2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO 1,1,2,2-TETRACHLOROETHANE IN THE UNITED STATES

1,1,2,2-Tetrachloroethane is currently used as a chemical intermediate in the production of chlorinated hydrocarbons. In the past, this substance was used as an industrial solvent and extractant and was even a component of a few pesticide formulations; however, its manufacture and use as an end-product appears to have ceased in the United States. Present sources of 1,1,2,2-tetrachloroethane are largely attributable to fugitive emissions or discharges when it is generated as a byproduct and to emissions or discharges stemming from its production and use as a chemical intermediate.

1,1,2,2-Tetrachloroethane released onto soil is expected to partly volatilize, with the remainder leaching into the subsurface soil profile and, possibly, groundwater. Most of the 1,1,2,2-tetrachloroethane released to surface water is expected to volatilize, with the remainder dissolving in water where it would undergo degradation through hydrolysis and biodegradation. Degradation products include 1,1,2,2-trichloroethylene, 1,2-dichloroethylene, 1,1,2-trichloroethane, 1,2-dichloroethane, and vinyl chloride. In the ambient air, the dominant process for removal of 1,1,2,2-tetrachloroethane is the reaction with photochemically generated hydroxyl radicals. The half-life of this reaction is 54 days. Some 1,1,2,2-tetrachloroethane may diffuse upward into the stratosphere where it can participate in reactions that produce ozone-destroying chlorine radicals. However 1,1,2,2-tetrachloroethane is not expected to contribute significantly to the destruction of the ozone layer since <1% of the tropospheric 1,1,2,2-tetrachloroethane is predicted to reach the stratosphere.

Reported average concentrations of 1,1,2,2-tetrachloroethane measured in ambient air from both urban and rural locations across the United States are generally <10 ppt. However, average urban air concentrations as high as 57 ppb have been reported during the 1980's. More recent data are not available, but would be expected to be lower. As reported in the EPA STORET database for 1999–2006 (www.epa.gov/storet/dw_home.html), 1,1,2,2-tetrachloroethane was detected in approximately 43% of 12,476 water samples (surface water and groundwater), but only 3% of the samples contained 1,1,2,2-tetrachloroethane above the quantifiable limit. The range of quantifiable concentrations in these water samples was 0.1–25 ppb, with a mean of 0.6 ppb. 1,1,2,2-Tetrachloroethane was detected in

<0.001% of 166,599 public water system samples collected in the United States between 1993 and 1997. 1,1,2,2-Tetrachloroethane has not been detected in table-ready foods.

Based on the low levels of 1,1,2,2-tetrachloroethane measured in the environment and the decreased use of this substance in non-industrial settings, exposure of the general population to 1,1,2,2-tetrachloroethane is expected to be very low. However, individuals located near hazardous waste sites or facilities where 1,1,2,2-tetrachloroethane is used as a chemical intermediate may be exposed to this substance by inhalation of contaminated air, by ingestion of contaminated drinking water, or by dermal contact with contaminated soil. Children residing in these areas are likely to be exposed to 1,1,2,2-tetrachloroethane by the same routes that affect adults. Occupational exposures are expected to occur primarily via inhalation and dermal contact.

1,1,2,2-Tetrachloroethane is well absorbed from the respiratory and gastrointestinal tracts in humans and laboratory animals, and absorption through the skin after dermal exposure has been demonstrated in animals. Following oral or inhalation exposure, 1,1,2,2-tetrachloroethane is extensively metabolized and excreted mainly as metabolites in the urine and breath. In rats and mice, 1,1,2,2-tetrachloroethane is metabolized to trichloroethanol, trichloroacetic acid, and dichloroacetic acid, which is then broken down to glyoxalic acid, oxalic acid, and carbon dioxide; a small percentage of the dose is exhaled in the breath as the parent compound. Both reductive and oxidative metabolism occurs, producing reactive radical and acid chloride intermediates, respectively.

