and/or residential proximity to vinyl chloride facilities and birth defects reported links to fetal loss and defects of the central nervous system, alimentary tract, genitalia, and incidence of club foot. Other studies found no such association or suggested that inappropriate or inadequate study designs and statistical methodology were employed. In animals, a few studies have identified reproductive and developmental effects. Decreased testicular weight, reduced male fertility, and spermatogenic epithelial necrosis resulted from intermediate-duration inhalation exposures of 100–500 ppm, but were not observed in rats exposed to up to 1,100 ppm. Gestational exposures of 2,500 ppm resulted in ureter dilation in rat offspring, while delayed ossification was observed following 500 ppm exposures in mice. This exposure also resulted in 17% maternal mortality. A no-observed-adverse-effect level (NOAEL) of 50 ppm was associated with delayed ossification in mice and is the basis for the acute-duration inhalation MRL.

The Department of Health and Human Services has determined vinyl chloride to be a known human carcinogen. 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). Similarly, EPA concluded 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, EPA considers vinyl chloride *highly likely to be carcinogenic by the dermal route* because it acts systemically. EPA derived an inhalation unit risk of 8.8×10^{-6} per $\mu g/m^3$ for continuous lifetime exposure from birth based on the incidence of liver tumors observed in rats exposed to vinyl chloride via inhalation. An inhalation unit risk of 4.4×10^{-6} per $\mu g/m^3$ for continuous lifetime exposure during adulthood was also estimated by EPA. An oral slope factor for continuous lifetime exposure from birth was estimated by EPA to be 1.5 per mg/kg/day based on the incidence of liver tumors in rats. An oral slope factor of 7.5×10^{-1} per mg/kg/day for continuous lifetime exposure during adulthood was also estimated by EPA.

Noncancerous hepatotoxicity and carcinogenicity of vinyl chloride are discussed in greater detail below. The Reader is referred to Section 3.2, Discussion of Health Effects by Route of Exposure, for additional information on other effects.

Noncancerous Hepatic Effects.   The liver appears to be the most sensitive target organ of vinyl chloride toxicity. Liver effects serve as the basis for the intermediate-duration inhalation MRL and the chronic-duration oral MRL (see Section 2.3). Changes in the liver have been observed in workers exposed to unknown levels of vinyl chloride via inhalation. The characteristic pattern of changes detected by peritoneoscopy and confirmed in several studies include 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 periportal and intralobular perisinusoidal regions. In fact, the extent of hepatic fibrosis appears to represent the primary difference between effects observed in animals and humans, as reticulin and collagen deposition in human liver tissue was greater than that observed in animals. Species differences in fibrosis may also have been impacted by co-exposure to ethanol via alcohol consumption. Case studies suggest that portal fibrosis and portal hypertension contributed to worker mortality. Further, liver cirrhosis was implicated in increased mortality in an IARC update of a multi-center cohort of workers exposed to moderate to high concentrations of vinyl chloride and in a cohort of workers from five PVC production sites in Taiwan. Though the critical confounding factor of alcohol consumption by workers at these sites was not considered, an analysis of another large cohort of vinyl chloride workers suggested that vinyl chloride exposure was an independent risk factor for liver cirrhosis, which exhibited a

synergistic interaction with alcohol consumption. Regardless of species differences, it is possible that the development of fibrosis resulted via an immune-mediated mechanism rather than cytotoxicity, as structural changes occurring in the livers of humans and animals were not generally accompanied by changes in serum hepatic enzyme activities. The lack of change in serum biochemistry may have been due to the limited scope of the necrotic changes.

