

APPENDIX A: BACKGROUND INFORMATION FOR CHLOROFORM

This appendix was written based primarily on the Toxicological Profile for Chloroform (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.

A.1 Toxicokinetics

Following inhalation exposure, absorption of chloroform appears to be rapid and extensive. While numerous studies in humans have demonstrated that inhaled chloroform is absorbed into the blood and extrapulmonary tissues, a quantitative measurement of absorption fraction or rate has not been reported (Aggazzotti et al. 1993; Cammann and Hübner 1995; Levesque et al. 1994; Nashelsky et al. 1995). Animal toxicity studies of inhaled chloroform have provided evidence for absorption, but quantitative estimates have not been reported (see ATSDR 1997). A study of absorption of an oral dose of ¹³C-labeled chloroform (0.5 grams in a gelatin capsule) in volunteers revealed that absorption was both rapid and complete, with nearly 100% of the dose absorbed and peak blood levels in 1 hour after exposure (Fry et al. 1972). Experiments in mice, rats, and monkeys indicate that oral doses (up to 60 mg/kg) of ¹⁴C-labeled chloroform in olive oil were almost completely absorbed, as indicated by an 80–96% recovery of radioactivity in expired air, urine, and carcass (Brown et al. 1974; Taylor et al. 1974). Absorption in mice and monkeys was rapid; the peak blood levels were reached 1 hour after oral administration of 60 mg/kg chloroform in olive oil. Oral absorption of chloroform from an aqueous vehicle has been shown to be more rapid than from an oil vehicle (Pereira 1994; Withey et al. 1983), although absorption is complete by both routes.

Due to its lipophilic character, chloroform accumulates to a greater extent in tissues of high lipid content. Following absorption, the relative concentrations of chloroform in various tissues generally decrease as follows: adipose tissue > brain > liver > kidney > blood. The chloroform levels in seven patients who died after excessive administration during chloroform anesthesia were: brain, 372–480 mg/kg; lungs, 355–485 mg/kg; and liver, 190–275 mg/kg tissue wet weight (Gettler and Blume 1931); chloroform levels in patients under anesthesia who died from other causes were: brain, 120–182 mg/kg; lungs, 92–145 mg/kg; and liver, 65–88 mg/kg tissue wet weight. After whole-body autoradiography to study the distribution of inhaled ¹⁴C-labeled chloroform in mice, most of the radioactivity was found in fat immediately after exposure, while the concentration of radioactivity in the liver increased during the postanesthetic period, most likely due to covalent binding to lipid and protein in the liver (Cohen and Hood 1969). Radioactivity from ¹⁴C-labeled chloroform was detected in the placenta and fetuses of mice

shortly after inhalation exposure (Danielsson et al. 1986). Studies of distribution of chloroform in humans following oral exposure are not available. Following oral exposure in animal studies, distribution of chloroform appears to be similar to following inhalation exposure, with the primary concentrations in lipophilic tissues (Brown et al. 1974; Pfaffenberger et al. 1980; Taylor et al. 1974).

Metabolism of chloroform occurs primarily by cytochrome p-450-dependent pathways, with CYP2E1 (ethanol-inducible) being the primary isozyme responsible (Wang et al. 1994). The initial reaction results in the formation of a reactive intermediate, which gives off hydrochloric acid to form phosgene, which is then free to react with cellular macromolecules (including GSH, proteins, and nucleic acids) or conjugate with water to form carbon dioxide and hydrochloric acid (Ade et al. 1994; Branchflower et al. 1984; Pohl et al. 1981; Smith et al. 1984; Stevens and Anders 1981). On the basis of pharmacokinetic results obtained in rats and mice exposed to chloroform by inhalation, and of enzymatic studies in human tissues *in vitro*, *in vivo* metabolic rate constants ($V_{\max}C = 15.7$ mg/hour/kg, $K_m = 0.448$ mg/L) were defined for humans (Corley et al. 1990). Interspecies differences in the rate of chloroform conversion were observed in mice, rats, and squirrel monkeys, with species differences in metabolism being highly dose-dependant. The conversion of chloroform to carbon dioxide was highest in mice (80%) and lowest in squirrel monkeys (18%) (Brown et al. 1974). Similarly, chloroform metabolism was calculated to be slower in humans than in rodents.

Regardless of the route of exposure, chloroform is excreted from the body primarily as expired carbon dioxide, although at higher concentrations, where metabolism is saturated, appreciable levels of parent compound may be exhaled as well (Brown et al. 1974; Corley et al. 1990; Taylor et al. 1974). Only small amounts of chloroform or metabolites are excreted in the urine (Brown et al. 1974; Mink et al. 1986). The calculated biological half-time for chloroform in humans following inhalation exposure is on the order of 8 hours (Gordon et al. 1988). Nearly all of a single inhaled dose of chloroform is eliminated within 48 hours in rats and mice (Corley et al. 1990). In humans given a single oral dose of chloroform, most of the dose was exhaled as parent compound and carbon dioxide (Fry et al. 1972). Very little was excreted in the urine. Results in mice and rats given single oral doses of chloroform (Brown et al. 1974; Mink et al. 1986; Taylor et al. 1974) were similar to those seen from single inhalation exposures.

Numerous PBPK models exist for chloroform in both humans and animals. While a detailed discussion of these models is beyond the scope of this document (a complete discussion of the models can be found in ATSDR 1997), the models, in general, are structured as multicompartment models with up to eight compartments, not including arterial and venous blood, and inputs for inhalation, oral, and dermal exposure. Models have been developed in mice, rats, and humans (Chinery and Gleason 1993; Corley

et al. 1990; Gearhart et al. 1993; McKone 1993; Reitz et al. 1990) and have been used to predict blood and tissue concentrations for multiple routes of exposure.

