2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO TETRACHLORO-ETHYLENE IN THE UNITED STATES

The use of tetrachloroethylene as a dry cleaning agent, chemical intermediate, and metal degreasing agent has led to its release to the environment. Tetrachloroethylene has also been shown to be produced naturally by several temperate and subtropical marine macroalgae, but the majority of exposure to tetrachloroethylene is still through anthropogenic sources. It is primarily released to the air where it is slow to degrade, with estimated atmospheric half-lives of approximately 100 days. Data compiled from the EPA Air Quality System indicate that the ambient atmospheric level of tetrachloroethylene is typically <1 µg/m^3. Due to its long atmospheric half-life, it is subject to long-range transport and has been identified in atmospheric samples in remote locations such as Antarctica where no local sources of this substance exist. Levels for tetrachloroethylene in the indoor air tend to be higher. The median value for indoor air in the United States, from 2,195 entries in the EPA's database of volatile organic contaminants (VOC-AMBI), was approximately 4.9 µg/m^3, with an average value of 20.7 µg/m^3.

Tetrachloroethylene is a volatile liquid. When tetrachloroethylene is released to surface water or surface soil, it tends to volatilize quickly; however, tetrachloroethylene is also mobile in soil and has the potential to leach below the soil surface and contaminate groundwater and the air space between soil particles. Tetrachloroethylene can also biodegrade to trichloroethylene, dichloroethylene, vinyl chloride, and ethene through reductive dechlorination. Members of the population can also be exposed to the degradation products, trichloroethylene and vinyl chloride, that are often found as a contaminant in products with tetrachloroethylene. More information on trichloroethylene can be found in ATSDR's *Toxicological Profile for Trichloroethylene*. Information on vinyl chloride can be found in ATSDR's *Toxicological Profile for Vinyl Chloride* and the *Addendum to the Toxicological Profile for Vinyl Chloride*.

Tetrachloroethylene was identified in approximately 4% of 3,498 aquifer samples at a median concentration of 0.090 µg/L in a U.S. Geological Survey (USGS) study. Tetrachloroethylene was among the 15 most frequently detected volatile organic compounds (VOCs). Sampling between 1985 and 1992 at a heavily contaminated site at Camp Lejeune, North Carolina, revealed tetrachloroethylene levels as high as 30,000 µg/L in water samples taken from hydrocone penetration sites, levels as much as 1,580 µg/L in water supply well samples, and levels >200 µg/L in tap water samples.

Tetrachloroethylene has been measured in some foods; however, these levels are generally low. Higher levels of tetrachloroethylene have been detected in foods that were in shops directly above dry cleaning facilities.

The most important routes of exposure to tetrachloroethylene for the general population appear to be inhalation of the compound in the outdoor (ambient) and indoor air and ingestion of contaminated drinking water. People working in the dry cleaning industries or using metal degreasing products may be exposed to elevated levels of tetrachloroethylene. In addition, people residing near contaminated sites or dry cleaning locations may also be exposed to higher levels than the general population. Exposure to tetrachloroethylene and other VOCs can also occur via soil vapor intrusion, which is of particular concern indoors. In addition, exposure can occur from background sources, or indoor sources other than vapor intrusion. Background indoor sources can include consumer products, building materials, combustion processes, dry-cleaned clothing or draperies, drinking water, or occupant activities. Tetrachloroethylene is one of the most commonly detected chemicals in background indoor sources.

Blood concentrations of tetrachloroethylene were below the limit of detection for many of the participants of the U.S. National Health and Nutrition Examination Survey (NHANES); however, the 95th percentile concentrations were 0.190 ng/mL (978 participants), 0.140 ng/mL (1,317 participants), and 0.126 ng/mL (2,940 participants) for survey years 2001–2002, 2003–2004, and 2005–2006, respectively.