These findings in epidemiology studies are supported by studies in animals. The animal data indicate a progression of effects across doses and durations. Acute- and intermediate-duration effects seen in the livers of animals that inhaled 50,000–300,000 ppm of vinyl chloride included fatty liver changes, hepatocellular hypertrophy, vacuolization, sinusoidal compression, and liver congestion. Centrilobular degeneration and necrosis resulted from intermediate-duration exposure of 50–200 ppm. Centrilobular hypertrophy occurred in rats following an intermediate-duration inhalation of 10 ppm. The dose-related progression of effect intensity from the minimally adverse increase in size of centrilobular hepatocytes to degeneration and necrosis is consistent with the appearance of highly reactive metabolites due to focused MFO metabolism of vinyl chloride in the liver (see discussion below). Low-level intermediate- and chronic-duration inhalation exposures of 50 ppm also resulted in the development of hepatic angiosarcoma, though it is not known if carcinogenicity was preceded by or independent of a progression of non-cancer effects. Chronic oral exposures resulted in areas of cellular alteration, polymorphism, and necrosis in the livers of rats given 2 mg/kg/day vinyl chloride in the diet, while the appearance of basophilic foci, considered a pre-neoplastic lesion, occurred following exposures of 0.02 mg/kg/day.

Though the mechanism of toxicity for liver effects of vinyl chloride is not well understood, the parent compound is metabolized to the reactive metabolites 2-chloroethylene oxide and, subsequently, 2-chloroacetaldehyde via MFOs, whose activity is primarily concentrated in the liver. The presence of the reactive 2-chloroacetaldehyde likely results in protein adduction, which can interfere with normal cellular function, resulting in cytotoxicity. This is consistent with the progression of effects from hypertrophy to fatty changes, hyperplasia, and necrosis. The effects of hepatic fibrosis may be a secondary effect of the initiation of immune responses to cytotoxicity. This is consistent with enhanced collagen deposition observed in workers, which is believed to be an immune-mediated response.

Cancer.   The development of cancer in humans as a result of vinyl chloride exposure has been demonstrated in a number of studies of workers in the vinyl chloride production industry. The strongest evidence comes from the cluster of reports of greater than expected incidences of liver angiosarcoma. Though no exposure data were available for these workers, there is a convincing association between

vinyl chloride exposure and the development of liver angiosarcoma, as this type of liver cancer is considered to be very rare in humans (25–30 cases/year in the United States). The latency period for the development of hepatic angiosarcoma appears to be quite lengthy, as angiosarcoma continues to occur in workers employed prior to 1960; workers diagnosed after 1975 showed a latency of 27–47 years.

Other types of cancer that have shown a significant increase in incidence among vinyl chloride workers include hepatocellular carcinoma and cholangiocellular carcinoma, cancer of the lung and respiratory tract, the lymphatic/hematopoietic system, and the brain and central nervous system. However, uncertainty exists in the association of vinyl chloride exposure and some soft tissue tumors. A meta-analysis of data for over 22,000 workers suggested no excess cancer risk for soft tissue sarcoma, brain, lymphoid, and hematopoietic system cancers. More recent follow-up studies have failed to find a significant association between vinyl chloride exposure and respiratory tract and brain cancer.

Studies in several animal species support the conclusion that vinyl chloride is carcinogenic. In rats, chronic exposure to 5–5,000 ppm vinyl chloride vapors resulted in significant incidence of mammary gland carcinomas, Zymbal's gland carcinomas, nephroblastoma, and liver angiosarcoma. Intermediate- and chronic-duration exposures of 50–2,500 ppm vinyl chloride resulted in significant incidence of liver angiosarcoma, carcinoma, and angioma, lung adenoma, mammary gland carcinoma, adipose tissue hemangiosarcoma, and hemangiosarcoma of the subcutis and peritoneum in mice. With the exception of liver angiosarcomas, which have been observed in all species (including humans), there is little consistency in tumor types across species. Chronic-duration oral administration of 2–6 mg/kg/day of vinyl chloride resulted in the development of neoplastic liver nodules, hepatocellular carcinoma, and lung and liver angiosarcoma in rats.