A.2 Health Effects

Hepatic Effects: Chloroform inhalation has been demonstrated to induce hepatic effects in both humans and animals. Acute, high-dose inhalation exposure to chloroform, such as in chloroform anesthesia, has been shown to cause jaundice, necrosis, liver enlargement and tenderness, and increased sulfobromophthalein retention in humans (Lunt 1953; Royston 1924; Smith et al. 1973; Townsend 1939; Whitaker and Jones 1965). Workers exposed to 14–400 ppm chloroform for 1–6 months developed toxic hepatitis and other effects including jaundice, nausea, and vomiting, without fever (Phoon et al. 1983). Toxic hepatitis (with hepatomegaly, enhanced serum glutamic pyruvic transaminase [SGPT] and serum glutamic oxaloacetic transaminase [SGOT] activities, and hypergammaglobulinemia) was observed in workers exposed chronically to 2–205 ppm chloroform (Bomski et al. 1967). Exposure of swimmers to lower levels of chloroform (18–24 ppm) did not result in detectable hepatic changes (Aiking et al. 1994). Animal studies of inhaled chloroform have also identified hepatic effects as a sensitive target, including altered liver enzymes, fatty changes, centrilobular degranulation, and necrosis (Baeder and Hofmann 1988; Culliford and Hewitt 1957; Deringer et al. 1953; Ikatsu and Nakajima 1992; Kylin et al. 1963; Lundberg et al. 1986; Schwetz et al. 1974; Torkelson et al. 1976).

The liver is a primary target of oral chloroform toxicity in humans, with some evidence that suggests that the damage may be reversible (Wallace 1950). Hepatic injury occurred in patients within 1–3 days following chloroform ingestion (Piersol et al. 1933; Schroeder 1965; Storms 1973), which included jaundice and liver enlargement and tenderness, as well as several altered blood biochemical parameters (increased SGOT, SGPT, and lactate dehydrogenase (LDH) activities and increased bilirubin levels). At autopsy, fatty degeneration and extensive centrilobular necrosis were observed in one fatal case (Piersol et al. 1933). Increased sulfobromophthalein retention indicated impaired liver function in an individual who ingested 21 mg/kg/day chloroform in a cough medicine for 10 years (Wallace 1950); the changes resolved after exposure was discontinued. Biochemical tests indicate that liver function in male and female humans was not affected by the use of mouthwash providing 0.96 mg/kg/day chloroform for ≤5 years (De Salva et al. 1975). The liver is also a target organ for oral chloroform toxicity in animals. Following acute oral doses of 34 mg/kg or greater, hepatic effects included increased liver weight, fatty changes, and necrosis (Jones et al. 1958; Larson et al. 1994b; Moore et al. 1982; Munson et al. 1982; Nakajima et al. 1995; Ruddick et al. 1983; Thompson et al. 1974; Wang et al. 1994, 1995). A NOAEL of 26 mg/kg/day (4 days) was identified in mice (Larson et al. 1994b). Liver effects in animals have been

reported in numerous oral studies of intermediate duration (Chu et al. 1982a; Eschenbrenner and Miller 1945; Larson et al. 1995b). Hepatic changes from intermediate-duration oral studies have included increased liver weight, increased levels of liver enzymes in serum, histological changes in hepatocytes, increased cell proliferation, and necrosis (Bull et al. 1986; Chu et al. 1982a, 1982b; Eschenbrenner and Miller 1945; Larson et al. 1995a, 1995b; Munson et al. 1982; Palmer et al. 1979; Pereira 1994). The early effects of oral chloroform exposure appear to be reversible (EPA 1980). The lowest intermediate duration exposure at which hepatic effects were seen was 30 mg/kg/day, with a NOAEL of 15 mg/kg/day, in the dog (Heywood et al. 1979). Results of chronic-duration oral studies have also identified hepatic effects as a sensitive effect of chloroform exposure, with effects including altered liver enzymes, hyperplasia, fatty liver, and fibrosis (Heywood et al. 1979; NCI 1976; Tumasonis et al. 1985, 1987); the lowest level at which chronic effects were seen was 15 mg/kg/day, the lowest exposure tested, in the dog (Heywood et al. 1979).

Renal Effects: Studies of the effects of inhaled chloroform in humans have not clearly identified the kidney as a sensitive target of chloroform toxicity, although acute high-dose exposure has been shown to result in renal effects (Aiking et al. 1994; Li et al. 1993; Royston 1924). Acute- and intermediate-duration animal inhalation studies have suggested renal effects of chloroform, particularly tubular cell proliferation and necrosis (Culliford and Hewitt 1957; Deringer et al. 1953; Larson et al. 1996; Torkelson et al. 1976). Acute, high-dose oral exposure to chloroform in humans results in albinuria, urinary casts, epithelial swelling, and fatty degeneration of kidney tubules (Piersol et al. 1933; Schroeder 1965), while similar urinary symptoms were seen in one subject who ingested 21 mg/kg/day chloroform in cough medicine for 10 years (Wallace 1950). No indications of renal effects were observed in humans who ingested estimated doses of 0.34–0.96 mg/kg/day chloroform in mouthwash for 5 years (De Salva et al. 1975). Acute, high-dose animal studies of oral chloroform exposure have also identified renal effects, including cytoplasmic vacuolization, swelling, and necrosis of proximal tubule cells (Chu et al. 1982a; Larson et al. 1993, 1995a, 1995b; Moore et al. 1982; Thompson et al. 1974). Intermediate-duration animal studies have also identified renal changes, including increased kidney weight, inflammation, renal cell proliferation, and proximal tubular necrosis (Chu et al. 1982a; Gulati et al. 1988; EPA 1980; Larson et al. 1994a, 1994b, 1995a, 1995b; Lipsky et al. 1993; Munson et al. 1982; Palmer et al. 1979). The lowest LOAEL and NOAEL reported by ATSDR (1997) for renal effects of intermediate duration oral exposure are 6.0 and 17.4 mg/kg/day for increased foci of regenerating renal proximal tubules in mice given chloroform in their drinking water for 3 weeks (Larson et al. 1995a). In chronic oral studies, no definite renal effects were observed in rats exposed to ≤ 200 mg/kg/day or mice exposed to < 477 mg/kg/day time-weighted average (TWA) (Heindel et al. 1995; Jorgenson et al. 1985; NCI 1976;

Roe et al. 1979). In dogs, however, fat deposition in renal glomeruli was observed at a dose of 30 mg/kg/day chloroform for 7.5 years, but not at 15 mg/kg/day (Heywood et al. 1979).