2.2 SUMMARY OF HEALTH EFFECTS

Available human and animal data indicate that the central nervous system is a primary target for tetrachloroethylene toxicity. Acute overexposure to tetrachloroethylene vapors results in effects that may include central nervous system depression, loss of consciousness, and even death, while neurobehavioral effects and vision changes are seen with prolonged exposure to concentrations as low as 2–10 ppm. Neurobehavioral changes occur at lower concentrations than other effects. Available animal data also identify the kidney, liver, reproductive system, and developing fetus as targets of tetrachloroethylene toxicity. It is not clear whether these effects might also occur in humans, because humans and animals differ in how their bodies handle tetrachloroethylene. Effects on the liver and kidney are believed to be mediated by metabolites of tetrachloroethylene, while the parent compound is considered to be the active neurotoxicant. Liver effects, including tumors, in mice may be induced primarily by oxidative metabolites, which are produced in larger quantities by mice than are produced in humans or rats. There is suggestive evidence for subtle perturbations of the immune system in animals exposed to

tetrachloroethylene, but the data are limited and the relevance to humans is uncertain at present; further research is needed. Tetrachloroethylene has been shown to cause respiratory, ocular, and dermal irritation, as well as reduced body weight gain. Increased incidences of tumors in the kidney, liver, and lymphoid tissues have been reported in chronic bioassays of rats and mice exposed to tetrachloroethylene via inhalation and oral exposure routes. Available human data provide suggestive, but weak evidence for tetrachloroethylene-induced non-Hodgkin's lymphoma, multiple myeloma, and bladder cancer in humans.

The neurological symptoms of acute inhalation exposure to high levels of tetrachloroethylene are well documented in humans exposed accidentally and include headache, dizziness, drowsiness, ataxia, and mood changes; at higher levels, coma and seizures have occurred. Controlled human exposure studies using lower concentrations of tetrachloroethylene (50–100 ppm) for a few hours per day up to 5 days have also shown alterations in visual-evoked potentials and electroencephalograms (EEGs), as well as deficits in neurobehavioral tests for vigilance and eye-hand coordination.

Neurobehavioral effects have also been observed with prolonged occupational exposure to tetrachloroethylene. Deficits in behavioral tests that measured short-term memory for visual designs, reaction times, perceptual function, attention, and intellectual function were observed in dry cleaning workers exposed to concentrations between 8 and 15 ppm. In addition, loss of color vision (primarily in the blue-yellow range) has been reported in dry cleaning workers exposed to tetrachloroethylene at an average of 7.3 ppm for 2 years; these studies did not assess the potential confounding effect of concomitant occupational exposure to other chemicals. This finding was supported by another study that did not quantify tetrachloroethylene exposure levels. A chronic inhalation Minimal Risk Level (MRL) of 0.006 ppm has been derived based on the lowest-observed-adverse-effect level (LOAEL) of 1.7 ppm identified in a study by Cavalleri et al. (1994); another study was identified as a supportive study for the chronic inhalation MRL (Gobba et al. 1998). The chronic inhalation MRL study was also used as the basis for the chronic oral MRL of 0.008 mg/kg/day, which was derived by route-to-route extrapolation using physiologically based pharmacokinetic (PBPK) modeling. In addition, the chronic-duration inhalation and chronic-duration oral MRLs were adopted as the acute- and intermediate-duration MRLs.

Several studies have been conducted examining neurological or visual function in small numbers of residents of buildings that also housed dry cleaning facilities. One study observed increased reaction times and increased numbers of incorrectly-identified visual stimuli in exposed subjects compared with controls (Altmann et al. 1995). Studies reported decreases in visual contrast sensitivity at low concentrations of tetrachloroethylene (0.05–0.3 ppm); however, these studies were potentially limited by

selection bias and by deficiencies in the testing methods. Further studies of larger numbers of residentially-exposed persons are needed to confirm this finding.

Neurological effects of tetrachloroethylene exposure in laboratory rodents are qualitatively similar to those seen in human studies. Mice and rats have exhibited anesthetic effects after acute exposure to high concentrations (1,750–2,000 ppm), while acute- and intermediate-duration exposures to lower concentrations (200–1,000 ppm) have resulted in effects on visual-evoked potentials, EEG patterns, and neurobehavioral tests in laboratory rodents. Alterations in brain chemistry were noted in rats and gerbils exposed to concentrations from 60 to 320 ppm. Neurological effects in animals exposed orally are similar to those seen after inhalation exposure, and have occurred at doses as low as 5 mg/kg/day.

