

reported at acute exposure concentrations as low as 15 ppm for 23 hours/day for 5 days (Short et al. 1977c), or at higher concentrations for shorter durations (Henck et al. 1979; Jackson and Conolly 1985; Jaeger et al. 1977a, 1977b; Reitz et al. 1980; Reynolds et al. 1980; Watanabe et al. 1980). The hepatotoxic effects of 1,1-dichloroethylene following intermediate or chronic inhalation exposure in animals are similar to those described above for acute exposure (Gage 1970; Lee et al. 1977; Plummer et al. 1990; Quast et al. 1986). Using a NOAEL of 5 ppm and a LOAEL of 15 ppm for mottled livers (with increased SGPT and alkaline phosphatase activity and decreased lipid content occurring at 48 ppm) in guinea pigs exposed to 1,1-dichloroethylene for 24 hours per day for 90 days (Prendergast et al. 1967), ATSDR (1994) derived an intermediate-duration MRL of 0.02 ppm. Two chronic inhalation studies of 1,1-dichloroethylene in animals have reported similar hepatic changes (Lee et al. 1977; Quast et al. 1986), including fatty changes in the liver, but the studies provide only suggestive evidence because of the poor presentation of the data. Similar effects on the liver are seen when 1,1-dichloroethylene is given orally, with acute effects at doses from 25 to 100 mg/kg including changes in liver serum enzymes, bile canalicular injury, and histological changes in liver cells (Andersen and Jenkins 1977; Jenkins and Andersen 1978; Kanz and Reynolds 1986; Kanz et al. 1991; Moslen et al. 1989). Chronic oral exposure studies in animals have identified minor hepatic effects at exposure levels between 9 and 20 mg/kg/day (Nitschke et al. 1983; Quast et al. 1983; Rampy et al. 1977); the chronic oral MRL of 0.009 mg/kg/day for 1,1-dichloroethylene is based on a LOAEL of 9 mg/kg/day for hepatocellular changes in rats exposed *in utero* and throughout adulthood (Quast et al. 1983).

Adverse effects have been observed in the kidneys of laboratory animals following acute, intermediate, and chronic inhalation exposure to 1,1-dichloroethylene. These effects are manifested as enzyme changes (decreases in kidney monooxygenase and epoxide hydrolase levels) (Oesch et al. 1983), tubular alterations (hemoglobinuria) (McKenna et al. 1978b), gross changes (increase in organ weight) (Henck et al. 1979; Quast et al. 1986), and histological changes (tubular swelling, degeneration, and necrosis) (Henck et al. 1979; Jackson and Conolly 1985; Lee et al. 1977; McKenna et al. 1978b; Prendergast et al. 1967; Reitz et al. 1980; Short et al. 1977c; Watanabe et al. 1980). Effects have been reported in animals exposed by inhalation acutely to 10–300 ppm or chronically to 25–75 ppm (Henck et al. 1979; Maltoni et al. 1985; Prendergast et al. 1967; Quast et al. 1986; Reitz et al. 1980; Short et al. 1977b; Watanabe et al. 1980). Similar renal effects have been reported following acute oral exposure to 200–400 mg/kg (Chieco et al. 1981; Jenkins and Andersen 1978), but no renal effects were noted in animals following intermediate oral exposure to 25 mg/kg/day, an exposure level that did not produce any adverse effects (Quast et al. 1983) or chronic oral exposure to 30 mg/kg/day, an exposure level that resulted in mild hepatic effects (Rampy et al. 1977)

Following inhalation exposure in mice, rats, and rabbits, 1,1-dichloroethylene has been shown to produce effects on the developing organism, but generally only at exposure levels (15–160 ppm) that also produced maternal effects (Murray et al. 1979; Short et al. 1977a); observed effects in the offspring included increased skeletal and soft tissue anomalies and fetal resorptions. One oral study of neural tube defects in human newborns after maternal exposure to 1,1-dichloroethylene via contaminated water has been published (NJDH 1992a, 1992b), but it provided only suggestive evidence of an association of 1,1-dichloroethylene with developmental effects. A single study reported no developmental effects from oral exposure of 40 mg/kg/day of 1,1-dichloroethylene in rats, an exposure level that produced no effects (on body weight gain, liver weight, food or water consumption) in the dams (Murray et al. 1979). A three-generation reproductive study in rats (Nitschke et al. 1983) reported no dose-related changes at up to 30 mg/kg/day in the limited pup indices that were investigated. Mild liver effects (hepatocellular fatty change) were reported in the adults at 9–30 mg/kg/day.

Chronic occupational exposure to 1,1-dichloroethylene was not associated with the occurrence of angiosarcoma in rubber-plant workers (Waxweiler 1981). Similarly, no association was found between occupational exposure and cancer mortality in 1,1-dichloroethylene production and polymerization plant workers (Ott et al. 1976). The carcinogenicity of 1,1-dichloroethylene in laboratory animals following inhalation exposure has been evaluated in intermediate and chronic studies with rats, mice, and Chinese hamsters (Hong et al. 1981; Lee et al. 1977, 1978; Maltoni et al. 1982; Quast et al. 1986; Rampy et al. 1977; Viola and Caputo 1977). Exposure concentrations of 1,1-dichloroethylene in these studies ranged from 10 to 200 ppm. Of the long-term inhalation bioassays conducted in laboratory animals to date, only the results of a study by Maltoni et al. (1985) in mice have provided some suggestive evidence of a carcinogenic effect associated with 1,1-dichloroethylene exposure.

No studies were located regarding cancer in humans after oral exposure to 1,1-dichloroethylene. A number of chronic studies in rats and mice have evaluated the carcinogenicity of 1,1-dichloroethylene by oral exposure (Maltoni et al. 1982, 1985; NTP 1982; Ponomarkov and Tomatis 1980; Quast et al. 1983; Rampy et al. 1977) at dose levels from 0.5 to 150 mg/kg/day; a trend toward increased incidence of malignant and nonmalignant tumors in 1,1-dichloroethylene-treated animals has been reported (NTP 1982; Ponomarkov and Tomatis 1980; Quast et al. 1983), but in the majority of cases, the increase in tumor frequencies have not been statistically significant. Reported tumor types have included meningiomas, mammary gland fibroadenomas and adenofibromas, and liver cell adenomas and carcinomas; tumor types have not been consistent across studies.

B.3 Mechanisms of Action

The toxicity of 1,1-dichloroethylene is the result of biotransformation reactions and not to the parent compound (Andersen et al. 1978, 1980; Jaeger et al. 1977a; Jones and Hathway 1978c). 1,1-Dichloroethylene is initially oxidized by the hepatic cytochrome P450 system, primarily CYP2E1, resulting in the formation of reactive and electrophilic products such as epoxides, acyl chlorides, and halogenated aldehydes, which are responsible for the liver toxicity via alkylation of macromolecules (Forkert et al. 1986). These reactive intermediates form GSH S-conjugates by the action of glutathione S-transferases located in the hepatic cytosol and microsomes. GSH S-conjugates that are primarily secreted from the hepatocytes into plasma and S-conjugates entering the circulation after reabsorption from the small intestine are ultimately delivered to the kidney where they undergo glomerular filtration (Dekant et al. 1989). In the kidney, GSH S-conjugates may be metabolized to the corresponding cysteine S-conjugate, which may be acetylated to form the corresponding mercapturic acid and excreted in the urine (Vamvakas and Anders 1990). However, cysteine S-conjugates may also be metabolized by β -lyase, an enzyme located in the renal proximal tubule cells; the resulting unstable thiols in turn yield electrophilic products whose interactions with macromolecules are associated with nephrotoxicity. In summary, GSH S-conjugate formation of nephrotoxic haloalkenes competes with hepatic cytochrome P450 for substrates. The relative extent of these reactions *in vivo* appears to be decisive for the initiation of adverse effects either in the liver (via oxidation products generated by P450 system) or in the kidney (via formation and renal processing of S-conjugates).

B.4 Health Guidelines

ATSDR (1994) did not derive an acute-duration inhalation MRL for 1,1-dichloroethylene.