2.2 SUMMARY OF HEALTH EFFECTS

A limited amount of information is available on the health effects of 1,1,2,2-tetrachloroethane in humans. The information in humans is generally very dated and incomplete and provides no information on dose-response. There has been only one epidemiological study involving this chemical and this study did not report on or classify exposure levels. However, the human database does suggest that 1,1,2,2-tetrachloro-ethane can target certain systems (nervous system, liver, mucous membranes) following high-dose exposure; it is also possible that more modern studies would be able to detect other types of effects in exposed populations. Reports of inhaled and ingested 1,1,2,2-tetrachloroethane indicate that central nervous system depression is the predominant effect of high-level acute exposure. Irritation of the mucous membranes also has been observed following acute exposure to high concentrations of 1,1,2,2-tetrachloroethane vapor. Occupational studies suggest that repeated inhalation exposures can

affect the liver as well as the nervous system; hepatic effects that have been reported include liver enlargement and jaundice.

Animal studies have clearly demonstrated that the central nervous system and liver are the main targets of 1,1,2,2-tetrachloroethane toxicity following acute- and intermediate-duration inhalation and oral exposure. Neurotoxicity has mainly been associated with near-lethal to lethal exposures; typical effects include a progression of clinical signs ranging from lethargy and incoordination to respiratory depression and loss of consciousness. Hepatic effects are prevalent at lower levels of exposure and include increases in serum enzymes and liver fat content, increased hepatic deoxyribonucleic acid (DNA) synthesis and mitotic activity, hepatocellular cytoplasmic vacuolation and other mild histological alterations, fatty degeneration, and hepatocellular necrosis. Chronic oral exposure to 1,1,2,2-tetrachloroethane induced liver cancer (hepatocellular carcinoma) in mice.

Little information is available on other effects of 1,1,2,2-tetrachloroethane. Reduced body weight gain and weight loss are effects of repeated oral exposures in rats and mice that generally occurred at high dose levels and, in dietary studies, were partly due to decreased food consumption from taste aversion. Intermediate-duration inhalation and oral exposures have been reported to cause hematological and immunological alterations in rats and rabbits. Chronic oral exposure to high doses induced kidney lesions (chronic inflammation and acute toxic nephrosis) in mice. Reproductive and developmental toxicity have not been adequately evaluated. Intermediate-duration oral exposure to doses that caused body weight loss also caused atrophy in reproductive tissues in male and female rats; alterations in sperm motility and estrus cycle of unclear toxicological significance were observed at lower doses. There were no effects on reproductive function in male rats following intermediate-duration inhalation of a low concentration of 1,1,2,2-tetrachloroethane, but testing of reproductive performance in female animals has not been conducted. Gestational exposure to 1,1,2,2-tetrachoroethane caused fetotoxicity in rats (decreased fetal body weight) and mice (litter resorptions) at oral doses that were maternally toxic, but fetuses were not examined for malformations.

A greater detailed discussion of 1,1,2,2-tetrachloroethane-induced neurological effects, hepatic effects and cancer follows. The reader is referred to Section 3.2, Discussion of Health Effects by Route of Exposure, for additional information on these effects and other health effects.

Neurological Effects. Acute inhalation exposure to high levels of 1,1,2,2-tetrachloroethane caused clinical signs of neurotoxicity in humans that included drowsiness, nausea, headache, and weakness, and

at extremely high concentrations, unconsciousness and respiratory failure. A limited experimental study found similar effects (vertigo and fatigue) in two volunteers who were exposed to 146 ppm for 30 minutes or 336 ppm for 10 minutes, which are levels that also caused irritation of the mucous membranes.

In animals that inhaled 1,1,2,2-tetrachloroethane, clinical signs of neurotoxicity (e.g., incoordination, loss of reflexes, labored respiration, prostration, and loss of consciousness) typically preceded death, which occurred at concentrations as low as 1,000–1,168 ppm for 1.5–4 hours in rats and mice. A sublethal exposure of 576 ppm for 30 minutes caused reduced activity and alertness in rats and guinea pigs. The effective concentration for a 50% decrease in spontaneous motor activity in rats was 360 ppm for a 6-hour exposure. Intermediate-duration intermittent exposure to high concentrations of 1,1,2,2-tetrachloroethane caused neurological effects in mice similar to those observed in acute studies. Data on the neurotoxicity of single or repeated daily exposures to low levels of 1,1,2,2-tetrachloroethane vapor were not located.