Numerous epidemiological and experimental animal studies have assessed the potential carcinogenicity of tetrachloroethylene. The Health and Human Services Department (HHS) has classified tetrachloroethylene as "reasonably anticipated to cause cancer in humans based on sufficient evidence from studies in experimental animals". IARC has classified tetrachloroethylene as "probably carcinogenic to humans" based on limited evidence in humans and sufficient evidence in animals (Group 2A), and concluded that "positive associations have been observed for cancer of the bladder" in humans. The National Research Council concluded that there was suggestive evidence for an association between tetrachloroethylene exposure and lymphoma, despite weak and sometimes inconsistent data; limited evidence from epidemiological studies for an association with esophageal cancer; and insufficient evidence for an association with other cancer types including liver, kidney, cervical, lung, and bladder cancer. EPA has characterized tetrachloroethylene as "likely to be carcinogenic in humans by all routes of exposure." The EPA Toxicological Review concluded that epidemiological data support a pattern of association between tetrachloroethylene exposure and bladder cancer, multiple myeloma, and non-Hodgkin's lymphoma. EPA also concluded that epidemiological studies suggest possible associations with other cancers (esophageal, kidney, lung, liver, cervical, and breast cancer), but the data on these cancers were more limited and/or inconsistent.

Animal studies have shown increases in liver cancer in mice exposed via inhalation and gavage, and mononuclear cell leukemia and kidney cancer in rats exposed via inhalation.

The EPA concluded that tetrachloroethylene is likely to be carcinogenic in humans by all routes of exposure based on sufficient evidence in animals and suggestive evidence of a causal association between tetrachloroethylene exposure in humans and bladder cancer, multiple myeloma, and non-Hodgkin's

lymphoma. NTP concluded that tetrachloroethylene is reasonably anticipated to be a human carcinogen based on sufficient evidence in experimental animals. Based on increased risks of esophageal cancer, cervical cancer, and non-Hodgkin's lymphoma in several epidemiologic studies, and increased liver tumors in mice, increased mononuclear cell leukemia in rats, and renal tumors in male rats, the International Agency for Research on Cancer classified tetrachloroethylene as probably carcinogenic to humans (Group 2A).

Tetrachloroethylene has been shown to cause hepatotoxic effects in humans following inhalation exposure and in animals exposed by the inhalation and oral routes. Mice are much more sensitive to the hepatic effects of tetrachloroethylene than rats or humans because of their higher rate of oxidative metabolism of tetrachloroethylene to trichloroacetic acid; trichloroacetic acid, and to a lesser extent dichloroacetic acid, which is believed to be the primary hepatotoxic metabolite of tetrachloroethylene. Acute-duration, accidental exposure of humans to tetrachloroethylene vapors has been reported to cause reversible kidney damage. In addition, a study by Calvert et al. (2011) observed a significantly increased incidence of hypertensive end-stage renal disease among dry cleaning workers exposed to tetrachloroethylene. Studies of tetrachloroethylene exposure in animals have demonstrated renal effects in both rats and mice. Rats are more sensitive to the renal effects of tetrachloroethylene than mice; available data suggest that the rate of formation of reactive metabolites in the kidneys is higher in rats than in mice or humans.

Few human data pertaining to immune system effects of tetrachloroethylene are available, and the studies conducted to date do not provide a clear picture of potential immunotoxic effects. Recent animal studies observed enhancement of antigen-stimulated allergic responses in rats and mice, and enhanced inflammation in rats, after exposure to very low oral doses of tetrachloroethylene (0.0009–0.09 mg/kg/day); however, the effects are of uncertain toxicological and human health relevance, as the degree of change that should be considered adverse is unclear. Additional study of the potential immunotoxicity of tetrachloroethylene is needed; this area represents a significant data gap.