Immunological Effects: Some evidence of immunological effects from inhalation exposure to chloroform has been reported in humans, for which a LOAEL of 2 ppm for splenomegaly was identified in humans exposed occupationally for 1–4 years (Bomski et al. 1967). A 6-month inhalation study in animals did not detect splenic changes in rats exposed to 25 ppm of chloroform (Torkelson et al. 1976). Information on potential immunological effects in humans exposed orally to chloroform was not located. Acute and intermediate duration oral studies have identified reduced lymphocyte counts in rats (Chu et al. 1982a), and depression of humoral immunity (assessed as antibody-forming cells/spleen) and at higher doses, cell-mediated immunity (delayed hypersensitivity) in mice (Munson et al. 1982). A LOAEL of 50 mg/kg/day of chloroform for depression of humoral immunity was identified in mice treated for 14 and for 90 days, with effects being more marked at the shorter duration (Munson et al. 1982).

Neurological Effects: The neurological effects of high-dose inhaled chloroform are well-documented; chloroform was once used as an anesthetic in humans. Levels of 3,000–30,000 ppm were used to induce anesthesia (Featherstone 1947; Smith et al. 1973; Whitaker and Jones 1965), while concentrations of \approx 40,000 ppm, if continued for several minutes, could result in death (Featherstone 1947). Concentrations $<$ 1,500 ppm are insufficient to induce anesthesia, while concentrations of 1,500–2,000 ppm cause light anesthesia (Goodman and Gilman 1980). Exhaustion was reported in 10 women exposed to \geq 22 ppm chloroform during intermediate- and chronic-duration occupational exposures (Challen et al. 1958). Chronic exposure to chloroform concentrations \geq 77 ppm caused exhaustion, lack of concentration, depression, or irritability in 9 of 10 occupationally exposed women. A case report of an individual addicted to chloroform inhalation for \approx 12 years reported psychotic episodes, hallucinations and delusions, and convulsions (Heilbrunn et al. 1945). Neurological effects have been reported in case reports of humans who ingested very high doses of chloroform (Piersol et al. 1933; Schroeder 1965; Storms 1973) and in oral studies in animals (Balster and Borzelleca 1982; Bowman et al. 1978; Jones et al. 1958; Kanada et al. 1994; Landauer et al. 1982), with overt signs generally seen only at very high exposure levels. The NOAEL and LOAEL for neurobehavioral effects were 31.1 mg/kg/day (up to 90 days) and 100 mg/kg/day (60 days), as determined by a battery of behavioral tests in mice administered the chemical by gavage in aqueous emulphor (Balster and Borzelleca 1982).

Developmental Effects: Data on the developmental effects of chloroform in humans following inhalation exposure are not available, and the single study of chloroform-associated developmental effects following exposure to chloroform through disinfected drinking water is confounded by co-exposure to numerous

other substances (Kramer et al. 1992). Animal studies of chloroform inhalation have consistently identified developmental effects, including growth retardation, decreased crown-rump length, altered ossification, cleft palate, and fetal resorption (Baeder and Hofmann 1988; Murray et al. 1979; Newell and Dilley 1978; Schwetz et al. 1974), generally beginning at 30 ppm chloroform or greater. Oral exposure of rats to 316 mg/kg/day or greater on days 6–15 of gestation has resulted in decreased pup body weight and increased resorptions, but not in increased frequency of malformations (Ruddick et al. 1983; Thompson et al. 1974). The NOAEL and LOAEL for decreased fetal weight were 50 and 126 mg/kg/day on gestation days 6–15 in the rat (Thompson et al. 1974). A serious LOAEL of 63 mg/kg/day on days 6–18 of gestation for abortion in rabbits was reported by ATSDR (1997), but this LOAEL is not well supported because it was from the preliminary range-finding portion of a study with only 5 rabbits/group, with no report of results in controls, and in which abortion occurred in both controls and treated animals in the main part of the study (Thompson et al. 1974). The potential developmental toxicity of intermediate oral exposure to chloroform is even less well characterized in animals. No neurobehavioural effects were reported in offspring of mice treated with 31.1 mg/kg/day for 6–10 weeks (Burkhalter and Balster 1979). In a continuous breeding study in mice, F₁ males had increased epididymal weights and degeneration of the epididymal epithelium and F₁ females had increased liver weight and hepatocellular degeneration at 41 mg/kg/day for 105 days (Gulati et al. 1988).

Cancer: No studies were located regarding cancer in humans or animals after inhalation exposure to chloroform. Epidemiology studies suggest an association between cancer in humans and the consumption of chlorinated drinking water, but the results are not conclusive at this time (Alavanja et al. 1978; Cantor et al. 1978; Ijsselmuiden et al. 1992; McGeehin et al. 1993; Young et al. 1981; Zierler et al. 1988). Such an association implicates chloroform because chloroform is a known animal carcinogen and is the predominant trihalomethane in chlorinated drinking water; however, it is important to note that some of the many chemicals produced in the process of water chlorination are highly mutagenic and/or carcinogenic, and human data have not been able to adequately control for these co-exposures. Evidence of chloroform carcinogenicity is mixed following intermediate-duration oral exposure in animals, with studies suggesting that following exposures of <52 weeks to <250 mg/kg/day, no increase in tumor formation is noted (Klaunig et al. 1986; Stoner et al. 1986) but with one study reporting that a 30-day exposure to 594 mg/kg/day in mice resulted in increased formation of hepatomas (Eschenbrenner and Miller 1945). Chloroform has been shown to be carcinogenic in numerous chronic animal studies, resulting in tumors of the liver and kidney (Dunnick and Melnick 1993; Jorgenson et al. 1985; NCI 1976; Roe et al. 1979; Tumasonis et al. 1987). In general, studies of exposure levels of 60 mg/kg/day or greater resulted in increased incidence of tumors, while carcinogenicity at lower exposure levels was less clear.

A.3 Mechanisms of Action

Chloroform is widely distributed to many tissues of the body in laboratory animals and, presumably, in humans; however, many studies have demonstrated that chloroform does not tend to accumulate in the body for extended periods. Chloroform may accumulate to some degree in the body fat stores; however, it quickly partitions out of the fat and is excreted by the normal routes and mechanisms. The liver (primary) and kidneys (secondary) are considered to be the target organs for chloroform toxicity in both humans and laboratory animals.

Chloroform is largely metabolized in many tissues (particularly the liver and kidney) to carbon dioxide in humans and animals (Brown et al. 1974; Corley et al. 1990; Fry et al. 1972). Chloroform metabolism is catalyzed by cytochrome P450, isozyme CYP2E1 in particular, initiating an oxidative cleavage of the C-H bond producing trichloromethanol. Trichloromethanol is unstable and is rapidly transformed to phosgene (COCl_2). Phosgene may react with water to form CO_2 , which can be exhaled by the lung or excreted in the urine as carbonate or bicarbonate, and hydrochloric acid. Phosgene can also react with other molecules such as cysteine, deplete hepatic GSH (Docks and Krishna 1976; Pohl et al. 1981), and form adducts with microsomal proteins (Corley et al. 1990).