Information on the neurotoxicity of oral exposure to 1,1,2,2-tetrachloroethane in humans is available from case reports. People who intentionally ingested a lethal amount usually lost consciousness within approximately 1 hour and died 3–20 hours postingestion. No deaths occurred in patients who were accidentally given an estimated oral dose of 68–118 mg/kg as medicinal treatment for hookworm, although they experienced loss of consciousness and other clinical signs of narcosis that included shallow breathing, faint pulse, and pronounced lowering of blood pressure. In animals, lethargy and central nervous system depression occurred in rats gavaged with 270–300 mg/kg/day for 1–12 days. Information on neurological effects of lower acute oral doses are limited to a poorly reported rat study in which a single gavage dose of 100 mg/kg caused ataxia and 50 mg/kg caused decreased passive avoidance to an electric shock, possibly due to an increased threshold of shock perception due to a subtle anesthetic effect. In studies of dietary (nonbolus) exposure, no clinical signs of neurotoxicity occurred in rats and mice that were exposed to 320 and 1,400 mg/kg/day, respectively, for 14 weeks. Comprehensive neurobehavioral evaluations (functional observational batteries, FOBs) in these studies showed no effects at doses as high as 80 mg/kg/day in the rats and 700 mg/kg/day in the mice (higher doses not evaluated).

Hepatic Effects and Cancer. Some humans exposed to 1,1,2,2-tetrachloroethane vapors in the workplace have developed jaundice and an enlarged liver. Specific clinical signs were not associated with specific exposure levels, although vapor concentrations in one study ranged from 1.5 to 248 ppm. Liver cirrhosis was not increased in an epidemiological study of men occupationally exposed to unmeasured levels of 1,1,2,2-tetrachloroethane fumes in a clothing plant. Liver congestion and necrosis

were observed in the autopsies of three humans who died following inhalation or oral exposure to 1,1,2,2-tetrachloroethane.

Information on the hepatotoxicity of inhaled 1,1,2,2-tetrachloroethane includes gross observations of fatty degeneration in rats, mice, and guinea pigs that died following acute- or intermediate-duration intermittent exposures to ≥1,000 ppm concentrations. Studies in which rats were exposed to lower concentrations of 1,1,2,2-tetrachloroethane for 4 hours, 4 hours/day for 8 of 10 days, or 5 days/week for 15 weeks found generally mild hepatic effects as indicated by clinical chemistry and histological alterations, but reporting limitations, insufficient quantitative data, and other study inadequacies preclude identification of reliable effects levels. Effects in these studies included increases in serum enzymes, increases in serum and liver triglycerides, changes in serum protein fractions, and fine droplet fatty degeneration and cytoplasmic vacuolation.

Hepatic effects of oral exposure included hepatocellular degeneration in mice exposed to a lethal dietary dose of 2,394 mg/kg/day for 6 days, increased serum aspartate aminotransferase (AST) in rats given a single gavage dose of 574 mg/kg, and increased liver cell DNA synthesis, mitotic activity, and centrilobular swelling in rats and/or mice exposed to 75–300 mg/kg/day by gavage for 4 days. Liver effects in intermediate-duration studies included cytoplasmic vacuolation in rats exposed to 104 mg/kg/day by gavage for 21 days, and hepatocellular degeneration in mice exposed to 337.5 mg/kg/day by gavage for 16 days or 599 mg/kg/day in the diet for 15 days. Comprehensive 14-week dietary studies showed that the liver was the most sensitive target of 1,1,2,2-tetrachloroethane toxicity for intermediate-duration exposure in rats and mice. Hepatic effects in the rats included biologically significant increases in serum alanine aminotransferase (ALT), sorbitol dehydrogenase (SDH), alkaline phosphatase (ALP) and bile acids, hepatocyte necrosis, bile duct hyperplasia, and liver pigmentation at 170–320 mg/kg/day. Hepatic effects in the mice included biologically significant increases in serum ALT and SDH, and necrosis, pigmentation, and bile duct hyperplasia at ≥300 mg/kg/day.