The available epidemiological data on reproductive and developmental effects of exposure to tetrachloroethylene in occupational settings or in contaminated drinking water suffer from a number of limitations (including lack of measured exposure levels, coexposure to other solvents, lack of control for potential confounders, and small numbers of subjects) and do not provide sufficient bases to draw conclusions. Some studies have suggested that there may be an increased risk of adverse reproductive effects, primarily menstrual disorders and spontaneous abortions in women exposed occupationally.

Other studies investigating the populations exposed via drinking water contamination have suggested that there may be an association between birth defects (especially oral cleft and neural tube defects) or growth retardation and tetrachloroethylene contamination.

In animals, increased pre- and post-implantation losses, decreased litter sizes, and decreased survival during lactation have been reported in rats and rabbits, but not in mice, exposed during gestation to concentrations between 300 and 1,254 ppm. Decreased fetal and maternal weight and delayed skeletal development were observed in rats and mice exposed to concentrations of 300–664 ppm during gestation. Gestational exposure to 900 ppm tetrachloroethylene was associated with behavioral and neurochemical alterations in some rat offspring. A gavage study in rats reported that tetrachloroethylene caused an increase in micro/anophthalmia in the offspring of rats treated by gavage with tetrachloroethylene at 900 mg/kg/day on gestation days 6–13. Following oral exposure of mice to 5 mg tetrachloroethylene/kg for 7 days beginning at 10 days of age, hyperactivity was observed at 60 days of age, but not at 17 days of age. Reduced *in vitro* fertilization was seen in the oocytes of rats exposed to 1,700 ppm for 2 weeks, and spermhead abnormalities were observed in mice exposed to 500 ppm for up to 10 weeks, suggesting possible effects on gametes.

2.3 MINIMAL RISK LEVELS (MRLs)

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

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

bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, existing MRLs will be revised.

Inhalation MRLs

- An MRL of 0.006 ppm has been derived for acute-duration inhalation exposure (14 days or less) to tetrachloroethylene.

Data available for acute-duration inhalation MRL derivation include three controlled human exposure studies and several animal studies. The lowest effect levels were identified in the human exposure studies by Altmann et al. (1990, 1992). In the study by Altmann et al. (1992), male volunteers were exposed to tetrachloroethylene at 10 or 50 ppm, 4 hours/day for 4 days. Corresponding equivalent continuous exposure concentrations are 2 and 10 ppm. At 50 ppm, pattern reversal visual-evoked potential latencies increased ($p<0.05$) and significant performance deficits for vigilance ($p=0.04$) and eye-hand coordination ($p=0.05$) were observed. No effects on brainstem auditory-evoked potential were noted at either concentration. Because faint odor was reported by 33% of the subjects at 10 ppm and 29% of the subjects at 50 ppm on the first day of testing, and by 15% of the subjects at 10 ppm and 36% of the subjects at 50 ppm on the last day of testing, the investigators concluded that only a few subjects could identify their exposure condition. In a similar study by Altmann et al. (1990), significant ($p<0.05$) increased latencies for pattern reversal visual-evoked potentials were observed in 10 male volunteers exposed to tetrachloroethylene at 50 ppm, compared to 12 men exposed at 10 ppm. Exposures in this study were also 4 hours/day for 4 days, resulting in equivalent continuous exposure concentrations of 2 and 10 ppm. Effects on brainstem auditory-evoked potentials were not observed in the Altmann et al. (1990) study. Tetrachloroethylene in the blood increased with exposure duration, and linear regression to associate blood tetrachloroethylene with pattern reversal visual-evoked potential latencies was significant ($r=-0.45$, $p<0.03$). Additional tests of neurological function were not conducted in this study. These two studies identified a no-observed-adverse-effect level (NOAEL) of 2 ppm (equivalent continuous exposure concentration).