ATSDR (1994) derived an intermediate-duration inhalation MRL of 0.02 ppm for 1,1-dichloroethylene based on a NOAEL of 5 ppm for hepatic effects in guinea pigs continuously exposed (24 hours/day, 7 days/week) to 1,1-dichloroethylene (Prendergast et al. 1967). The LOAEL was 15 ppm for mottled livers (with increased SGPT and alkaline phosphatase activity and decreased lipid content occurring at 45 ppm). The NOAEL was divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability) and a modifying factor of 3 was used to account for the close proximity of serious effects observed at the range of 10–25 ppm.

ATSDR (1994) did not derive a chronic-duration inhalation MRL for 1,1-dichloroethylene, citing inadequate chronic data. The chronic data of Quast et al. (1986) was not used because a serious LOAEL

of 15 ppm for developmental effects in rats and mice following acute exposure to 1,1-dichloroethylene was reported by Short et al. (1977a), which precluded derivation of a chronic-duration inhalation MRL.

ATSDR (1994) did not derive an acute-duration oral MRL for 1,1-dichloroethylene because the available suitable NOAEL of 40 mg/kg/day from a developmental toxicity study in rats (Murray et al. 1979) was too close to the 50 mg/kg single dose that was lethal in fasted rats (Andersen and Jenkins 1977).

ATSDR (1994) did not derive an intermediate-duration oral MRL for 1,1-dichloroethylene because only one study was available, in which the highest dose tested, 25 mg/kg/day, was a NOAEL (Quast et al. 1983).

ATSDR (1994) derived a chronic-duration oral MRL of 0.009 mg/kg/day based on a LOAEL of 9 mg/kg/day in rats for hepatocellular changes in a two-year exposure study (Quast et al. 1983), and using an uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for animal to human extrapolations, and 10 for intrahuman variability).

EPA (IRIS 2005) derived a chronic RfD of 0.05 mg/kg/day for 1,1-dichloroethylene based on benchmark dose analysis of hepatic effects (fatty liver) in a chronic study in rats (Quast et al. 1986) and an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for intrahuman variability).

EPA (IRIS 2005) derived a chronic RfC of 0.2 mg/m³ for 1,1-dichloroethylene based on benchmark concentration analysis of hepatic effects (fatty liver) in a chronic study in rats exposed to 25 or 75 ppm for 6 hours/day, 5 days/week (Quast et al. 1986) and an uncertainty factor of 30 (3 for animal to human extrapolation using dosimetric adjustment and 10 for intrahuman variability).

EPA classified 1,1-dichloroethylene in Group C, *possible human carcinogen*, under the 1986 cancer guidelines (EPA 1986). Under the draft revised guidelines for carcinogen risk assessment (EPA 1996), EPA concluded that 1,1-dichloroethylene exhibits suggestive evidence of carcinogenicity but not sufficient evidence to assess human carcinogenic potential following inhalation exposure in studies in rodents. EPA (IRIS 2005) has not performed quantitative assessments of carcinogenic potential for 1,1-dichloroethylene for either the oral or inhalation route.

NTP's Eleventh Report on Carcinogens (NTP 2005) does not list 1,1-dichloroethylene. The International Agency for Research on Cancer (IARC) (1999) notes that 1,1-dichloroethylene is *not classifiable as to its carcinogenicity to humans* (Group 3).

B.5 Derivation of Target-Organ Toxicity Dose (TTD) Values

The endpoints of concern for 1,1-dichloroethylene in this mixture are hepatic, renal, and developmental effects. For endpoints that are not the basis of the MRL, TTDS are derived below, using the methods described by ATSDR (2004). The derivations are based primarily on data provided in ATSDR (1994), and in particular, the LSE tables.

Inhalation TTDS

Following EPA (1994) methodology, the human equivalent concentration ($\text{NOAEL}_{\text{HEC}}$) for an extrarrespiratory effect produced by a category 3 gas, such as 1,1-dichloroethylene, is calculated by multiplying the duration-adjusted animal NOAEL by the ratio of the blood:gas partition coefficients in animals and humans $[(\text{Hb/g})_{\text{A}} / \text{Hb/g})_{\text{H}}]$. Since information on the partition coefficients in humans was not available (IRIS 2005), a default value of 1 is used for the ratio.

Hepatic Effects, Intermediate Inhalation: The intermediate inhalation MRL for 1,1-dichloroethylene is 0.02 ppm is based on hepatic effects.

Renal Effects, Intermediate Inhalation: Maltoni et al. (1985) identified a NOAEL of 10 ppm for renal effects in mice exposed 4 hours/day, 5 days/week for 52 weeks. This duration of this study is applicable to intermediate and chronic exposure. The NOAEL was duration-adjusted to 1.2 ppm for a continuous exposure scenario, and converted to a $\text{NOAEL}_{\text{HEC}}$ of 1.2 ppm using the method described previously under the heading Inhalation TTDS. Application of an uncertainty factor of 30 (3 for animal to human extrapolation using a dosimetric adjustment and 10 for intrahuman variability) yields a $\text{TTD}_{\text{RENAL}}$ of 0.04 ppm.

Developmental Effects, Intermediate Inhalation: Short et al. (1977a) reported incomplete ossification in the offspring of mice exposed to 15 ppm of 1,1-dichloroethylene for 23 hours/day throughout gestation. The LOAEL of 15 ppm was duration-adjusted to 14.4 ppm for a continuous exposure scenario, and converted to a $\text{LOAEL}_{\text{HEC}}$ of 14.4 ppm as described previously under the heading Inhalation TTDS. Application of an uncertainty factor of 300 (10 for use of a LOAEL, 3 for animal to human extrapolation using a dosimetric adjustment, and 10 for intrahuman variability) yields a $\text{TTD}_{\text{DEVEL}}$ of 0.05 ppm.

Hepatic Effects, Chronic Inhalation: A $\text{TTD}_{\text{HEPATIC}}$ of 0.007 ppm is derived from the intermediate MRL based on hepatic effects; see explanation in Chapter 3.

Renal Effects, Chronic Inhalation: Maltoni et al. (1985) identified a NOAEL of 10 ppm for renal effects in mice exposed 4 hours/day, 5 days/week for 52 weeks. This duration of this study is applicable to intermediate and chronic exposure. The NOAEL was duration-adjusted to 1.2 ppm for a continuous exposure scenario, and converted to a NOAEL_{HEC} of 1.2 ppm as described previously under the heading Inhalation TTDs. Application of an uncertainty factor of 30 (3 for animal to human extrapolation using a dosimetric adjustment and 10 for intrahuman variability) yields a TTD_{RENAL} of 0.04 ppm.

Developmental Effects, Chronic Inhalation: A TTD_{DEVEL} of 0.02 ppm is derived from the corresponding intermediate value; see explanation in Chapter 3.

Oral TTDs

Hepatic Effects, Intermediate Oral: EPA (IRIS 2005) reported NOAELs for hepatic effects of 40 mg/kg/day, 5 days/week (adjusted to 28.6 for continuous exposure) in the NTP (1982) 13-week study in rats and mice. The LOAELs for both species were 100 mg/kg/day. Applying an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for intrahuman variability), to the NOAEL, a TTD_{HEPATIC} of 0.3 mg/kg/day is estimated.

Renal Effects, Intermediate Oral: 1,1-Dichloroethylene has not been adequately tested for non-hepatic effects in intermediate-duration oral studies, but chronic oral studies did not report renal effects at dose levels that caused mild hepatic effects. Thus, there are no dose-response data suitable for derivation of a TTD. The chemical, however, caused renal effects in animals in acute oral studies, and in acute and intermediate-to-chronic inhalation studies. Thus, the weight of evidence for renal effects suggests that 1,1-dichloroethylene would cause renal damage at higher doses than tested in intermediate and chronic oral studies. The intermediate oral TTD_{HEPATIC} of 3.0 mg/kg/day can be adopted as an interim value for the TTD_{RENAL} for intermediate exposure.