Chloroform toxicity can be attributed to the presence of both the parent compound and the formation of phosgene in most instances of toxicosis. High doses of inhaled chloroform have been reported to cause death (due to respiratory depression), ataxia, narcosis, and central nervous system depression, and are due to the direct effects of the parent compound. Lower doses of chloroform in the air, feed, or water, or administered by gavage, with variable exposure times, may induce toxicity due to the presence of the parent compound or to production of phosgene during metabolism. It appears that the metabolite is responsible for hepatocellular damage, resulting in the ultimate leakage of hepatic enzymes (SGPT, SGOT, GGT, etc.) into the serum and cellular damage/necrosis. The accumulation of chloroform in the renal cortex of mice with the subsequent metabolism to phosgene most likely contributes to the renal toxicity of chloroform seen in male mice. Tubular necrosis, calcification, nephritis, increased kidney weight, alterations in Na/K excretion, and other cellular anomalies were observed in response to one or both of these toxicants.

A.4 Health Guidelines

ATSDR (1997) derived an acute-duration inhalation MRL of 0.1 ppm for chloroform, based on a NOAEL of 3 ppm for hepatic changes in mice exposed for 7 days and an uncertainty factor of 30 (3 for extrapolation from animals to humans and 10 for human variability).

ATSDR (1997) derived an intermediate-duration inhalation MRL of 0.05 ppm for chloroform, based on a LOAEL of 14 ppm in human workers for vomiting and toxic hepatitis. The LOAEL of 14 ppm was divided by an uncertainty factor of 100 (10 for the use of a LOAEL and 10 for human variability) and a modifying factor of 3 (insufficient diagnostic data to determine the seriousness of hepatotoxic effects) to arrive at the MRL of 0.05 ppm.

ATSDR (1997) derived a chronic-duration inhalation MRL of 0.02 ppm for chloroform, based on a LOAEL of 2 ppm for hepatic effects (hepatomegaly, fatty liver, jaundice) in chloroform-exposed workers. The LOAEL of 2 ppm was divided by an uncertainty factor of 100 (10 for use of a LOAEL and 10 for human variability) to arrive at the MRL of 0.02 ppm.

ATSDR (1997) derived an acute-duration oral MRL of 0.3 mg/kg/day for chloroform, based on a NOAEL of 26 mg/kg/day in the drinking water for 4 days for hepatic effects in mice (Larson et al. 1994b) and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

ATSDR (1997) derived an intermediate-duration oral MRL of 0.1 mg/kg/day for chloroform, based on a NOAEL of 15 mg/kg/day for hepatic effects in dogs dosed with chloroform in a capsule 1 time/day, 6 days/week for 6 weeks (Heywood et al. 1979) and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

ATSDR (1997) derived a chronic-duration oral MRL of 0.01 mg/kg/day for chloroform, based on a LOAEL of 15 mg/kg/day for hepatic effects in dogs dosed with chloroform 6 days/week for 7.5 years (Heywood et al. 1979) and an uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).

EPA (IRIS 2005) has not derived a reference concentration (RfC) for chloroform.

EPA (IRIS 2005) derived a reference dose (RfD) of 0.01 mg/kg/day for chloroform, based on a LOAEL of 15 mg/kg/day for hepatic effects in dogs dosed with chloroform 6 days/week for 7.5 years (Heywood et al. 1979) and an uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).

Under the 1986 U.S. EPA Guidelines for Carcinogen Risk Assessment, chloroform has been classified as Group B2, *probable human carcinogen*, based on "sufficient evidence" of carcinogenicity in animals (IRIS 2005). Under U.S. EPA's Proposed Guidelines for Carcinogen Risk Assessment (EPA 1996), chloroform is *likely to be carcinogenic to humans* by all routes of exposure under high-exposure conditions that lead to cytotoxicity and regenerative hyperplasia in susceptible tissues (IRIS 2005).

Chloroform is *not likely to be carcinogenic to humans* by any route of exposure under exposure conditions that do not cause cytotoxicity and cell regeneration. Due to the mode of action of chloroform carcinogenicity (repeated cellular damage and regenerative hyperplasia), the RfD of 0.01 mg/kg/day can be considered protective against cancer risk for chloroform.

NTP's Eleventh Report on Carcinogens (NTP 2005) states that chloroform is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity in experimental animals. IARC (1999) classifies chloroform as *possibly carcinogenic to humans* (Group 2B) based on inadequate evidence in humans and sufficient evidence in experimental animals.

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

The endpoints of concern for chloroform in this mixture are hepatic, renal, immunological, neurological, and developmental. 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 (1997), and in particular, the Levels of Significant Exposure (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 chloroform, 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 1997), a default value of 1 is used for the ratio.

Hepatic Effects, Intermediate Inhalation: The intermediate inhalation MRL for chloroform is 0.05 ppm based on hepatic effects.

Renal Effects, Intermediate Inhalation: Larson et al. (1996) identified a NOAEL of 1.99 ppm and a LOAEL of 10 ppm for nephropathy and enlarged nuclei of the proximal tubule cells of male mice exposed to chloroform for 6 hours/day, 7 days/week, for 13 weeks. The NOAEL of 1.99 ppm was duration-adjusted to 0.5 ppm for a continuous exposure scenario, and converted to a $\text{NOAEL}_{\text{HEC}}$ of 0.5 ppm as described in the Toxicological Profile. Application of an uncertainty factor of 30 (3 for animal to human extrapolations and 10 for intrahuman variability) would yield a $\text{TTD}_{\text{RENAL}}$ of 0.02 ppm. However, as this would fall below the MRL, the intermediate-duration MRL of 0.05 ppm will be adopted as the $\text{TTD}_{\text{RENAL}}$ for chloroform.

Immunological Effects, Intermediate Inhalation: The Toxicological Profile for Chloroform (ATSDR 1997) lists only one intermediate-duration inhalation study that evaluated immunological effects of chloroform (Torkelson et al. 1976). However, the study did not identify an effect level for immunological effects, making it unsuitable for use in TTD derivation. The chronic study of Bomski et al. (1967) identified immunological effects as sensitive effects in humans following chronic exposure, resulting in a chronic TTD_{IMMUNO} equal to the chronic MRL. The intermediate TTD_{IMMUNO} is therefore set at 0.05 ppm, equal to the intermediate MRL.