Hake and Stewart (1977) did not find any changes in flash-evoked potentials or equilibrium tests in four male subjects exposed to increasing concentrations of tetrachloroethylene 7.5 hours/day for 5 days. The subjects were sequentially exposed to 0, 20, 100, and 150 ppm (each concentration 1 week). Corresponding equivalent continuous exposure concentrations are 6.25, 31, and 47 ppm. Subjective evaluation of EEG scores suggested cortical depression in subjects exposed at 100 ppm. Decreases in the Flanagan coordination test were observed at ≥100 ppm.

Animal studies of acute-duration exposure to tetrachloroethylene have demonstrated neurological effects, but at higher concentrations than the human study by Altmann et al. (1990) (>16 ppm continuous equivalent concentration; Boyes et al. 2009; DeCeurriz et al. 1983; Mattsson et al. 1998; NTP 1986; Oshiro et al. 2008; Savolainen et al. 1977). PBPK modeling simulations suggest equivalent tetrachloroethylene blood areas under the curve (AUCs) for rats and humans exposed to the same inhaled concentrations (Chiu and Ginsberg 2011), indicating that the human-equivalent concentrations for these studies are also ≥16 ppm and higher than the human effect levels identified by Altmann et al. (1990, 1992). Thus, animal studies were not considered to be suitable options for acute-duration MRL derivation.

An acute-duration inhalation MRL could be obtained using the controlled human exposure study by Altmann et al. (1990, 1992). This study identified a NOAEL of 2 ppm (equivalent continuous exposure concentration) for neurobehavioral changes. This value is very close to the LOAEL of 1.7 ppm for color vision decrements in the chronic-duration epidemiological study by Cavalleri et al. (1994). Given that the NOAEL was from a study in which exposures were for only 4 hours/day for 4 days, it is uncertain whether this value would be adequately protective for longer exposures (up to 14 days). In male volunteers exposed to 1 ppm tetrachloroethylene for 6 hours, venous blood concentrations continued to increase between 4 and 6 hours (Chiu et al. 2007); likewise, when venous blood was sampled before each of four daily 4-hour exposures to tetrachloroethylene at 10 or 50 ppm, concentrations continued to increase each day from 36 μg/L before the second exposure to 10 ppm, up to 56 μg/L 1 day after the fourth daily exposure (Altmann et al. 1990). These data suggest that continuous or repeated exposures over durations >4 days may yield higher blood levels than seen after four daily 4-hour exposures, and that the NOAEL of 2 ppm observed in the study by Altmann et al. (1990) may not be adequately protective for exposures up to 2 weeks. Because it is very close to the NOAEL from acute-duration exposure, the chronic-duration LOAEL of 1.7 ppm (continuous equivalent exposure concentration) from Cavalleri et al. (1994) represents a better basis for acute and intermediate-duration MRLs. A PBPK model (Chiu and Ginsberg 2011) was used to evaluate the effect of exposure duration on the arterial blood concentration of tetrachloroethylene and the AUC of the blood concentration-time curve at a continuous exposure of 1.7 ppm. While it is not certain whether the neurological effects of tetrachloroethylene result from the parent compound or one or more of its metabolites, the AUC of the tetrachloroethylene blood concentration-time curve is assumed to represent a reasonable surrogate for the internal dose of the ultimate toxicant(s). This simulation showed that arterial blood concentrations and 24-hour AUC blood concentration-time values are very similar after 14 days, 90 days, 365 days, and 2 years of exposure.

These results predict that the blood AUC of tetrachloroethylene is nearly constant after 2 weeks of continuous exposure. The blood concentration reaches approximately 90% of steady state at about 2 weeks of continuous exposure and 99% of steady state at 90 days. Given that the blood concentration of tetrachloroethylene after acute-duration exposure is very similar to that after chronic exposure to the same concentration, the chronic-duration inhalation MRL was adopted as the acute-duration inhalation MRL.

- An MRL of 0.006 ppm has been derived for intermediate-duration inhalation exposure (15–365 days) to tetrachloroethylene.