In the only chronic study of 1,1,2,2-tetrachloroethane, rats were exposed to time-weighted average (TWA) doses of 0, 62, or 108 mg/kg/day (males) or 0, 43, or 76 mg/kg/day (females) by gavage on 5 days/week for 78 weeks, followed by an observation period of 32 weeks. Fatty degeneration of the liver occurred at 108 mg/kg/day, but no significant increases in tumor incidences were observed. Mice of both sexes were similarly exposed to TWA doses of 0, 142, or 284 mg/kg/day for 78 weeks followed by 12 weeks of observation. Significant, dose-related increases in the incidence of hepatocellular carcinoma

were observed in males (3/36, 13/50, and 44/49 in the control, low-dose, and high-dose groups, respectively) and females (1/40, 30/48, and 43/47, respectively). Based mainly on the results of this study, in an assessment conducted in 1994, the EPA has classified the carcinogenicity of 1,1,2,2-tetrachloroethane as Group C, possible human carcinogen. The International Agency for Research on Cancer (IARC) cancer classification for 1,1,2,2-tetrachloroethane is Group 3, not classifiable with regard to its carcinogenicity to humans. The National Toxicology Program (NTP) has not classified 1,1,2,2-tetrachloroethane for human carcinogenicity.

The mode of action of the hepatocarcinogenicity of 1,1,2,2-tetrachloroethane is incompletely characterized. It is likely that liver tumor formation by 1,1,2,2-tetrachloroethane involves its metabolism to one or more active compounds, although there is no direct evidence linking one or more metabolites to its carcinogenic effects. Genotoxicity studies provide only limited evidence of a genotoxic mode of action. 1,1,2,2-Tetrachloroethane has weak genotoxic activity, with *in vitro* genotoxicity tests generally reporting negative results except for assays of sister chromatid exchange (SCE) and cell transformation; *in vivo* tests of genotoxicity have shown a similar pattern.

2.3 MINIMAL RISK LEVELS (MRLs)

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made for 1,1,2,2-tetrachloroethane. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

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

Inhalation MRLs

No acute-duration inhalation MRL has been derived for 1,1,2,2-tetrachloroethane due to insufficient data. Reports in humans indicate that high-dose acute inhalation exposure to 1,1,2,2-tetrachloroethane can cause central nervous system depression and mucous membrane irritation (Coyer 1944; Hamilton 1917; Lehmann and Schmidt-Kehl 1936), but exposure-response data are lacking or insufficient. The preponderance of information on the acute inhalation toxicity of 1,1,2,2-tetrachloroethane in animals pertains to neurological and hepatic effects of near-lethal to lethal exposures to concentrations above approximately 1,000 ppm (Carpenter et al. 1949; Horiuchi et al. 1962; NIOSH 1978; Pantelitsch 1933; Schmidt et al. 1980b). The lowest effective concentration for a serious neurotoxic effect (50% decrease in spontaneous motor activity) was 360 ppm for 6 hours in rats (Horvath and Frantik 1973). No information is available on neurotoxicity at lower concentrations, precluding identification of a less-serious lowest-observed-adverse-effect level (LOAEL) or no-observed-adverse-effect level (NOAEL). Hepatic effects that include histological alterations and serum and liver biochemical changes have been reported in studies of rats exposed to concentrations as low as 60 ppm for 4 hours (Schmidt et al. 1980b) and 2.2 ppm for 4 hours/day for 8 of 10 days (Gohlke and Schmidt 1972; Schmidt et al. 1972), but these studies are inadequate for identifying a reliable NOAEL or LOAEL and deriving an acute inhalation MRL due to insufficient data on incidence, magnitude, and/or severity of effects.