Studies in rats, mice, and hamsters provide evidence that exposure early in life increases the risk of hemangiosarcoma in liver, skin, and spleen, stomach angiosarcoma, and mammary gland carcinoma, as compared to the risk associated with exposure after 12 months of age. Due to the latency period for vinyl chloride-induced cancer, exposure of animals early in life may have increased the likelihood of developing tumors and affect the type of tumor that develops.

The metabolism of vinyl chloride to the highly reactive metabolites, the observance of DNA adduction in mechanistic studies, and the observed carcinogenicity resulting from a single, high level inhalation exposure in animals, suggest that the primary mechanism of vinyl chloride carcinogenicity involves direct DNA interactions rather than secondary responses to cytotoxicity. The mutation profile of DNA adducts

formed by the reactive metabolites of vinyl chloride, 2-chloroethylene oxide and 2-chloroacetaldehyde, includes the four cyclic etheno-adducts $1,N^6$-ethenoadenine, $3,N^4$-ethenocytosine, $3,N^2$-ethenoguanine, and $1,N^2$-ethenoguanine. These adducts produce base-pair transitions during transcription and DNA crosslinks. Such mutations have resulted in the mutation of *ras* oncogenes, as observed in hepatic angiosarcoma tumors of workers exposed to high levels of vinyl chloride. Further, mutations in the p53 tumor suppressor gene, which has been associated with a variety of tumor types, have been identified in vinyl chloride workers. Mutations in p53 of vinyl chloride-exposed rats were similar to those reported in humans.

2.3   MINIMAL RISK LEVELS (MRLs)

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made for vinyl chloride. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

Inhalation MRLs

Epidemiological and case studies in humans did not provide sufficient data regarding exposure levels and durations and their correlation with hepatic, neurological, immunological, and carcinogenic 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 (≤14 days) to vinyl chloride.

A number of studies in animals identified acute-duration lowest-observed-adverse-effect levels (LOAELs) for frank narcosis and severe lung, liver, and kidney damage following exposures of 5,000–400,000 ppm of vinyl chloride. Exposure of pregnant rats to 2,500 ppm 7 hours/day over gestational days 6–15 resulted in ureter dilation in the offspring (John et al. 1977, 1981). In the same study, pregnant mice exposed to 500 ppm for the same duration exhibited delayed ossification in the fetuses. A NOAEL of 50 ppm was identified for mice.

The study of John et al. (1977, 1981) study serves as the principal study for the derivation of an acute-duration inhalation MRL based on the NOAEL of 50 ppm for delayed ossification. In this study, groups of 19–26 pregnant CF-1 mice were exposed to 0, 50, or 500 ppm vinyl chloride for 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. At the LOAEL of 500 ppm, delayed ossification was observed. A significant increase in fetal resorptions and reduced litter size at 500 ppm was considered to have been within historical control limits. There was frank maternal toxicity at 500 ppm (17% death).

The duration-adjusted NOAEL ($NOAEL_{ADJ}$) was calculated as follows:

$$NOAEL_{ADJ} = 50 \text{ ppm x 7 hours / 24 hours} = 15 \text{ ppm}$$

The human equivalent concentration ($NOAEL_{HEC}$) for an extrarespiratory effect produced by a category 3 gas, such as vinyl chloride, was calculated by multiplying the $NOAEL_{ADJ}$ 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, a default value of 1 is used for the ratio, resulting in a $NOAEL_{HEC}$ of 15 ppm. The acute-duration inhalation MRL of 0.5 ppm was derived by dividing the $NOAEL_{HEC}$ of 15 ppm by an uncertainty factor of 30 (3 for species extrapolation with dosimetric adjustment and 10 for human variability).