Epidemiological data in humans and studies in animals have identified the central nervous system as the system most affected at the lowest inhalation exposures. There are no intermediate-duration human epidemiology studies. Available intermediate-duration studies that examined or observed neurological or neurobehavioral effects in animals (e.g., Karlsson et al. 1987; Kyrklund et al. 1988, 1990; Mattsson et al. 1992,1998; Rosengren et al. 1986; Tinston 1995; Wang et al. 1993) identified effect levels much higher than the acute-duration human studies (Altmann et al. 1990, 1992; Hake and Stewart 1977). In addition, the available data suggest that low effect levels in humans from acute-duration exposure are similar to those for the chronic-duration LOAEL of 1.7 ppm (continuous equivalent exposure concentration) from Cavalleri et al. (1994), suggesting that the same MRL is likely applicable to all exposure durations. A PBPK model (Chiu and Ginsberg 2011) was used to evaluate the effect of exposure duration on the arterial blood concentration of tetrachloroethylene and the AUC of the blood concentration-time curve at a continuous exposure of 1.7 ppm. While it is not certain whether the neurological effects of tetrachloroethylene result from the parent compound or one or more of its metabolites, the AUC of the tetrachloroethylene blood concentration-time curve is assumed to represent a reasonable surrogate for the internal dose of the ultimate toxicant(s). This simulation showed that arterial blood concentrations and 24-hour AUC blood concentration-time values are very similar after 14 days, 90 days, 365 days, and 2 years of exposure. These results indicate that the blood concentration of tetrachloroethylene reaches steady state at about 2 weeks of continuous exposure, and that longer exposure durations will not yield higher blood concentrations. Given that the blood concentration of tetrachloroethylene after acute-duration exposure is very similar to that after chronic exposure to the same concentration, the chronic-duration inhalation MRL was adopted as the intermediate-duration inhalation MRL.

- An MRL of 0.006 ppm has been derived for chronic-duration inhalation exposure (≥1 year) to tetrachloroethylene.

This MRL was derived from a study by Cavalleri et al. (1994) with support from a follow-up study by Gobba et al. (1998). Cavalleri et al. (1994) evaluated color vision in 35 tetrachloroethylene-exposed workers (22 dry cleaners and 13 ironers). Color vision was evaluated by the Lanthany 15 Hue desaturated panel (D-15d) test, which is designed for early detection of acquired dyschromatopsia, and results were expressed as Color Confusion Index (CCI). For the entire group of 35 workers (dry cleaners plus ironers), a multivariate analysis showed a significant association between increasing tetrachloroethylene concentration and decreased color vision ($p<0.01$). This association was highly influenced by outcomes for three subjects whose exposures exceeded 12.5 ppm. Mean CCI scores were 1.192±0.133 in dry cleaners compared with 1.089±0.117 in controls ($p=0.007$). Reexamination of the workers 2 years later showed that those workers whose exposure to tetrachloroethylene had increased experienced further decrements in color vision, after controlling for age (which showed a significant association with increasing CCI), while those whose exposure had decreased experienced no changes in color vision (Gobba et al. 1998). A LOAEL of 7.3 ppm was identified for this study. The Cavalleri et al. (1994) and Gobba et al. (1998) studies have some important limitations for deriving exposure-response relationship for effects of tetrachloroethylene on the visual system. The study included a relatively small number of subjects (n=35) who may have experienced exposures to other solvents. Exposure estimates were based on personal air monitoring conducted on a single day, which may be an uncertain metric for long-term exposure of individuals. However, it is not certain whether long-term cumulative exposure is an important determinant of central nervous system and/or visual impairment induced by tetrachloroethylene. Studies conducted in rodents suggest that acute (<15 days) of exposure to tetrachloroethylene can result in changes to visual-evoked potentials (Albee et al. 1991; Boyes et al. 2009; Mattsson et al. 1998), EEG patterns (Albee et al. 1991), and performance in neurobehavioral tests (Oshiro et al. 2008; Savolainen et al. 1977). Therefore, it is possible that the concurrent measurements of exposure, such as those reported in the Cavalleri et al. (1994) and Gobba et al. (1998) studies, are relevant dose-metrics for visual disturbances.