Developmental Effects, Intermediate Oral: No developmental effects were reported in the only oral developmental toxicity study of 1,1-dichloroethylene available, which tested a single exposure level, 40 mg/kg/day, in rats on days 6–15 of gestation (Murray et al. 1979). This test was inadequate because the dose produced no effects in the dams (on body weight gain, liver weight, food, or water consumption). A three-generation reproductive study in rats (Nitschke et al. 1983) reported no dose-related changes at up to 30 mg/kg/day in the limited pup indices (number of pups/litter, postnatal survival and body weight) that were investigated. Mild liver effects (hepatocellular fatty change) were reported in the adults at 9–30 mg/kg/day. Although there are no data to indicate that this endpoint is affected by the oral route, the available studies are not fully adequate, and only one species, the rat, was tested. Data from the

inhalation route indicate that 1,1-dichloroethylene was developmentally toxic at exposures that also were maternotoxic, and that the mouse was the most sensitive species. Given the possibility that 1,1-dichloroethylene may also be developmentally toxic by the oral route, the intermediate oral $TTD_{HEPATIC}$ of 0.3 mg/kg/day can be adopted as an interim value for the TTD_{DEVEL} for chronic exposure.

Hepatic Effects, Chronic Oral: The chronic oral MRL of 0.009 mg/kg/day is based on hepatic effects.

Renal Effects, Chronic Oral: Chronic oral studies in animals did not report renal effects at dose levels of 1,1-dichloroethylene that caused mild hepatic effects, and this chemical has not been adequately tested for non-hepatic effects in intermediate-duration oral studies. Thus, there are no dose-response data suitable for derivation of a TTD. The chemical, however, caused renal effects in animals in acute oral studies, and in acute and intermediate-to-chronic inhalation studies. Thus, the weight of evidence suggests that 1,1-dichloroethylene may cause renal damage at higher doses than tested in intermediate and chronic oral studies. The chronic oral MRL of 0.009 mg/kg/day can be adopted as an interim value for the TTD_{RENAL} for chronic exposure.

Developmental Effects, Chronic Oral: No developmental effects were reported in the only oral developmental toxicity study of 1,1-dichloroethylene available, which tested a single exposure level, 40 mg/kg/day, in rats on days 6–15 of gestation (Murray et al. 1979). This test was inadequate because the dose produced no effects in the dams (on body weight gain, liver weight, food, or water consumption). A three-generation reproductive study in rats (Nitschke et al. 1983) reported no dose-related changes at up to 30 mg/kg/day in the limited pup indices (number of pups/litter, postnatal survival and body weight) that were investigated. Mild liver effects (hepatocellular fatty change) were reported in the adults at 9–30 mg/kg/day. Although there are no data to indicate that this endpoint is affected by the oral route, the available studies are not fully adequate, and only one species, the rat, was tested. Data from the inhalation route indicate that 1,1-dichloroethylene was developmentally toxic at exposures that also were maternotoxic, and that the mouse was the most sensitive species. Given the possibility that 1,1-dichloroethylene may also be developmentally toxic by the oral route, the chronic oral MRL of 0.009 mg/kg/day can be adopted as an interim value for the TTD_{DEVEL} for chronic exposure.

Summary (TTDs for 1,1-Dichloroethylene)

Intermediate Inhalation TTDs:

$MRL_{HEPATIC} = 0.02$ ppm

$TTD_{RENAL} = 0.04$ ppm

$TTD_{DEVEL} = 0.05$ ppm

Chronic Inhalation TTDs:

$$\text{MRL}_{\text{HEPATIC}} = 0.007 \text{ ppm}$$

$$\text{TTD}_{\text{RENAL}} = 0.04 \text{ ppm}$$

$$\text{TTD}_{\text{DEVEL}} = 0.02 \text{ ppm}$$

Intermediate Oral TTDs:

$$\text{TTD}_{\text{HEPATIC}} = 0.3 \text{ mg/kg/day}$$

$$\text{TTD}_{\text{RENAL}} = 0.3 \text{ mg/kg/day}$$

$$\text{TTD}_{\text{DEVEL}} = 0.3 \text{ mg/kg/day}$$

Chronic Oral TTDs:

$$\text{MRL}_{\text{HEPATIC}} = 0.009 \text{ mg/kg/day}$$

$$\text{TTD}_{\text{RENAL}} = 0.009 \text{ mg/kg/day}$$

$$\text{TTD}_{\text{DEVEL}} = 0.009 \text{ mg/kg/day}$$

B.6 References

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APPENDIX C: BACKGROUND INFORMATION FOR TRICHLOROETHYLENE

This appendix was written based primarily on the Toxicological Profile for Trichloroethylene (ATSDR 1997). Primary references are cited for the reader's convenience in identifying pertinent studies. For additional information beyond what is presented here, the reader is referred to the Toxicological Profile.

C.1 Toxicokinetics

Studies of humans and rats indicate that inhaled trichloroethylene is rapidly and efficiently absorbed (ATSDR 1997). Initial rates of uptake are high, but decrease as steady state conditions are approached. Studies in humans indicated that 37–64% of inhaled trichloroethylene was absorbed. Ingested trichloroethylene is rapidly and completely absorbed by the gastrointestinal tract (ATSDR 1997). Fasted rats given gavage doses of 5–25 mg/kg trichloroethylene displayed peak blood concentrations within 6–10 minutes and absorbed >90% of the dose within 9 hours (D'Souza et al. 1985). Dermal absorption is rapid as indicated by observations of peak blood and exhaled air concentrations occurring within 5 minutes after a human subject immersed one hand in a trichloroethylene solution (ATSDR 1997). Once absorbed, trichloroethylene is widely distributed to organs throughout the body (including the developing fetus) and, due to its lipophilic properties, can accumulate in fat to a limited degree (ATSDR 1997). For example, 17 hours after a 6-hour/day, 4-day exposure of rats to 200 ppm, trichloroethylene was detected in perirenal fat and blood, but was not detected in other tissues (Savolainen et al. 1977).

Studies of humans and rodents indicate that inhaled trichloroethylene is eliminated from the body predominately in the urine as metabolites and, to a lesser degree, in exhaled breath as the parent chemical or other volatile metabolites such as trichloroethanol and carbon dioxide (ATSDR 1997). For example, following single or sequential daily exposures of human subjects to 50–380 ppm: 11 and 2% of the dose was eliminated as trichloroethylene and trichloroethanol in exhaled breath; 58% was eliminated as urinary metabolites; and 30% was unaccounted for (Monster et al. 1976, 1979). Trichloroethylene was detected in exhaled breath of humans 18 hours after exposure ended due to the relatively long elimination half-life of trichloroethylene in fatty tissue (3.5–5 hours) compared with other tissues. Following inhalation exposure to radiolabeled trichloroethylene, mice excreted 75% of radioactivity in the urine and 9% as carbon dioxide in exhaled breath (Stott et al. 1982). Similar patterns of elimination were observed in mice and rats following oral administration of trichloroethylene (Koizumi et al. 1986).

The principal urinary metabolites of trichloroethylene in humans and animals are trichloroethanol, trichloroethanol-glucuronide, and trichloroacetic acid (ATSDR 1997; Lash et al. 2000). Trichloro-

ethylene is principally metabolized in the liver, but metabolism can also occur in Clara cells of the lungs and in the kidney. The principal pathway in humans and animals involves initial oxidation catalyzed by CYP isozymes (CYP2E1 and 2B1/2). It has been proposed that this reaction forms an epoxide intermediate (trichloroethylene oxide) that rapidly converts to chloral hydrate, but an alternative proposal indicates that chloral hydrate formation involves chlorine migration in an oxygenated trichloroethylene-CYP transition state (Lash et al. 2000). Chloral hydrate can be oxidized to trichloroacetic acid via chloral hydrate dehydrogenase or reduced to trichloroethanol via alcohol dehydrogenase. Trichloroacetic acid is a strong inducer of peroxisome proliferation and has been associated with hepatocarcinogenicity in rodents. Trichloroethanol can be conjugated with glucuronic acid via glucuronyl transferase to form trichloroethanol-glucuronide. Studies with human hepatic microsomes indicate that CYP2E1 is the predominant isozyme responsible for the initial steps in trichloroethylene metabolism, although there is evidence that CYP isozymes induced by phenobarbital (i.e., CYP2B1/2) may also be involved. At high exposure levels, enzymes involved in the main oxidative metabolic pathway can be saturated, leading to conjugation with GSH to produce S-(1,2-dichlorovinyl)glutathione (DCVG). DCVG is acted on by γ -glutamyl transferase to remove glutamine, and the glycine is removed by the action of dipeptidases to yield S-(1,2-dichlorovinyl)-L-cysteine (DCVC). Cleavage of the cysteine by β -lyase in the kidney can lead to intermediates with reactive thiol groups that can react with cellular macromolecules leading to renal cytotoxicity and carcinogenicity.