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

Reduced male fertility, decreased tested weight, and spermatogenic epithelial necrosis was observed in male rats exposed from 11 weeks to 10 months to 100–500 ppm vinyl chloride (Bi et al. 1985; Short et al. 1977; Sokal et al. 1980). Decreased white blood cell counts resulted from exposure of rats to 20,000 ppm for 3 months (Lester et al. 1963), while increased lymphocyte proliferation resulted in mice exposed to 10 ppm for up to 8 weeks (Sharma and Gehring 1979). Exposures of 10–1,000 ppm resulted in increases and decreases in various relative and absolute organ weights (Sharma and Gehring 1979), including the liver (Bi et al. 1985; Sokal et al. 1980; Torkelson et al. 1961). Adverse histopathological changes in the liver of rats and mice exposed to 2,000–3,000 ppm have been observed in several other intermediate-duration inhalation studies (Lester et al. 1963; Schaffner 1978; Sokal et al. 1980; Torkleson et al. 1961; Wisniewska-Knypl et al. 1980). Centrilobular degeneration and necrosis was observed in rabbits exposed to 200 ppm for 6 months (Torkleson et al. 1961). Fatty liver changes were also observed in two studies of rats exposed to 50 ppm for 10 months (Sokal et al. 1980; Wisniewska-Knypl et al. 1980). The lowest observed effect level was 10 ppm, which resulted in centrilobular hypertrophy in F1 female rats exposed for 19 weeks (Thornton et al. 2002).

While effects were observed in both mice and rats exposed to 10 ppm, the rat study provided data for centrilobular hypertrophy in F1 offspring, a minimally adverse effect in a sensitive subpopulation (offspring) of the target organ (liver) that is sensitive to both inhalation and oral exposures. Further, the rat study provided data for a longer exposure period than the mouse study. Therefore, the study of Thornton et al. (2002) was chosen as the principal study for derivation of the intermediate-duration inhalation MRL, providing a critical effect level of 10 ppm as the LOAEL for centrilobular hypertrophy.

In the Thornton et al. (2002) study, groups of 30 male and female Sprague-Dawley rats were exposed to 0, 10, 100, or 1,100 ppm vinyl chloride, 6 hours/day for 10 weeks prior to mating and during a 3-week mating period. F_0 females were exposed during gestation and lactation. Absolute and relative mean liver weights were significantly increased at all exposure levels in F_0 males and in 100 and 1,100 ppm F_1 males. Slight centrilobular hypertrophy resulted in 1,100-ppm male and female F_0 and F_1 rats, 100 ppm male and female F_0 and F_1 rats, and in the 10 ppm F_0 and F_1 female rats. The incidence rate for centrilobular hypertrophy in the F_1 females was statistically significant.

An intermediate-duration inhalation MRL of 0.03 ppm was derived for vinyl chloride, based on a benchmark concentration of 5 ppm derived from the concentration-response data for hepatic centrilobular

hypertrophy in female Sprague-Dawley rats (Thornton et al. 2002). Using the Benchmark Dose Software
(BMDS version 1.3.2), incidence data were fit to eight dichotomous models to derive the lower
95% confidence limit (LEC_{10}) of a 10% extra risk for hepatic centrilobular hypertrophy, which 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 5 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 5 ppm was
duration-adjusted for intermittent exposure as follows:

$$LEC_{10ADJ} = 5 \text{ ppm x 6 hours } / 24 \text{ hours} = 1 \text{ ppm.}$$

The human equivalent concentration (LEC_{10HEC}) was calculated using EPA (1994g) methodology for an
extrarespiratory effect produced by a category 3 gas by multiplying the LEC_{10ADJ} by the ratio of the
blood:gas partition coefficients in animals and humans ($[H_{b/g}]_A / [H_{b/g}]_H$). The partition coefficient in rats
is greater than that in humans. Therefore, a default value of 1 is used for the ratio, resulting in a LEC_{10HEC}
of 1 ppm. The intermediate-duration inhalation MRL of 0.03 ppm was derived by dividing the LEC_{10HEC}
of 1 ppm in rats by an uncertainty factor of 30 (3 for species extrapolation with a dosimetric adjustment
and 10 for human variability).