The nervous system is a well-established target of tetrachloroethylene exposure in humans and animals, and effects on this system occur at lower concentrations than effects in other target organs such as the liver or kidney. A substantial number of studies evaluated the effects of inhaled tetrachloroethylene in occupationally exposed individuals, particularly those engaged in dry cleaning activities. More recent studies (Schreiber et al. 2002; Storm et al. 2011) have also provided suggestive evidence of changes in visual contrast sensitivity at low concentrations (one-half to one-thirtieth of the continuous-equivalent concentration used to derive the MRL), in residential populations living in buildings that also housed dry cleaning facilities or in buildings in close proximity to such facilities. These studies were not selected for

use due to limitations including small sample size and study design problems (lack of blinding of investigators, differences between exposed and referent groups that could confound the comparison) that weaken the conclusions that can be drawn from them. The human epidemiological studies in occupationally-exposed populations (especially Cavalleri et al. 1994; Echeverria et al. 1995; Gobba et al. 1998; Seeber 1989), combined with a small number of human controlled exposure experiments (Altmann et al. 1990; Hake and Stewart 1977), have identified central nervous system effects after acute- and chronic-duration exposures to low-level exposures to tetrachloroethylene.

Neurological effects of tetrachloroethylene exposure in laboratory rodents are qualitatively similar to those seen in human studies. Mice and rats have exhibited anesthetic effects after acute exposure to high concentrations (Friberg et al. 1953; Goldberg et al. 1964; NTP 1986; Rowe et al. 1952), while lower concentrations have resulted in effects on visual-evoked potentials (Albee et al. 1991; Boyes et al. 2009; Mattsson et al. 1998), EEG patterns (Albee et al. 1991), neurobehavioral tests (Oshiro et al. 2008; Savolainen et al. 1977), and brain chemistry (Karlsson et al. 1987; Kyrklund et al. 1988; Rosengren et al. 1986; Wang et al. 1993) in laboratory rodents or gerbils.

The LOAEL of 7.3 ppm from Cavalleri et al. (1994) was converted to an equivalent continuous exposure concentration of 1.7 ppm (7.3 ppm x 8/24 hours x 5/7 days). Using the LOAEL of 1.7 ppm, a chronic-duration inhalation MRL of 0.006 ppm is obtained after application of an uncertainty factor of 100 (10 for human variability and 10 for use of a LOAEL). Several genetic polymorphisms in enzymes involved in tetrachloroethylene metabolism (e.g., glutathione-S-transferase, N-acetyl transferase) may contribute to variability in tetrachloroethylene toxicokinetics (Chiu and Ginsberg 2011; Spearow et al. 2017) that, together with toxicodynamics uncertainty, support a total uncertainty factor of 10 for human variability. A modifying factor of 3 was applied for database deficiencies (for inadequate information on potential low-dose immune system effects).

Oral MRLs

- An MRL of 0.008 mg/kg/day has been derived for acute-duration oral exposure (14 days or less) to tetrachloroethylene.

There is abundant evidence for neurological and neurobehavioral effects after chronic, low-level exposures to tetrachloroethylene. While this evidence is primarily available from studies of inhalation exposure, effects after oral exposure are expected to be similar based on the available oral data and pharmacokinetic studies suggesting similar blood levels of parent compound after inhalation and oral

exposure of humans to tetrachloroethylene (see for example, the PBPK model by Chiu and Ginsberg [2011]). Other acute-duration studies using rats and evaluating neurological responses used doses at least 10-fold higher. Fredriksson et al. (1993) identified a LOAEL of 5 mg/kg/day for hyperactivity in male NMRI mice exposed via gavage for 7 days beginning on postnatal day 10 (Fredriksson et al. 1993). Significant pharmacokinetic differences between mice and humans lead to markedly different blood levels of parent compound after oral exposure to tetrachloroethylene; thus, mice are not a good model for neurological effects of tetrachloroethylene exposure in humans. Furthermore, this LOAEL is similar to the LOAEL for chronic human exposure (2.3 mg/kg/day) obtained by route-to-route extrapolation from the inhalation study (Cavalleri et al. 1994) used to derive the chronic inhalation and oral MRLs. Inhalation studies (e.g., Altmann et al. 1990, 1992; Cavalleri et al. 1994) have shown that neurobehavioral effects occur at similar exposure levels after acute- and chronic-duration exposure. Given the lack of suitable acute-duration oral data, and based on the expectation that acute-duration effect levels in humans would be similar to chronic-duration effect levels, the acute-duration oral MRL was set equal to the chronic oral MRL.