Minor metabolic pathways arising from the initial intermediate, trichloroethylene oxide, or the trichloroethylene-CYP transition state, include: (1) transformation to dichloroacetic acid through a dichloroacetyl chloride intermediate (this path appears to be more important in rodents than humans); (2) hydrolytic dechlorinations to form formic acid and carbon monoxide; and (3) hydrolytic dechlorinations to form carbon dioxide via, sequentially, glyoxylic acid chloride, glyoxylic acid, and oxalic acid (ATSDR 1997; Lash et al. 2000). Dichloroacetic acid can be conjugated with GSH followed by sequential removal of glutamine and glycine to form dichlorovinyl-cysteine. Dichlorovinyl-cysteine can be transported to the kidney, where cleavage by β -lyase produces an intermediate with a reactive thiol group that can react with proteins and DNA leading to kidney cytotoxicity and kidney tumor development.

PBPK models have been developed for the disposition of trichloroethylene in mice, rats, and humans, including the prediction of target organ (e.g., liver, lung, brain, kidney) doses of biologically-active metabolites (ATSDR 1997; Clewell et al. 2000; Fisher 2000). The models are being used to aid assessment of noncancer and cancer human health risks based on rodent exposure-response data (Barton and Clewell 2000; Rhomberg 2000).

C.2 Health Effects

Results from studies of trichloroethylene-exposed humans and animals indicate that the primary targets for trichloroethylene's noncarcinogenic toxicity are the nervous system, liver, heart, and kidneys (ATSDR 1997). The critical target (i.e., the target in which effects occur at the lowest exposure level) is expected to be the nervous system. Studies involving acute- or intermediate-duration inhalation or oral exposures have observed changes in neurobehavior in humans and animals at lower exposure levels (50–200 ppm) than those associated with liver effects (liver enlargement and cellular hypertrophy) and kidney effects (increased kidney weights and cytomegaly and karyomegaly in renal tubular epithelial cells) observed in animal studies (ATSDR 1997). For example, Stewart et al. (1970) found no changes in liver function tests in humans who were exposed to 200 ppm for 7 hours/day for 5 days and reported experiencing headache, fatigue, and drowsiness. Effects on the heart appear to be restricted to cardiac arrhythmias due to trichloroethylene sensitization of the heart to epinephrine and other catecholamines, and appear to be a high exposure/dose phenomenon. Additional endpoints of concern are immunological effects and effects on the developing organism. There is suggestive but inconclusive evidence in humans for these effects (ATSDR 1997). In animal studies, evidence of immunotoxicity (Aranyi et al. 1986; Sanders et al. 1982) and evidence of developmental toxicity (ATSDR 1997; Dorfmueller et al. 1979; Isaacson et al. 1989) has also been reported from both these routes of exposure.

Occupational exposure to trichloroethylene has been widespread due to its use in dry cleaning, for metal degreasing, and as a solvent for oils and resins. A recent article (Wartenberg et al. 2000) reviewed over 80 published papers and letters on the epidemiology of cancer in groups of people occupationally exposed to trichloroethylene. Elevated relative risks, ranging from 1.1 to 2.0, have been reported for kidney cancer, liver cancer, and non-Hodgkin's lymphoma in several cohorts of workers repeatedly exposed to trichloroethylene in workplace air (see Wartenberg et al. 2000). Workers in these studies, however, were also exposed to other solvents (e.g., tetrachloroethylene). Accurate adjustment for this and other confounding factors is not possible from the available data. Wartenberg et al. (2000) concluded that there is "moderate support" for a causative relationship between exposure to trichloroethylene and cancer using Hill's criteria of causation. Reflecting this assessment, IARC (1995) earlier concluded that the human evidence for trichloroethylene carcinogenicity is limited.

Chronic-duration animal studies have shown that cancer can be caused by inhalation or oral exposure to trichloroethylene, but do not point to a single target organ for increased tumor incidence. Carcinogenic responses have been observed in the liver, kidney, testes, lymphatic system, and lung, but the observed responses are not consistent across studies of different species and strains of animals (ATSDR 1997).

In general, carcinogenic responses to trichloroethylene are thought to involve trichloroethylene metabolites (Bull 2000; Green 2000; Lash et al. 2000). This hypothesis is supported by observations that mice appear to be uniquely susceptible to trichloroethylene-induced liver and lung tumors and display higher rates of trichloroethylene metabolism than do rats. In contrast, rats appear to be uniquely susceptible to trichloroethylene-induced kidney damage and tumors. Based on its review of available data, ATSDR (1997) concluded that there is adequate evidence to indicate that trichloroethylene is carcinogenic in mice, that the evidence for trichloroethylene carcinogenicity in rats is equivocal, and that further study is required to determine whether or not the processes that induce liver cancer in mice also operate in the human liver. EPA-supported monographs on trichloroethylene health risks have been recently published and are being used to develop updated EPA health risk characterizations for trichloroethylene (Scott and Cogliano 2000).

C.3 Mechanisms of Action

Like other solvents, nervous system effects from trichloroethylene are likely to involve disruption of neural membranes by the parent chemical, but trichloroethanol is also involved. In support of this hypothesis, Mikiskova and Mikiska (1966) reported that intraperitoneally administered trichloroethanol was 5–6 times more effective than trichloroethylene in altering electrophysiological variables associated with central nervous system depression in guinea pigs. Blain et al. (1992) found that effects on electrophysiological endpoints in rabbits exposed to trichloroethylene by inhalation correlated better with blood levels of trichloroethanol than trichloroethylene.

Metabolism of trichloroethylene is expected to produce cytotoxic and carcinogenic metabolites, including trichloroacetic acid, dichloroacetic acid, chloral hydrate, and 2-chloroacetaldehyde (ATSDR 1997). Drinking water administration of trichloroacetic acid to rodents has produced carcinogenic changes in the liver that are associated with the proliferation of peroxisomes. Reactive oxygen species produced by peroxisomes are thought to be involved in a sequence of DNA damage, cytotoxicity, regenerative cell growth, and tumor development. Phenobarbital pretreatment and induction of hepatic CYP isozymes appear to be associated with enhancement of acute trichloroethylene hepatotoxicity in rodents (Allemand et al. 1978; Moslen et al. 1977; Nakajima et al. 1990), providing further support for the idea that metabolites are responsible for the hepatotoxicity of trichloroethylene. Trichloroethylene-induced liver cancer and peroxisomal proliferation have been associated with rapid metabolism of trichloroethylene to trichloroacetic acid in mice, but this metabolic pathway appears to be limited in rats and humans. Dichloroacetic acid has also been shown to produce liver cancer in mice, but its hepatocarcinogenicity has been hypothesized to involve some other, as yet unspecified, mechanism of action. The mouse liver

Renal Effects, Intermediate Oral: Tucker et al. (1982) reported a NOAEL of 217 mg/kg/day and a LOAEL of 393 mg/kg/day in male mice for renal effects (elevated urinary protein and ketone) from 6 months of exposure to trichloroethylene in the drinking water. Application of an uncertainty factor of 100 (10 for animal to human extrapolations, 10 for intrahuman variability) results in a TTD_{RENAL} of 2 mg/kg/day.