Neurological Effects, Intermediate Inhalation: Adequate studies of the neurological effects of chloroform following intermediate-duration inhalation exposure are not available. Chronic exposure to chloroform has resulted in neurological effects, including dizziness, fatigue, somnolence, insomnia, and anorexia, in workers exposed to 13.49 ppm chloroform for 1–15 years (Li et al. 1993). The chronic TTD_{NEURO} , based on these effects, is 0.03 ppm. As this is below the intermediate-duration MRL and no intermediate-duration studies are available to derive an intermediate-duration TTD_{NEURO} , the intermediate-duration MRL of 0.05 ppm will be adopted as the TTD_{NEURO} .

Developmental Effects, Intermediate Inhalation: Both Schwetz et al. (1974) and Baeder and Hoffman (1988) reported less serious developmental LOAELs of 30 ppm in rats exposed for 7 hours/day during organogenesis. The LOAEL was adjusted to 8.75 ppm for a continuous exposure scenario, and converted to a $NOAEL_{HEC}$ of 8.75 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) would yield a TTD_{DEVEL} of 0.03 ppm. However, as this would fall below the MRL, the intermediate-duration MRL of 0.05 ppm will be adopted as the TTD_{RENAL} for chloroform.

Hepatic Effects, Chronic Inhalation: The chronic inhalation MRL for chloroform is 0.02 ppm based on hepatic effects.

Renal Effects, Chronic Inhalation: Larson et al. (1996) identified a $NOAEL$ of 1.99 ppm and a LOAEL of 10 ppm for nephropathy and enlarged nuclei of the proximal tubule cells of male mice exposed to chloroform for 6 hours/day, 7 days/week, for 13 weeks. The $NOAEL$ of 1.99 ppm was duration-adjusted to 0.5 ppm for a continuous exposure scenario, and converted to a $NOAEL_{HEC}$ of 0.5 ppm as described previously under the heading Inhalation TTDs. Application of an uncertainty factor of 30 (3 for animal to human extrapolations using a dosimetric adjustment) and 10 for intrahuman variability) yields a TTD_{RENAL} of 0.02 ppm.

Immunological Effects, Chronic Inhalation: In the same study from which the MRL was derived for hepatic effects, splenomegaly was reported at the same exposure level, 2 ppm, as hepatic effects in humans exposed to chloroform by inhalation for 1–4 years (Bomski et al. 1967). The MRL of 0.02 ppm is therefore applicable for immunological effects as well.

Neurological Effects, Chronic Inhalation: Li et al. (1993) reported numerous neurological effects, including dizziness, fatigue, somnolence, insomnia, and anorexia, in workers exposed to 13.49 ppm chloroform for 1–15 years. The LOAEL of 13.49 ppm was duration-adjusted for a continuous exposure scenario, resulting in a LOAEL_{HEC} of 3.21 ppm. An uncertainty factor of 100 (10 for use of a LOAEL and 10 for intrahuman variability) was applied to derive the TTD_{NEURO} of 0.03 ppm.

Developmental Effects, Chronic Inhalation: Both Schwetz et al. (1974) and Baeder and Hofmann (1988) reported less serious developmental LOAELs of 30 ppm in rats exposed for 7 hours/day during organogenesis. The LOAEL was adjusted to 8.75 ppm for a continuous exposure scenario, and converted to a NOAEL_{HEC} of 8.75 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 TTD_{DEVEL} of 0.03 ppm.

Oral TTDs

Hepatic Effects, Intermediate Oral: The intermediate oral MRL for chloroform is 0.1 mg/kg/day, based on hepatic effects.

Renal Effects, Intermediate Oral: Larson et al. (1995a) identified a NOAEL of 6.0 mg/kg/day and a LOAEL of 17.4 mg/kg/day for increased foci of regenerating renal proximal tubules in mice given chloroform in their drinking water for 3 weeks (Larson et al. 1995a). Application of an uncertainty factor of 100 (10 for animal to human extrapolations and 10 for intrahuman variability) would result in a TTD_{RENAL} of 0.06 mg/kg/day. Because this value is lower than the MRL, the intermediate-duration oral MRL of 0.1 mg/kg/day will be adopted as the TTD_{RENAL} for chloroform

Immunological Effects, Intermediate Oral: Munson et al. (1982) identified a LOAEL for depressed humoral immunity in mice dosed orally with 50 mg/kg/day of chloroform for 90 days. No NOAEL was identified. Because application of an uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for animal to human extrapolation, and 10 for intrahuman variability) to this LOAEL would result in a TTD_{IMMUNO} that is less than the MRL, the intermediate oral MRL of 0.1 mg/kg/day is adopted as the TTD_{IMMUNO}

Neurological Effects, Intermediate Oral: The NOAEL and LOAEL for neurobehavioral effects were 31.1 mg/kg/day (up to 90 days) and 100 mg/kg/day (60 days), as determined by a battery of behavioral tests in mice administered chloroform by gavage in aqueous emulphor (Balster and Borzelleca 1982). Application of an uncertainty factor of 100 (10 for animal to human extrapolations and 10 for intrahuman variability) to the NOAEL of 15 mg/kg/day 6 days/week (12.9 mg/kg/day for continuous exposure) results in a TTD_{NEURO} of 0.3 mg/kg/day.

Developmental Effects, Intermediate Oral: Gulati et al. (1988) reported that, in a continuous breeding study in mice, F_1 males had increased epididymal weights and degeneration of the epididymal epithelium and F_1 females had increased liver weight and hepatocellular degeneration following oral dosing (starting with the parental generation) with 41 mg/kg/day for 105 days (Gulati et al. 1988). Application of an uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for animal to human extrapolation, and 10 for intrahuman variability) would result in a TTD_{DEVEL} of 0.04, which is lower than the MRL. Therefore, the intermediate-duration oral MRL of 0.1 mg/kg/day will be adopted as the TTD_{DEVEL} for chloroform.

Hepatic Effects, Chronic Oral: The chronic oral MRL for chloroform is 0.01 mg/kg/day, based on hepatic effects.