No intermediate-duration inhalation MRL has been derived for 1,1,2,2-tetrachloroethane due to insufficient data. Intermittent intermediate-duration exposure to lethal concentrations of 1,1,2,2-tetrachloroethane (7,000–9,000 ppm) caused central nervous system depression and fatty liver degeneration in rats and mice (Horiuchi et al. 1962). Information on effects of lower concentrations of 1,1,2,2-tetrachloroethane is available from poorly reported studies in rats and rabbits (Kulinskaya and Verlinskaya 1972; Schmidt et al. 1972; Shmuter 1977; Truffert et al. 1977; Union Carbide Corporation 1947). Findings in these studies included transient histological alterations in the liver of rats exposed to 560 ppm for 5 hours/day, 5 days/week for 15 weeks (Truffert et al. 1977), hematological alterations and increased liver fat content in rats exposed to 1.9 ppm for 4 hours/day for 265 days (Schmidt et al. 1972), alterations in serum acetylcholinesterase activity in rabbits exposed to 1.5 ppm for 3 hours/day, 6 days/week for 7–8.5 months (Kulinskaya and Verlinskaya 1972), and immunological alterations in rabbits exposed to 0.3–14.6 ppm for 3 hours/day, 6 days/week for 8–10 months (Shmuter 1977). None of these studies are adequate for identification of reliable NOAELs or LOAELs or MRL derivation due to insufficient data on incidence, magnitude, and/or severity of effects and other reporting limitations.

No chronic-duration inhalation MRL has been derived for 1,1,2,2-tetrachloroethane due to insufficient data. Information on the chronic inhalation toxicity of 1,1,2,2-tetrachloroethane in humans is available from several occupational studies (Jeney et al. 1957; Lobo-Mendonca 1963; Minot and Smith 1921; Norman et al. 1981) that are inadequate for identification of effect levels due to limitations that include insufficient characterization of exposure levels, lack of control data, dermal exposures, and/or mixed chemical exposures. Although not sufficient for identification of effect levels or MRL derivation, the occupational studies provide limited supporting information on the neurotoxicity and hepatotoxicity of 1,1,2,2-tetrachloroethane. Chronic inhalation studies in animals have not been performed.

Oral MRLs

No acute-duration oral MRL has been derived for 1,1,2,2-tetrachloroethane due to insufficient data. Single oral doses in the range of 68–118 mg/kg are estimated to be serious LOAELs for neurotoxicity in humans based on unconsciousness and other clinical signs observed in case reports (Hepple 1927; Lilliman 1949; Mant 1953; Sherman 1953; Ward 1955). The preponderance of information on the acute oral toxicity of 1,1,2,2-tetrachloroethane in animals is provided by gavage studies in rats and mice exposed to near-lethal to lethal dose levels. Rats were more sensitive than mice and the nervous system was more sensitive than the liver. Central nervous system depression and death, but no clearly adverse effects in the liver, occurred in rats exposed to gavage doses as low as 270–300 mg/kg/day for 1–4 days or 208 mg/kg/day for 13–14 days (Hanley et al. 1988; NTP 1993a, 1993b, 1996). Information on effects of lower acute oral doses in animals is limited to a rat study in which a single gavage dose of 100 mg/kg caused ataxia and 50 mg/kg caused decreased passive avoidance to an electric shock, possibly due to an increased threshold of shock perception due to a subtle anesthetic effect (Wolff 1978). The possible anesthetic effect suggests that 50 mg/kg is a LOAEL for neurotoxicity in rats, but evaluation of the study and the significance of the effect level is complicated by incomplete reporting and insufficient quantitative data. Derivation of an acute MRL is precluded by the uncertain reliability of the 50 mg/kg/day LOAEL in rats and, particularly, its proximity to the 68–118 mg/kg doses causing serious neurotoxicity in humans.

- An MRL of 0.5 mg/kg/day has been derived for intermediate-duration (15–364 days) oral exposure to 1,1,2,2-tetrachloroethane.