Immunological Effects, Intermediate Oral: There are some indications of immune abnormalities in limited studies of populations exposed to contaminated drinking water, but the evidence is inconclusive (ATSDR 1997). Sanders et al. (1982) reported a NOAEL of 200 mg/kg/day and a LOAEL of 400 mg/kg/day of trichloroethylene for suppressed humoral and cellular immunity in mice exposed in the drinking water for 4–6 months. To the NOAEL of 200 mg/kg/day, an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for intrahuman variability) was applied to give the TTD_{IMMUNO} of 2 mg/kg/day.

Neurological Effects, Intermediate Oral: ATSDR (1997) has developed an acute-duration (14 days or less) MRL of 0.2 mg/kg/day for trichloroethylene based on a LOAEL for behavioral changes in mice administered 50 mg/kg/day by gavage for 7 days starting at 10 days of age; effects were seen at 60 days of age. This LOAEL is similar to the LOAEL of 37 mg/kg/day in an intermediate-duration developmental study for behavioral changes at 60 days of age and a decreased number of myelinated fibers in the hippocampus at 21 days of age in rats exposed through their dams (ATSDR 1997). The dams were exposed to trichloroethylene in their drinking water starting 14 days before mating and throughout gestation and lactation. ATSDR (1997), however, also mentions a LOAEL of 23.3 mg/kg/day for behavioral effects and decreased brain myelination in adult rats exposed to trichloroethylene in their drinking water for 4 weeks, followed by 2 weeks of nonexposure, and 2 more weeks of exposure (Isaacson et al. 1990). Chronic oral studies in rats and mice have reported overt signs of neurotoxicity, but have only examined higher dose levels. Using the LOAEL of 23.3 mg/kg/day for adult rats and an uncertainty factor of 300 (10 for LOAEL, 10 for species extrapolation, and 3 for human variability because a potentially sensitive subpopulation has been tested) would result in a TTD_{NEURO} of 0.08 mg/kg/day.

Developmental Effects, Intermediate Oral: The lowest oral LOAEL for developmental effects reported by ATSDR (1997) is 37 mg/kg/day for behavioral changes at 60 days of age and a decreased number of myelinated fibers in the hippocampus at 21 days of age in rats exposed through their dams (Isaacson and Taylor 1989). The dams were exposed to trichloroethylene in their drinking water starting 14 days before mating and throughout gestation and lactation. To this LOAEL an uncertainty factor of 1,000 (10 for the

use of a LOAEL, 10 for species extrapolation, and 10 for human variability because pups represent a sensitive subpopulation) was applied, resulting in a TTD_{DEVEL} of 0.1 mg/kg/day.

Hepatic Effects, Chronic Oral: Chronic studies of trichloroethylene toxicity have failed to report hepatic effects, even at doses as high as 1,000 mg/kg/day. The highest subchronic NOAEL that is still below available subchronic LOAEL values is from the study of Stott et al. (1982) who exposed B6C3F1 mice to trichloroethylene by gavage for 5 days/week for 3 weeks. The study identified a NOAEL of 250 mg/kg/day and a LOAEL of 500 mg/kg/day for increased hepatic DNA content/gram of tissue. This NOAEL value and an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for intrahuman variability) were used to derive the TTD of 3 mg/kg/day for hepatic effects.

Renal Effects, Chronic Oral: Chronic studies of trichloroethylene have reported kidney effects in rats and mice (NCI 1976; NTP 1988, 1990). The lowest LOAEL was 500 mg/kg/day, 5 days/week; a NOAEL was not defined. Tucker et al. (1982) reported a NOAEL of 217 mg/kg/day and a LOAEL of 393 mg/kg/day in male mice for renal effects (elevated urinary protein and ketone) from 6 months of exposure to trichloroethylene in the drinking water. Application of an uncertainty factor of 100 (10 for animal to human extrapolations, 10 for intrahuman variability) results in a TTD_{RENAL} of 2 mg/kg/day.

Immunological Effects, Chronic Oral: Sanders et al. (1982) reported a NOAEL of 200 mg/kg/day and a LOAEL of 400 mg/kg/day of trichloroethylene for suppressed humoral and cellular immunity in mice exposed in the drinking water for 4–6 months. To the NOAEL of 200 mg/kg/day, an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for intrahuman variability) was applied to give the TTD_{IMMUNO} of 2 mg/kg/day. The duration of exposure was judged sufficient to be applicable to chronic as well as to intermediate exposure.

Neurological, Chronic Oral: ATSDR (1997) has developed an acute-duration (14 days or less) MRL of 0.2 mg/kg/day for trichloroethylene based on a LOAEL for behavioral changes in mice administered 50 mg/kg/day by gavage for 7 days starting at 10 days of age; effects were seen at 60 days of age. This LOAEL is similar to the LOAEL of 37 mg/kg/day in an intermediate-duration developmental study for behavioral changes at 60 days of age and a decreased number of myelinated fibers in the hippocampus at 21 days of age in rats exposed through their dams (ATSDR 1997). The dams were exposed to trichloroethylene in their drinking water starting 14 days before mating and throughout gestation and lactation. ATSDR (1997), however, also mentions a LOAEL of 23.3 mg/kg/day for behavioral effects and decreased brain myelination in adult rats exposed to trichloroethylene in their drinking water identified by Isaacson et al. (1990). Chronic oral studies in rats and mice have reported overt signs of neurotoxicity,

but have only examined higher dose levels. Using the LOAEL of 23.3 mg/kg/day for adult rats and an uncertainty factor of 300 (10 for LOAEL, 10 for species extrapolation, and 3 for human variability because a potentially sensitive subpopulation has been tested) would result in a TTD_{NEURO} of 0.08 mg/kg/day. Because of the short duration of exposure (4 weeks, followed by 2 weeks of nonexposure, and 2 more weeks of exposure), and the lack of investigation of dose-response relationships for sensitive neurological endpoints in chronic oral studies, an additional uncertainty factor of 10 for extrapolation to chronic exposure is appropriate. The total uncertainty factor of 3,000 results in a TTD_{NEURO} of 0.008 mg/kg/day.

Developmental Effects, Chronic Oral: The lowest oral LOAEL for developmental effects reported by ATSDR (1997) is 37 mg/kg/day for behavioral changes at 60 days of age and a decreased number of myelinated fibers in the hippocampus at 21 days of age in rats exposed through their dams (Isaacson and Taylor 1989). The dams were exposed to trichloroethylene in their drinking water starting 14 days before mating and throughout gestation and lactation. To this LOAEL an uncertainty factor of 300 (10 for the use of a LOAEL, 10 for species extrapolation, and 3 for human variability because pups represent a sensitive subpopulation) was applied, resulting in a TTD_{DEVEL} of 0.1 mg/kg/day.

Summary (TTDs for Trichloroethylene)

Intermediate Inhalation TTDs:

$TTD_{HEPATIC} = 1$ ppm
 $TTD_{RENAL} = 0.7$ ppm
 $TTD_{IMMUNO} = 0.1$ ppm
 $MRL_{NEURO} = 0.1$ ppm
 $TTD_{DEVEL} = 3$ ppm

Chronic Inhalation TTDs:

$TTD_{HEPATIC} = 0.3$ ppm
 $TTD_{RENAL} = 0.7$ ppm
 $TTD_{IMMUNO} = 0.03$ ppm
 $MRL_{NEURO} = 0.03$ ppm
 $TTD_{DEVEL} = 1$ ppm

Intermediate Oral TTDs:

$TTD_{HEPATIC} = 3$ mg/kg/day
 $TTD_{RENAL} = 2$ mg/kg/day
 $TTD_{IMMUNO} = 2$ mg/kg/day
 $MRL_{NEURO} = 0.08$ mg/kg/day
 $TTD_{DEVEL} = 0.1$ mg/kg/day

Chronic Oral TTDs:

$TTD_{\text{HEPATIC}} = 3 \text{ mg/kg/day}$

$TTD_{\text{RENAL}} = 2 \text{ mg/kg/day}$

$TTD_{\text{IMMUNO}} = 2 \text{ mg/kg/day}$

$MRL_{\text{NEURO}} = 0.008 \text{ mg/kg/day}$

$TTD_{\text{DEVEL}} = 0.1 \text{ mg/kg/day}$

C.6 References

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APPENDIX D: BACKGROUND INFORMATION FOR VINYL CHLORIDE

This appendix was written based primarily on the Toxicological Profile for Vinyl Chloride (ATSDR 2004b). Primary references are cited for the reader's convenience in identifying pertinent studies. For additional information beyond what is presented here, the reader is referred to the Toxicological Profile.