Renal Effects, Chronic Oral: Heywood et al. (1979) identified a NOAEL of 15 mg/kg/day and a LOAEL of 30 mg/kg/day for renal effects (fat deposition in the glomeruli) in dogs given chloroform in a capsule 6 days/week for 7.5 years (Heywood et al. 1979). An uncertainty factor of 100 (10 for animal to human extrapolations and 10 for intrahuman variability) is applied to the NOAEL of 15 mg/kg/day 6 days/week (12.9 mg/kg/day for continuous exposure), resulting in a TTD_{RENAL} of 0.1 mg/kg/day for chronic oral exposure.

Immunological Effects, Chronic Oral: Data for chronic exposure were not available. An intermediate duration oral study indicates that immunological effects, although not supported by a large database, may be sensitive effects of oral exposure to chloroform, and is supported by some data for the inhalation route. Therefore, it is recommended that the chronic oral MRL of 0.01 mg/kg/day be adopted as the TTD_{IMMUNO} for chloroform.

Neurological Effects, Chronic Oral: No chronic oral study of sensitive endpoints for neurological effects was available for chloroform. The NOAEL for neurobehavioral effects from intermediate exposure was 31.1 mg/kg/day in mice administered chloroform by gavage in aqueous emulphor for durations up to 90 days (Balster and Borzelleca 1982). In the same study, neurobehavioral effects were not seen at 100 mg/kg/day for 30 days, but did occur at this dose level after 60 days of exposure.

Application of an uncertainty factor of 100 (10 for animal to human extrapolations, 10 for intrahuman variability, and 10 for extrapolation from intermediate to chronic duration) to the NOAEL results in a TTD_{NEURO} of 0.03 mg/kg/day. The duration uncertainty factor was considered necessary because extending the duration of exposure in the intermediate duration study resulted in the expression of effects, and 10 was chosen because the chronic oral MRL is 10-fold lower than the intermediate oral MRL for chloroform.

Developmental Effects, Chronic Oral: Gulati et al. (1988) reported that, in a continuous breeding study in mice, F₁ males had increased epididymal weights and degeneration of the epididymal epithelium and F₁ females had increased liver weight and hepatocellular degeneration following oral dosing (starting with the parental generation) with 41 mg/kg/day (Gulati et al. 1988). Application of an uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for animal to human extrapolation, and 10 for intrahuman variability) results in a TTD_{DEVEL} of 0.04 mg/kg/day.

Summary (TTD for Chloroform)

Intermediate Inhalation TTDs:

$$MRL_{HEPATIC} = 0.05 \text{ ppm}$$

$$TTD_{RENAL} = 0.05 \text{ ppm}$$

$$TTD_{IMMUNO} = 0.05 \text{ ppm}$$

$$TTD_{NEURO} = 0.05 \text{ ppm}$$

$$TTD_{DEVEL} = 0.05 \text{ ppm}$$

Chronic Inhalation TTDs:

$$MRL_{HEPATIC} = 0.02 \text{ ppm}$$

$$TTD_{RENAL} = 0.02 \text{ ppm}$$

$$TTD_{IMMUNO} = 0.02 \text{ ppm}$$

$$TTD_{NEURO} = 0.03 \text{ ppm}$$

$$TTD_{DEVEL} = 0.03 \text{ ppm}$$

Intermediate Oral TTDs:

$$MRL_{HEPATIC} = 0.1 \text{ mg/kg/day}$$

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

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

$$TTD_{NEURO} = 0.3 \text{ mg/kg/day}$$

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

Chronic Oral TTDs:

$$MRL_{HEPATIC} = 0.01 \text{ mg/kg/day}$$

$TTD_{\text{RENAL}} = 0.1 \text{ mg/kg/day}$
 $TTD_{\text{IMMUNO}} = 0.01 \text{ mg/kg/day}$
 $TTD_{\text{NEURO}} = 0.03 \text{ mg/kg/day}$
 $TTD_{\text{DEVEL}} = 0.04 \text{ mg/kg/day}$

A.6 References

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APPENDIX B: BACKGROUND INFORMATION FOR 1,1-DICHLOROETHYLENE

This appendix was written based primarily on the Toxicological Profile for 1,1-Dichloroethylene (ATSDR 1994). 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.

B.1 Toxicokinetics

No studies evaluating the absorption of 1,1-dichloroethylene in humans following inhalation or oral exposure were located. Animal studies have demonstrated that 1,1-dichloroethylene is rapidly absorbed following inhalation exposure (Dallas et al. 1983; McKenna et al. 1978b), being detectable in blood following as little as 2 minutes of exposure (Dallas et al. 1983), and is linear up to concentrations of 150 ppm (Dallas et al. 1983). Animal studies of oral exposure of 1,1-dichloroethylene have similarly demonstrated a rapid and near-complete absorption (Reichert et al. 1979). Doses of 1,1-dichloroethylene ranging from 10 to 100 mg/kg were rapidly and almost completely absorbed from the gastrointestinal tract of rats and mice following oral administration in corn oil (Jones and Hathway 1978a; Putcha et al. 1986). Rapid absorption likewise occurred following oral administration of 200 mg/kg in an aqueous emulsion, as evidenced by the observation that the largest percentage of the dose was exhaled during the initial 15-minute period (Chieco et al. 1981). After oral administration to rats of 1,1-dichloroethylene labeled with radioactive carbon (^{14}C), 81–99.8% of the administered radioactivity was recovered within 72 hours (Reichert et al. 1979), indicating a very rapid and near-complete absorption.

No studies evaluating the distribution of 1,1-dichloroethylene in humans following inhalation or oral exposure were located. Following inhalation exposure of rats to 10 or 200 ppm of ^{14}C -labeled 1,1-dichloroethylene, the highest level of radioactivity was found in the liver and kidneys after 72 hours, with only very small amounts present in other tissues (McKenna et al. 1978b). Preferential accumulation of radioactivity was reported in the kidney and liver of rats exposed to 2,000 ppm radiolabeled 1,1-dichloroethylene for 2 hours (Jaeger et al. 1977a); fasted animals showed a higher accumulation of radiolabel than unfasted animals. 1,1-Dichloroethylene was rapidly distributed to all tissues examined following a single oral dose of the ^{14}C -labeled compound to rats (Jones and Hathway 1978b). The highest amount of radioactivity was found in the liver and kidneys within 30 minutes of administration, although more general redistribution throughout the soft tissues of the body followed.