In the absence of exposure level data, the human data base did not provide a suitable LOAEL or NOAEL
for derivation of a chronic-duration inhalation MRL. 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, the results of the Thornton et al. (2002)
study suggest that liver effects would occur at lower concentrations (10 ppm) than the reported testicular
effects. Though several other chronic-duration studies did report carcinogenicity in rats chronically
exposed to 5–250 ppm vinyl chloride (Drew et al. 1983; Lee et al. 1977a, 1978; Maltoni et al. 1981), they
did not report the incidence of noncancerous or precancerous histopathological lesions in the any tissue.
Therefore, no chronic-duration inhalation MRL was derived for vinyl chloride.

Oral MRLs

No studies of human adverse effects resulting from oral exposure to vinyl chloride were available.
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 (≥365 days) to vinyl chloride.

Chronic gavage doses of 30 mg/kg/day vinyl chloride in rats resulted in increased collagen deposition and skin thickness (Knight and Gibbons 1987). Decreased blood clotting time was observed in rats given 17 mg/kg/day (Feron et al. 1981). Doses of 6 mg/kg/day in female rats resulted in extensive hepatic necrosis and 100% early mortality (Feron et al. 1981). A number of effects were observed in rats given 1.7–1.8 mg/kg/day, including hepatocellular alterations (Feron et al. 1981), liver cell polymorphisms, and increased mortality (Til et al. 1983, 1991). The LOAEL of 1.7 mg/kg/day for liver cell polymorphism in both sexes and hepatic cysts in female rats was the lowest identified LOAEL and was associated with the lowest identified NOAEL for any chronic effect of 0.17 mg/kg/day. Liver cell polymorphism is not considered a precursor to carcinogenicity (Afzelius and Schoental 1967; Schoental and Magee 1957, 1959) and represents an effect to the target organ that is sensitive to both inhalation and oral exposures of vinyl chloride. For these reasons, the study of Til et al. (1983, 1991) was chosen as the critical study and the NOAEL of 0.17 mg/kg/day was chosen as the critical effect level for derivation of the chronic-duration oral MRL.

In the study of Til et al. (1983, 1991), groups of 50 or 100 male and female Wistar rats were administered vinyl chloride in the daily diet at 0, 0.46, 4.6, or 46 ppm for 149 weeks. Using measurements of evaporative loss of vinyl chloride from the diet, the study authors calculated the average oral intake of the combined sexes during the daily feeding periods to be 0, 0.018, 0.17, and 1.7 mg/kg/day for the 0, 0.49, 4.49, and 44.1ppm groups, respectively. Types and incidences of neoplastic and nonneoplastic liver lesions were determined at the end of the study. A LOAEL of 1.7 mg/kg/day was identified for significantly increased incidences of liver cell polymorphism in male and female rats and increased incidence of hepatic cysts in female rats. The NOAEL for nonneoplastic liver effects is 0.17 mg/kg/day. Other histopathologic lesions, described as hepatic foci of cellular alteration, were observed at all dose levels in female rats and in high-dose male rats, but were not used to derive an MRL because they are considered to be preneoplastic lesions.

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 female Wistar rats (Til et al. 1983, 1991) and application of the physiologically based pharmacokinetic (PBPK) model (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 exposure study were simulated in rats as 4-hour oral exposures with the NOAEL dose for liver effects of 0.17 mg/kg/day. The total amount of vinyl chloride metabolized in 24 hours per liter of liver volume was the rat internal dose metric used to determine the human oral dose that would result in an equivalent human internal dose. One kilogram of liver was assumed to have an approximate volume of 1 L. 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. The resulting human oral 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. The chronic-duration oral MRL of 0.003 mg/kg/day was derived by dividing the PBPK-modeled equivalent human NOAEL of 0.09 mg/kg/day for liver cell polymorphisms by an uncertainty factor of 30 (3 for species extrapolation with a dosimetric adjustment and 10 for human variability).

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