D.1 Toxicokinetics

Both human and animal studies have indicated a rapid absorption of vinyl chloride following inhalation exposure. For example, young adult male volunteers exposed to vinyl chloride concentrations of 2.9, 5.1, 11.7, or 23.5 ppm by gas mask for 6 hours (Krajewski et al. 1980) retained approximately 42% of the inhaled dose, regardless of concentration. Similar results have been reported in animal studies, and have been incorporated into PBPK models for vinyl chloride (described below). While no studies of the absorption of vinyl chloride in humans are available, vinyl chloride is rapidly and completely absorbed following oral exposure in animals (Feron et al. 1981; Watanabe et al. 1976a; Withey 1976), with peak blood levels being reached 10–20 minutes after a single gavage dose (Withey 1976).

Studies of the disposition of vinyl chloride in humans are not available for any route of exposure. In animals, vinyl chloride is rapidly distributed following inhalation exposure, with highest levels in the kidney and brain (Bolt et al. 1976; Buchter et al. 1977). Unless metabolism is inhibited, vinyl chloride does not appear to deposit or accumulate for long periods within the body (Buchter et al. 1977). A similar pattern is seen following oral exposure (Watanabe et al. 1976a). Vinyl chloride can cross the placenta following absorption (Ungvary et al. 1978).

The major metabolic pathway of vinyl chloride involves oxidation by mixed-function oxidases, specifically CYP2E1, to form a highly reactive epoxide intermediate, 2-chloroethylene oxide, which spontaneously rearranges to form 2-chloroacetaldehyde (Guengerich et al. 1979, 1981; Gwinner et al. 1983; Laib 1982). These intermediates are detoxified mainly through conjugation with GSH catalyzed by glutathione S-transferase enzymes. The conjugated products are excreted in urine as substituted cysteine derivatives and include thiodiglycolic acid, S-formyl-methylcysteine, and N-acetyl-S-(2-hydroxy-ethyl)cysteine (Bolt et al. 1980; Hefner et al. 1975). Metabolism is very rapid, and is saturable (Bolt et al. 1977; Buchter et al. 1980; Filser and Bolt 1979; Watanabe et al. 1976a) at high exposure levels (~250 ppm by inhalation, and between 1 and 100 mg/kg by oral exposure).

Regardless of route of exposure, vinyl chloride is rapidly eliminated in the urine, primarily as metabolites. However, at very high concentrations when metabolism becomes saturated, elimination in the expired air may become a relevant pathway (Watanabe and Gehring 1976; Watanabe et al. 1976b).

Numerous PBPK models for vinyl chloride exposure have been published, for both inhalation and oral exposure; modeled species include rats, mice, hamsters, and humans. Several different modifications of these models have been used to estimate human cancer risk following vinyl chloride inhalation (Clewell et al. 1995, 2001; Reitz et al. 1996). The PBPK model described in Clewell et al. (2001) and on IRIS (2005) was used to derive the chronic-duration MRL, based on exposures from the Til et al. (1983, 1991) dietary study. For additional details on PBPK models, see ATSDR (2004b).

D.2 Health Effects

Following both inhalation and oral exposure, the most sensitive effects of vinyl chloride are on the liver. Numerous studies of workers exposed to atmospheres containing vinyl chloride have reported hepatic changes, including hepatic proliferation, hepatomegaly, fibrosis, and hepatocellular degeneration (Berk et al. 1975; Falk et al. 1974; Gedigke et al. 1975; Ho et al. 1991; Jones and Smith 1982; Lilis et al. 1975; Liss et al. 1985; Marsteller et al. 1975; NIOSH 1977; Popper and Thomas 1975; Suciu et al. 1975; Tamburro et al. 1984; Vihko et al. 1984). While exposure characterization in these studies has been limited, effects have been reported at exposure levels ranging from 1 to 2,300 ppm (Ho et al. 1991; Suciu et al. 1975). The incidence and severity of the effects generally correlate well with the duration of exposure (Gedigke et al. 1975; Lilis et al. 1975; NIOSH 1977). Studies of humans following oral exposure to vinyl chloride are not available. Animal studies have identified noncancer hepatic effects beginning at inhaled concentrations of 10 ppm (Thornton et al. 2002) or oral doses of 1.7 mg/kg/day (Til et al. 1983, 1991). Chronic exposure to vinyl chloride by inhalation has also been demonstrated to result in hepatic cancer, specifically angiosarcoma (Fortwengler et al. 1999; Fox and Collier 1977; Infante et al. 1976; Jones et al. 1988; Rinsky et al. 1988; Weber et al. 1981; Wong et al. 1991; Wu et al. 1989).

Although evidence has been presented indicating that members of communities with nearby vinyl chloride polymerization facilities have significantly greater incidences of some forms of developmental toxicity, these studies failed to demonstrate a statistically significant correlation between the developmental toxicity and either parental occupation or proximity to the facility (Edmonds et al. 1978; Infante et al. 1976; Rosenman et al. 1989; Theriault et al. 1983). A number of inhalation studies have examined the effects of vinyl chloride exposure on pregnancy outcome in animals; results of these studies generally indicate that vinyl chloride produces adverse developmental effects (John et al. 1977, 1981;

Mirkova et al. 1978; Sal'nikova and Kotsovskaya 1980; Ungvary et al. 1978), but only at concentrations that are also toxic to maternal animals. For example, John et al. (1977, 1981) reported a NOAEL of 50 ppm and a LOAEL of 500 ppm for maternal toxicity and delayed ossification in fetuses of mice and rabbits exposed during organogenesis, while Ungvary et al. (1978) reported that rats exposed to 1,500 ppm showed changes in maternal relative liver weights as well as increased litter resorption. No studies of developmental effects following oral exposure in humans or animals were located.

The most commonly reported central nervous system effects of vinyl chloride inhalation in humans are ataxia or dizziness (Ho et al. 1991; Langauer-Lewowicka et al. 1983; Lilis et al. 1975; Marsteller et al. 1975; Spirtas et al. 1975; Suciú et al. 1963, 1975; Veltman et al. 1975), drowsiness or fatigue (Langauer-Lewowicka et al. 1983; Spirtas et al. 1975; Suciú et al. 1963, 1975; Walker 1976), loss of consciousness (NIOSH 1977), and/or headache (Langauer-Lewowicka et al. 1983; Lilis et al. 1975; Marsteller et al. 1975; NIOSH 1977; Spirtas et al. 1975; Suciú et al. 1963, 1975; Veltman et al. 1975). Other central nervous system effects that have been reported by vinyl chloride workers include euphoria and irritability (Suciú et al. 1963, 1975), visual and/or hearing disturbances (Marsteller et al. 1975), nausea (Marsteller et al. 1975; Spirtas et al. 1975), memory loss (Langauer-Lewowicka et al. 1983; Suciú et al. 1963, 1975), and nervousness and sleep disturbances (Langauer-Lewowicka et al. 1983; Suciú et al. 1963). Central nervous system tests revealed pyramidal signs and cerebellar disturbances in some exposed subjects (Langauer-Lewowicka et al. 1983). Reliable estimates of exposure levels producing these effects were not available, but they generally occur only at fairly high (>4,000 ppm) acute exposure levels (Lester et al. 1963; Patty et al. 1930). Chronic inhalation exposure to lower levels of vinyl chloride may result in the development of a peripheral neuropathy characterized by tingling (paresthesia) in the extremities (Lilis et al. 1975; Sakabe 1975; Spirtas et al. 1975; Suciú et al. 1963, 1975; Veltman et al. 1975; Walker 1976), numbness in the fingers (Lilis et al. 1975; Sakabe 1975), weakness (Langauer-Lewowicka et al. 1983; Suciú et al. 1963, 1975), depressed reflexes (NIOSH 1977), warmth in the extremities (Suciú et al. 1963, 1975), and pain in the fingers (Sakabe 1975). However, it is unclear whether some of these symptoms are associated with tissue anoxia due to vascular insufficiency, or whether they represent the direct toxic effects of vinyl chloride on peripheral nerves. Animal studies of inhaled vinyl chloride have also reported changes to nervous tissues, but generally only at very high (>5,000 ppm) exposure levels. No studies of neurological effects following oral exposure in humans or animals were located.