The metabolism of 1,1-dichloroethylene following oral administration in rats has been extensively studied (Jones and Hathway 1978a, 1978b; McKenna et al. 1978a; Reichert et al. 1979). The primary biotransformation pathway is believed to involve the metabolism by cytochrome CYP2E1 to a reactive epoxide, 1,1-dichloroethylene oxide (Jones and Hathway 1978b; McKenna et al. 1977; Reichert et al. 1979). These metabolites may react with cellular molecules, may be conjugated to GSH, or may rearrange to chloroacetyl chloride and eventually to monochloroacetic acid. It is believed that metabolism of 1,1-dichloroethylene is saturable, based on studies demonstrating that at high exposure levels, a greater amount of unchanged compound is eliminated in the expired air (Dallas et al. 1983; Jones and Hathway 1978b; McKenna et al. 1978a, 1978b; Reichert et al. 1979).

Regardless of route of exposure, elimination of 1,1-dichloroethylene is rapid and accomplished primarily in the form of metabolites in the urine, with elimination of the parent compound in the expired air becoming more prevalent as the exposure levels increase. At low doses (<150 ppm by inhalation or ≤ 1 mg/kg/day orally), very little (1% or less) of the parent compound is eliminated in the expired air, while at higher concentrations, the percentage eliminated as the parent compound increases (Dallas et al. 1983; Jones and Hathway 1978b; McKenna et al. 1978a; Reichert et al. 1979).

D'Souza and Andersen (1988) reported a PBPK model for 1,1-dichloroethylene in rats, based on the model for styrene developed by Ramsey and Andersen (1984). The model consists of four compartments (liver, slowly perfused, richly perfused, and fat) as well as blood, and contains inputs for both oral and inhalation exposure. Metabolism is assumed to occur in the liver compartment, and consists of an initial oxidation followed by conjugation with GSH. Values for organ volume and blood flow were taken from previous modeling efforts (Gargas et al. 1986). The model simulations were optimized using data from McKenna et al. (1978b) and Jones and Hathway (1978a, 1978b). Models for species other than the rat are not available.

B.2 Health Effects

Following both inhalation and oral exposure, the most sensitive effects of 1,1-dichloroethylene appear to be on the liver. A preliminary study of workers exposed to 1,1-dichloroethylene for 6 years or less in a 1,1-dichloroethylene polymerization plant revealed a high incidence of hepatotoxicity; however, a full study of these workers has not been reported (EPA 1976). Numerous studies in animals have identified hepatic effects, including both biochemical changes (e.g., alterations in serum enzyme levels indicative of liver injury and induction of hepatic enzymes) and marked histological changes (e.g., midzonal and centrilobular swelling of liver, degeneration, and necrosis of hepatocytes). These effects have been

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

displays much higher rates of metabolism of trichloroethylene, and is more susceptible to the hepatotoxicity and hepatocarcinogenicity of trichloroethylene, than are the livers of rats and humans. With chronic oral exposure to high doses of trichloroethylene by gavage, increased incidence of toxic nephrosis and renal tumors occurred in male rats, but in female rats, the nephrosis was not accompanied by an increase in kidney tumors. Trichloroethylene-induced kidney damage has been proposed to involve conjugation products of trichloroethylene with GSH. The conjugated products (e.g., dichlorovinyl-cysteine) can be hydrolyzed by β -lyase in the kidney forming a reactive thiol group that can react with cellular macromolecules and lead to cell damage. In support of this mechanistic hypothesis, chemical agents that inhibit β -lyase protected against dichlorovinyl-cysteine nephrotoxicity in rats (ATSDR 1997).

Trichloroethylene-induced cardiac arrhythmias are thought to involve parent-chemical sensitization of the heart to epinephrine-induced arrhythmias (ATSDR 1997). In animals, chemicals that inhibited the metabolism of trichloroethylene increased the potency of trichloroethylene to induce cardiac arrhythmias, whereas chemicals enhancing trichloroethylene metabolism decreased its potency.

C.4 Health Guidelines

ATSDR (1997) derived an acute inhalation MRL of 2 ppm for trichloroethylene based on a LOAEL of 200 ppm for subjective neurological symptoms such as fatigue and drowsiness in volunteers exposed 7 hours/day for 5 days (Stewart et al. 1970) and an uncertainty factor of 100 (10 for the use of a LOAEL and 10 to account for human variability).

ATSDR (1997) derived an intermediate-duration inhalation MRL of 0.1 ppm for trichloroethylene based on a LOAEL of 50 ppm for decreased wakefulness during exposure, decreased postexposure heart rate, and slow-wave sleep in rats exposed for 8 hours/day, 5 days/week for 6 weeks (Arito et al. 1994), and an uncertainty factor of 300 (10 for using a LOAEL, 3 for extrapolating from rats to humans, and 10 to account for human variability).

ATSDR (1997) did not derive a chronic inhalation MRL for trichloroethylene due to the lack of suitable data.

ATSDR (1997) derived an acute oral MRL of 0.2 mg/kg/day for trichloroethylene based on a LOAEL of 50 mg/kg/day for reduced rearing rate in mice and an uncertainty factor of 300 (10 for the use of a LOAEL, 10 for extrapolating from animals to humans, and 3 for human variability [a full factor of 10 was not used because pups were taken to represent a sensitive population]). The mice were exposed for

7 days beginning at 10 days of age and evaluated for locomotion, rearing, and total activity at 17 and 60 days of age; the effect was seen at 60 days of age (Fredriksson et al. 1993).

ATSDR (1997) did not derive intermediate or chronic oral MRLs for trichloroethylene due to the lack of suitable data.