- An MRL of 0.008 mg/kg/day has been derived for intermediate-duration oral exposure (15–365 days) to tetrachloroethylene.

There is abundant evidence for neurological and neurobehavioral effects at low exposures to tetrachloroethylene. While this evidence is primarily available from studies of inhalation exposure, effects after oral exposure are expected to be similar based on the available oral data and pharmacokinetic studies suggesting similar blood levels of parent compound after inhalation and oral exposure of humans to tetrachloroethylene (see for example, the PBPK model by Chiu and Ginsberg [2011]). Among human and animal studies of intermediate-duration oral exposure, only Chen et al. (2002) examined sensitive neurological or neurobehavioral effects. The 8-week study by Chen et al. (2002) identified a LOAEL of 3.6 mg/kg/day (adjusted to equivalent continuous dose from administered dose of 5 mg/kg/day, 5 days/week) for impaired nociception (increased latency to tail withdrawal from hot water and increased response latency to hot plate tests) and increased threshold for pentylenetetrazol-induced seizure initiation. PBPK modeling results reported by Chiu and Ginsberg (2011) indicate that the area under the tetrachloroethylene blood concentration-time curve for humans is about twice that of rats across a wide range of continuous oral doses (0.01–1,000 mg/kg/day). Thus, the human-equivalent LOAEL dose from the study by Chen et al. (2002) is 1.8 mg/kg/day. This LOAEL is very similar to the human oral LOAEL of 2.3 mg/kg/day obtained by route-to-route extrapolation from the Cavalleri et al. (1994) chronic inhalation study. Because the human data provide a better basis for MRL derivation than the rat data, the chronic-duration oral MRL was applied to all exposure durations.

- An MRL of 0.008 mg/kg/day has been derived for chronic-duration oral exposure (>1 year) to tetrachloroethylene.

The available human epidemiological studies of oral exposure to tetrachloroethylene do not provide sufficient exposure information to identify effect levels, and are thus not suitable for oral MRL derivation. The only available chronic-duration oral study of tetrachloroethylene in animals is the National Cancer Institute (NCI 1977) cancer bioassay. In this study, survival was decreased at the lowest dose in both rats and mice; thus, it is also not suitable for use in deriving a chronic-duration oral MRL. There is abundant evidence for neurological and neurobehavioral effects after chronic, low exposures to tetrachloroethylene. While this evidence is primarily available from studies of inhalation exposure, effects after oral exposure are expected to be similar based on the available oral data and pharmacokinetic studies suggesting similar blood levels of parent compound after inhalation and oral exposure of humans to tetrachloroethylene (see for example, the PBPK model by Chiu and Ginsberg [2011]). Given the lack of suitable chronic-duration oral data, and the availability of a robust PBPK model for route-to-route extrapolation, the chronic-duration MRL was derived based on route-to-route extrapolation from the chronic-duration inhalation MRL. The internal dose metric chosen for route-to-route extrapolation was the 24-hour AUC of the tetrachloroethylene blood concentration-time curve. Based on simulations of the Chiu and Ginsberg (2011) model, a continuous inhalation exposure to 1.7 ppm yields the same 24-hour AUC as a continuous oral dose of 2.3 mg/kg/day. Using the LOAEL of 2.3 mg/kg/day, a chronic-duration oral MRL of 0.008 mg/kg/day is obtained after application of an uncertainty factor of 100 (10 for human variability and 10 for use of a LOAEL), and a modifying factor of 3 for database deficiencies (for inadequate information on potential low-dose immune system effects).