Workers exposed to vinyl chloride have shown a number of immunological effects, including “vinyl chloride disease” characterized by a syndrome consisting of Raynaud's phenomenon, acroosteolysis, joint and muscle pain, enhanced collagen deposition, stiffness of the hands, and scleroderma-like skin changes; these changes are thought to be immunologic in nature. Sera obtained from patients with varying degrees

of severity of symptoms of vinyl chloride disease demonstrate a close correlation between the disease severity and the extent of the immunologic abnormality (Grainger et al. 1980; Langauer-Lewowicka et al. 1976; Ward 1976), although these symptoms have been reported without immunological findings (Black et al. 1986; Ostlere et al. 1992). In workers with severe clinical signs, there have also been reports of an increased incidence of B-cell proliferation, hyperimmunoglobulinemia (Ward 1976), cryoglobulinemia (Grainger et al. 1980), and complement activation (Grainger et al. 1980; Ward 1976). Exposed workers were also found to have significantly increased percentages of lymphocytes compared to controls (Fučić et al. 1995, 1997). Evidence of a structurally altered immunoglobulin G (IgG) has been obtained, and it has been proposed that vinyl chloride or a metabolite binds to IgG (Grainger et al. 1980). No studies of immunological effects of oral exposure to vinyl chloride in humans or animals were located.

The most compelling evidence for the carcinogenic potential of vinyl chloride in humans comes from the cluster of reports of greater than expected incidences of angiosarcoma of the liver in workers occupationally exposed to vinyl chloride (Byren et al. 1976; Creech and Johnson 1974; Fox and Collier 1977; Infante et al. 1976; Jones et al. 1988; Laplanche et al. 1992; Lee et al. 1996; Monson et al. 1975; Pirastu et al. 1990; Rinsky et al. 1988; Simonato et al. 1991; Teta et al. 1990; Theriault and Allard 1981; Waxweiler et al. 1976; Weber et al. 1981; Wong et al. 1991; Wu et al. 1989). Angiosarcoma of the liver is considered to be a very rare type of cancer (25–30 cases/year in the United States) (Heath et al. 1975). However, approximately 30 years after the introduction of vinyl chloride for use in the industrial production of PVC, it became apparent that workers exposed to high levels of vinyl chloride had an unusually high incidence of this type of tumor. Other liver tumors, including hepatocellular carcinoma and cholangiocellular carcinoma, have also been associated with occupational exposure to vinyl chloride (Cheng et al. 1999; Du and Wang 1998; Lelbach 1996; Saurin et al. 1997; Ward et al. 2001; Weihrauch et al. 2000; Wong et al. 2002, 2003). Based on this information, vinyl chloride is considered to be a carcinogen in humans by both IARC and EPA (IARC 1987; IRIS 2005). It has been suggested that inhalation exposure to vinyl chloride in humans may also result in increased incidences of cancers of the brain and central nervous system, respiratory tract, connective and other soft tissues, and lymphatic/hematopoietic systems (for additional detail, see ATSDR 2004b); however, the evidence for these tumors is considerably less convincing than the evidence for hepatic tumors. No data on the carcinogenicity of vinyl chloride following oral exposure in humans were located. Studies in animals by both the inhalation and oral routes have confirmed the carcinogenic properties of vinyl chloride (Adkins et al. 1986; Bi et al. 1985; Drew et al. 1983; Froment et al. 1994; Lee et al. 1977, 1978; Maltoni et al. 1981; Suzuki 1983).

D.3 Mechanisms of Action

The majority of the proposed mechanisms of vinyl chloride toxicity involve the metabolism of the compound by CYP2E1 to a reactive intermediate, such as 2-chloroethylene oxide or 2-chloroacetaldehyde. The intermediary metabolites bind to macromolecules in the body. 2-Chloroethylene oxide is believed to bind primarily to DNA and RNA, whereas 2-chloroacetaldehyde binds primarily to proteins (Bolt et al. 1986; Guengerich and Watanabe 1979; Guengerich et al. 1979, 1981; Kappus et al. 1976; Watanabe et al. 1978a, 1978b). Modification of proteins may result in toxicity, as is believed to occur in vinyl chloride-induced liver lesions, or may alter their antigenicity, possibly resulting in the autoimmune responses associated with vinyl chloride exposure. The mechanisms resulting in the neurological effects of vinyl chloride are not well-characterized.

Many studies have characterized the mutation profile associated with DNA adducts formed by the reactive metabolites of vinyl chloride (Akasaka et al. 1997; Chiang et al. 1997; Dosanjh et al. 1994; Guichard et al. 1996; Matsuda et al. 1995; Pandya and Moriya 1996; Zhang et al. 1995; Zielinski and Hergenbahn 2001). Four primary cyclic DNA etheno-adducts are formed by the reactive metabolites of vinyl chloride (1,N⁶-ethenoadenine, 3,N⁴-ethenocytosine, N^{2,3}-ethenoguanine, and 1,N²-ethenoguanine). These adducts can produce base-pair (i.e., purine-to-purine or pyrimidine-to-pyrimidine exchange) transitions during transcription (Cullinan et al. 1997; Pandya and Moriya 1996; Singer 1996; Singer et al. 1987). The role of etheno-adducts in the carcinogenesis of vinyl chloride has been recently reviewed (Albertini et al. 2003, Barbin 1998, 2000; Kielhorn et al. 2000; Whysner et al. 1996). DNA crosslinks can also be formed because chloroacetaldehyde is bifunctional (Singer 1996). The mechanisms for clastogenic effects of vinyl chloride exposure were examined by Fučić et al. (1990); since chromatid and bichromatid breaks most frequently occurred in the terminal A, B, and C group chromosomes, these investigators suggested that vinyl chloride or its metabolites might interact with specific sites along the chromosome.

D.4 Health Guidelines

ATSDR (2004b) derived an acute inhalation MRL for vinyl chloride of 0.5 ppm based on a NOAEL of 50 ppm for developmental effects in mice exposed 7 hours/day on gestational days 6–15 (John et al. 1977, 1981). The next higher exposure level, 500 ppm, produced mortality in the dams. The NOAEL of 50 ppm for intermittent exposure (7 hours/day) was converted to a continuous exposure (50 ppm x 7/24 = 15 ppm), and then converted to a human equivalent concentration (HEC) as described in EPA guidelines (EPA 1994). Since the partition coefficient in mice is greater than that in humans, a default

value of 1 was used for the ratio and the duration-adjusted animal NOAEL (15 ppm) was equivalent to the NOAEL_{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 NOAEL_{HEC} to derive the MRL of 0.5 ppm.

An intermediate-duration inhalation MRL of 0.03 ppm was derived for vinyl chloride, based on a lower 95% confidence limit (LEC₁₀) 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 LEC₁₀ 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 LEC₁₀ value of 3 ppm, derived from the simplest model (Weibull), was selected as the point of departure for calculating an intermediate-duration inhalation MRL. The LEC₁₀ of 3 ppm was duration-adjusted from intermittent (6 hours/day) to continuous exposure (3 ppm x 6/24 = 0.8 ppm). Following EPA (1994) methodology, the human equivalent concentration (LEC_{10HEC}) for an extrapulmonary effect produced by a category 3 gas was calculated by multiplying the duration-adjusted animal LEC₁₀ 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 was used for the ratio and the duration-adjusted animal LEC₁₀ (0.8 ppm) was equivalent to the LEC_{10HEC} (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 LEC_{10HEC} to derive the MRL of 0.03 ppm.