Liver effects data from a comprehensive 14-week study in rats were used as the basis for an intermediate-duration oral MRL. In this study (NTP 2004), groups of 10 male and 10 female F344 rats were exposed

to diet containing 1,1,2,2-tetrachloroethane in reported average daily doses of 0, 20, 40, 80, 170, or 320 mg/kg/day for 14 weeks. The study was comprehensive in scope and included extensive evaluations of histology, clinical chemistry, and neurotoxicity (FOBs). Effects included increases in hepatic cytoplasmic vacuolization at 20 mg/kg/day, liver weight at 40 mg/kg/day, and hepatocellular hypertrophy at 80 mg/kg/day. These hepatic effects are not considered adverse because the severity of the vacuolation was minimal to mild and did not increase with dose, and the increases in liver weight and hepatocellular hypertrophy are considered adaptive responses to chemical exposure. Increases in serum ALT and SDH and decreases in serum cholesterol also occurred at ≥80 mg/kg/day, but the magnitudes of these changes were biologically significant only at ≥170 mg/kg/day. Other effects that occurred at 170 and 320 mg/kg/day included increases in serum ALP and bile acids, hepatocyte necrosis, bile duct hyperplasia, hepatocellular mitotic alterations, foci of cellular alterations, and liver pigmentation. As discussed by NTP (2004), increases in serum ALT and SDH are specific markers of hepatocellular necrosis or increased cell membrane permeability (leakage) in rodents; increases in bile acids are markers of cholestasis, impaired hepatocellular function, or hepatocellular injury; increased ALP is another marker of cholestasis; and decreased serum cholesterol is possibly indicative of liver dysfunction (impaired cholesterol biosynthesis). There was no evidence of neurotoxicity, as shown by negative FOB testing at doses as high as 80 mg/kg/day (higher doses not tested) and lack of clinical signs in all dose groups. Additional information regarding the design and results of this study is presented in Appendix A. This study identified a NOAEL of 80 mg/kg/day and a LOAEL of 170 mg/kg/day for systemic toxicity based on adverse liver-related serum chemistry changes and histological manifestations of hepatocellular damage. This LOAEL is lower than or equal to the LOAELs for reproductive effects in males (320 mg/kg/day) and females (170 mg/kg/day). A LOAEL for neurotoxicity was not identified because there were no clinical signs of neurotoxicity or exposure-related findings in the FOB at doses as high as 80 mg/kg/day (highest tested dose in the FOB).

NTP (2004) also tested mice in a similarly designed 14-week dietary study that supports the rat data in showing that the liver was the most sensitive target of 1,1,2,2-tetrachloroethane toxicity. Hepatic effects in the mice included minimal hepatocellular hypertrophy, increases in serum SDH, ALT, and bile acids, and decreased serum cholesterol at 160–200 mg/kg/day, and increases in serum ALP and 5’-nucleotidase, necrosis, pigmentation, and bile duct hyperplasia at 300–370 mg/kg/day. The magnitudes of the serum chemistry changes were biologically significant at ≥300 mg/kg/day in females and ≥370 mg/kg/day in males. Based on the adverse serum chemistry and histopathological changes at 300 mg/kg/day and higher doses, this study identifies a LOAEL of 300 mg/kg/day for liver toxicity in mice; the corresponding NOAEL is 200 mg/kg/day. Additional information on the intermediate-duration oral toxicity of

1,1,2,2-tetrachloroethane is available from a 21-day gavage study in rats (NTP 1996), a 16-day gavage study in mice (NTP 1993d), 6-week gavage studies in rats and mice (NCI 1978), and 15-day diet studies in rats and mice (NTP 2004). These studies are mainly dose range-finding studies that used small numbers of animals and had limited or no evaluations of clinical chemistry and histology. The lowest LOAELs in these studies were 100–104 mg/kg/day for reduced body weight gain and hepatocyte cytoplasmic vacuolation in rats exposed by gavage (NCI 1978; NTP 1996) and 337.5 mg/kg/day for hepatocellular degeneration in mice exposed by gavage (NTP 1993d). The NTP (2004) 14-week dietary study is the best basis for MRL derivation because it tested wider ranges of doses and varieties of end points, identified lower LOAELs, and used a more relevant method of oral exposure than the other intermediate-duration studies.