NTP (2005) listed trichloroethylene as *reasonably anticipated to be a human carcinogen* based on limited evidence of carcinogenicity from studies in humans, sufficient evidence of malignant tumor formation in experimental animals, and convincing relevant information that trichloroethylene acts through mechanisms indicating it would likely cause cancer in humans. IARC (1995) assigned trichloroethylene to Cancer Group 2A, *probably carcinogenic to humans*, based on limited evidence in humans and sufficient evidence in experimental animals. IARC (1995) noted that (1) although a hypothesis linking the formation of mouse liver tumors with peroxisome proliferation is plausible, trichloroethylene also induced tumors at other sites in mice and rats, and (2) several epidemiological studies showed elevated risks for cancer of the liver and biliary tract and for non-Hodgkin's lymphoma. EPA's Integrated Risk Information System (IRIS) database (IRIS 2005) does not list an RfD, RfC, or a carcinogenicity assessment for trichloroethylene. As reviewed by ATSDR (1997), the EPA Scientific Advisory Board in 1988 offered the opinion that the weight of evidence for trichloroethylene carcinogenicity was on a Group B2/C continuum (i.e., on the border between Group B2 and Group C). EPA has not yet presented a more recent position on the weight-of-evidence classification for trichloroethylene carcinogenicity, but is currently evaluating several approaches to extrapolating from the animal tumor data for trichloroethylene to derive estimates of human cancer risks at environmentally relevant exposure levels (Scott and Cogliano 2000).

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

The endpoints of concern for trichloroethylene in this mixture are hepatic, renal, immunological, neurological, and developmental. TTDS are derived below for endpoints that are not the basis of the MRL, using the methods described by ATSDR (2004). The derivations are based primarily on data provided in ATSDR (1997), 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 trichloroethylene, is calculated by multiplying the duration-adjusted animal NOAEL by the ratio of the blood:gas partition coefficients in

animals and humans [(Hb/g)A / Hb/g)H]. Since the partition coefficients in rodents are greater than in humans, a default value of 1 is used for the ratio.

Hepatic Effects, Intermediate Inhalation: Kjellstrand et al. (1983) identified a NOAEL of 37 ppm and a LOAEL of 75 ppm for increased enzyme activity and liver weight in male mice exposed 24 hours/day for 30 days. The NOAEL is converted to a NOAEL_{HEC} of 37 ppm as described previously under the heading Inhalation TTDs. An uncertainty factor of 30 (3 for animal to human extrapolation using a dosimetric adjustment and 10 for intrahuman variability) was applied to the NOAEL_{HEC} to derive the TTD_{HEPATIC} of 1 ppm.

Renal Effects, Intermediate Inhalation: Intermediate duration studies identified NOAELs but no LOAELs for renal effects in animals exposed to chloroform by inhalation. Maltoni et al. (1988) reported a NOAEL of 100 ppm and a LOAEL of 300 ppm for renal tubule meganucleocytosis in male rats exposed 7 hours/day, 5 days/week for 104 weeks. The NOAEL was duration-adjusted to 20.8 ppm for a continuous exposure scenario, and to a NOAEL_{HEC} of 20.8 ppm as described previously under the heading Inhalation TTDs. An uncertainty factor of 30 (3 for animal to human extrapolation using a dosimetric adjustment and 10 for intrahuman variability) was applied to the NOAEL_{HEC} to derive the TTD_{RENAL} of 0.7 ppm.

Immunological Effects, Intermediate Inhalation: There are some indications of immune abnormalities in occupationally exposed persons (dermal sensitivity reactions) and in limited studies of populations exposed to contaminated drinking water, but the evidence is inconclusive (ATSDR 1997). Immunological effects have not been reported in intermediate or chronic duration studies of inhaled trichloroethylene in animals. Increased susceptibility to pulmonary infection with *Streptococcus zooepidemicus* occurred in mice by inhalation exposed to ≥ 10 ppm of trichloroethylene for 3 hours (Aranyi et al. 1986), and acute and intermediate studies of oral exposure to trichloroethylene in mice reported suppression of humoral and cellular immunity (Sanders et al. 1982). Therefore, the weight of evidence suggests that trichloroethylene may be immunotoxic, and the intermediate duration MRL of 0.1 ppm can be adopted as an interim value for the TTD_{IMMUNO}.

Neurological Effects, Intermediate Inhalation: The intermediate inhalation MRL of 0.1 ppm for trichloroethylene is based on neurological effects.

Developmental Effects, Intermediate Inhalation: While no single study has identified both a NOAEL and a LOAEL for developmental effects following inhalation of trichloroethylene, Beliles et al. (1980) and Hardin et al. (1981) identified a NOAEL of 500 ppm, while Dorfmueller et al. (1979) identified a

LOAEL of 1,800 ppm for decreased fetal weight and incomplete skeletal ossification. The NOAEL of 500 ppm was therefore selected, and duration-adjusted (from 7 hours/day, 5 days/week) to 104 ppm for continuous exposure. The NOAEL was converted to a NOAEL_{HEC} of 104 ppm as described previously under the heading Inhalation TTDs. An uncertainty factor of 30 (3 for animal to human extrapolation using a dosimetric adjustment and 10 for intrahuman variability) was then applied to derive the TTD_{DEVEL} of 3 ppm.

Hepatic Effects, Chronic Inhalation: A TTD_{HEPATIC} of 0.3 ppm is derived from the intermediate TTD_{HEPATIC}; see explanation in Chapter 3.

Renal Effects, Chronic Inhalation: Maltoni et al. (1988) reported a NOAEL of 100 ppm and a LOAEL of 300 ppm for renal tubule meganucleocytosis in male rats exposed 7 hours/day, 5 days/week for 104 weeks. The NOAEL was duration-adjusted to 20.8 ppm for a continuous exposure scenario, and converted to a NOAEL_{HEC} of 20.8 ppm as described previously under the heading Inhalation TTDs. An uncertainty factor of 30 (3 for animal to human extrapolation using a dosimetric adjustment, 10 for intrahuman variability) was applied to the NOAEL_{HEC} to derive the TTD_{RENAL} of 0.7 ppm.

Immunological Effects, Chronic Inhalation: A TTD_{IMMUNO} of 0.03 ppm is derived from the intermediate TTD_{IMMUNO}; see explanation in Chapter 3.

Neurological, Chronic Inhalation: A TTD_{NEURO} of 0.03 ppm is derived from the intermediate MRL; see explanation in Chapter 3.

Developmental Effects, Chronic Inhalation: A TTD_{DEVEL} of 1 ppm is derived from the intermediate TTD_{DEVEL}; see explanation in Chapter 3.

Oral TTDs

Hepatic Effects, Intermediate 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, 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:

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

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

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

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

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

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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 extrarespiratory 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 extrarrespiratory effect produced by a category 3 gas, such as vinyl chloride, is calculated by multiplying the duration-adjusted animal NOAEL by the ratio of the blood:gas partition coefficients in animals and humans $[(\text{Hb/g})_{\text{A}} / \text{Hb/g})_{\text{H}}]$. 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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