ATSDR (2004b) did not derive a chronic inhalation MRL for vinyl chloride because of the absence of a suitable LOAEL or NOAEL for derivation.

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 (ATSDR 2004b).

ATSDR (2004b) derived a chronic oral MRL of 0.003 mg/kg/day 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 PBPK model used to derive EPA's RfD (Clewell et al. 2001; IRIS 2005). 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 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.

EPA (IRIS 2005) derived a chronic RfD of 0.003 mg/kg/day for vinyl chloride using the same principal study, critical effect (hepatic changes), NOAEL, and PBPK model as described above for the chronic oral MRL for vinyl chloride. A total uncertainty factor of 30 (3 for extrapolating from animals to humans using a dose metric conversion and 10 for human variability) was applied.

EPA (IRIS 2005) derived a chronic RfC of 0.1 mg/m³ for vinyl chloride based on hepatic effects using a route-to-route extrapolation of the oral data from Til et al. (1983, 1991) using the Clewell et al. (2001) PBPK model. A total uncertainty factor of 30 (3 for extrapolating from animals to humans using a dose metric conversion and 10 for human variability) was applied.

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* (IRIS 2005). 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 (IRIS 2005). 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 8.8×10^{-6} per $\mu\text{g}/\text{m}^3$ for continuous lifetime exposure from birth was estimated by EPA (IRIS 2005) based on the incidence of liver tumors observed in rats in the inhalation study by Maltoni et al. (1981). An inhalation unit risk of 4.4×10^{-6} per $\mu\text{g}/\text{m}^3$ for continuous lifetime exposure during adulthood was also estimated by EPA (IRIS 2005). An oral slope factor for continuous lifetime exposure from birth was estimated by EPA (IRIS 2005) to be 1.5 per mg/kg/day based on the incidence of liver tumors in rats in the study by Feron et al. (1981). An oral slope factor of 7.5×10^{-1} per mg/kg/day for continuous lifetime exposure during adulthood was also estimated by EPA (IRIS 2005).

IARC (1987) lists vinyl chloride in Group 1 (*carcinogenic to humans*) based on sufficient evidence of carcinogenicity in humans and animals. NTP's Eleventh Report on Carcinogens (NTP 2005) reports that

vinyl chloride is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity in humans.

D.5 Derivation of Target-Organ Toxicity Dose (TTD) Values

The endpoints of concern for vinyl chloride in this mixture are hepatic, renal, immunological, and developmental. TTDS are derived below for endpoints that are not the basis of the MRL, using the methods described by ATSDR (2004a). The derivations are based primarily on data provided in ATSDR (2004b), and in particular, the LSE tables.

Inhalation TTDs

Following EPA (1994) methodology, the human equivalent concentration ($\text{NOAEL}_{\text{HEC}}$) for an extrapulmonary 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 $[(\text{Hb/g})_{\text{A}} / (\text{Hb/g})_{\text{H}}]$. Since the partition coefficients in rodents are greater than in humans (see ATSDR 2004b), a default value of 1 is used for the ratio.

Hepatic Effects, Intermediate Inhalation: The intermediate MRL for vinyl chloride is 0.03 ppm, based on hepatic effects.

Renal Effects, Intermediate Inhalation: Bi et al. (1985) identified a NOAEL of 10 ppm and a LOAEL of 100 ppm for increased kidney weights in rats exposed to vinyl chloride for 6 hours/day, 6 days/week for 12 months. This NOAEL, relevant to both intermediate and chronic duration exposure, was duration-adjusted to 2.1 ppm for continuous exposure, and a $\text{NOAEL}_{\text{HEC}}$ of 2.1 ppm was calculated as described previously under the heading Inhalation TTDs. Application of an uncertainty factor of 30 (3 for animal to human extrapolation using a dosimetric adjustment and 10 for intrahuman variability) yields a $\text{TTD}_{\text{RENAL}}$ of 0.07 ppm.

Immunological Effects, Intermediate Inhalation: Bi et al. (1985) reported a LOAEL of 10 ppm for increased spleen weight in rats exposed to vinyl chloride for 6 hours/day, 6 days/week for 6 months. The LOAEL was duration-adjusted to 2.1 ppm for a continuous exposure scenario, and a $\text{LOAEL}_{\text{HEC}}$ of 2.1 was calculated as described previously under the heading Inhalation TTDs. Application of an uncertainty factor of 300 (3 for animal to human extrapolation using a dosimetric adjustment, 10 for intrahuman variability, and 10 for use of a LOAEL) would yield a $\text{TTD}_{\text{IMMUNO}}$ of 0.007 ppm. However, this would fall below the MRL; the MRL of 0.03 ppm will be adopted as the $\text{TTD}_{\text{IMMUNO}}$ for vinyl chloride.

Developmental Effects, Intermediate Inhalation: The acute MRL of 0.5 ppm is based on developmental effects in mice exposed to 50 ppm of vinyl chloride for 7 hours/day (15 ppm NOAEL_{HEC}) during organogenesis, and is adopted as the TTD_{DEVEL} for intermediate exposure.

Hepatic Effects, Chronic Inhalation: A TTD_{HEPATIC} of 0.01 ppm was derived from the intermediate MRL; see explanation in Chapter 3.

Renal Effects, Chronic Inhalation: Bi et al. (1985) identified a NOAEL of 10 ppm and a LOAEL of 100 ppm for increased kidney weights in rats exposed to vinyl chloride for 6 hours/day, 6 days/week for 12 months. This NOAEL, relevant to both intermediate and chronic duration exposure, was duration-adjusted to 2.1 ppm for continuous exposure, and a NOAEL_{HEC} of 2.1 ppm was calculated as described previously under the heading Inhalation TTDs. Application of an uncertainty factor of 30 (10 for animal to human extrapolations and 10 for intrahuman variability) yields a TTD_{RENAL} of 0.07 ppm.

Immunological Effects, Chronic Inhalation: A TTD_{IMMUNO} of 0.01 ppm was derived from the intermediate TTD for that endpoint; see explanation in Chapter 3.

Developmental Effects, Chronic Inhalation: A TTD_{DEVEL} of 0.2 ppm was derived from the intermediate value, using the approach explained in Chapter 3.

Oral TTDs

Hepatic Effects, Intermediate and Chronic Oral: No appropriate data were available for intermediate-duration oral exposure. The chronic oral MRL of 0.003 mg/kg/day based on liver effects is adopted as a conservative value for intermediate exposure.

Renal Effects, Intermediate and Chronic Oral: No reports of renal effects following oral exposure to vinyl chloride were located.

Immunological Effects, Intermediate and Chronic Oral: No reports of immunological effects following oral exposure to vinyl chloride were located.

Developmental Effects, Intermediate and Chronic Oral: No studies of developmental effects following oral exposure to vinyl chloride were located.

Summary (TTDs for Vinyl Chloride)

Intermediate Inhalation TTDs:

 $MRL_{HEPATIC} = 0.03 \text{ ppm}$ $TTD_{RENAL} = 0.07 \text{ ppm}$ $TTD_{IMMUNO} = 0.03 \text{ ppm}$ $TTD_{DEVEL} = 0.5 \text{ ppm}$

Chronic Inhalation TTDs:

 $TTD_{HEPATIC} = 0.01 \text{ ppm}$ $TTD_{RENAL} = 0.07 \text{ ppm}$ $TTD_{IMMUNO} = 0.01 \text{ ppm}$ $TTD_{DEVEL} = 0.2 \text{ ppm}$

Intermediate and Chronic Oral TTDs:

 $MRL_{HEPATIC} = 0.003 \text{ mg/kg/day (chronic)}$, adopted as $TTD_{HEPATIC}$ for intermediate $TTD_{RENAL} = \text{Not derived, no data}$ $TTD_{IMMUNO} = \text{Not derived, no data}$ $MRL_{DEVEL} = \text{Not derived, no data}$

D.6 References

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