The NTP (2004) study found that the rat was more sensitive than the mouse, as reflected by the liver toxicity findings identifying a LOAEL and NOAEL that were lower in the rats (80 and 40 mg/kg/day) than in the mice (170 and 80 mg/kg/day). Potential points of departure for the intermediate-duration MRL were derived by benchmark dose (BMD analysis) of NTP (2004) rat liver data. Data for liver weight, hepatocyte necrosis, and serum ALT, SDH, bile acids, and cholesterol in one or both sexes were selected for modeling because these end points showed statistically significant changes and best reflected the progression and spectrum of hepatotoxic effects. All available dichotomous models in the EPA Benchmark Dose Software (BMDS version 1.3.2) were fit to the incidence data for hepatocyte necrosis. The continuous-variable models in the software were applied to the data for changes in relative liver weight and serum ALT, SDH, bile acids, and cholesterol.

Appropriate model fits were obtained for the hepatocyte necrosis and serum bile acids data in both sexes and serum ALT and SDH data in males. A summary of the predicted BMDs and 95% lower confidence limits (BMDLs) using the best fitting models for these end points, as well as details of the BMD modeling, are presented in Appendix A. For the hepatocyte necrosis incidence data, predicted doses associated with 30, 20, 10, 5, and 1% extra risks were calculated as possible alternative benchmark responses (BMRs) for the best fitting model. Conventionally, a 10% extra risk has served as a point of departure for MRL determination. However, because the NTP (2004) study examined only 10 animals per group, the limit of detection is above the 10% level, likely in the 20–30% range. For the continuous data, the calculated BMDs and BMDLs are estimates of the doses associated with a change of 1 standard deviation from the control. Predicted doses associated with an increase of 100% (i.e., 2-fold) were also calculated for the best fitting model for the changes in liver enzymes (serum ALT and SDH), as an

increase of this magnitude is sometimes considered to be an indicator of clinical significance for these effects.

The lowest BMDLs were calculated for the male rat serum ALT and SDH data using 1 standard deviation below the control mean as the BMR. The BMDLs for serum ALT (26.56 mg/kg/day) and serum SDH (25.13 mg/kg/day) are approximately half of the BMDL of 53.88 mg/kg/day calculated using the female rat hepatocyte necrosis incidence data and a BMR of 10%. The BMDLs for the serum enzyme changes appear to be overly conservative predictions that have questionable biological plausibilty because they are substantially below the study NOAEL of 80 mg/kg/day. Effects occurring at the NOAEL included increases in serum ALT and SDH that were not adverse and hepatocyte necrosis in 1/10 females. The BMDL10 of 53.88 mg/kg/day for minimal hepatocyte necrosis in female rats was selected as the point of departure for the MRL because it is reasonably consistent with the observed findings. The intermediate-duration oral MRL of 0.5 mg/kg/day was derived by dividing the BMDL by a composite uncertainty factor of 100 (10 for extrapolation from humans and 10 for human variability).

No chronic-duration oral MRL has been derived for 1,1,2,2-tetrachloroethane due to insufficient data. Information on the chronic oral toxicity of 1,1,2,2-tetrachloroethane is limited to a 78-week carcinogenicity bioassay in rats and mice that were exposed by gavage (NCI 1978). Interpretation of the rat study is confounded by high incidences of endemic chronic murine pneumonia, although this is unlikely to have contributed to effects observed in the liver; based on an increased incidence of hepatic fatty changes, a NOAEL of 62 mg/kg/day and LOAEL of 108 mg/kg/day were identified in the rats. The mouse study identified a serious LOAEL of 284 mg/kg/day for reduced survival and lethal kidney lesions (acute toxic tubular nephrosis), but high incidences of hepatocellular tumors in all exposed groups (142 and 284 mg/kg/day) precluded evaluation of noncancer effects in the liver and identification of a NOAEL or less-serious LOAEL in the mice. No chronic oral MRL was derived because lower LOAELs were identified in the more comprehensive and sensitive 14-week dietary study (NTP 2004) used to derive the intermediate-duration MRL.