APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99–499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (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 for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified route and duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive substance-induced endpoint considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that

are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology and Human Health Sciences, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology and Human Health Sciences, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop S102-1, Atlanta, Georgia 30329-4027.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Tetrachloroethylene
CAS Number: 127-18-4
Date: June 2019
Profile Status: Final
Route: [x] Inhalation [ ] Oral
Duration: [x] Acute [ ] Intermediate [ ] Chronic
Graph Key: 128
Species: Human

Minimal Risk Level: 0.006 [ ] mg/kg/day [x] ppm

Reference: Cavalleri A; Gobba F; Paltrinieri M; et al. 1994. Perchloroethylene exposure can induce colour vision loss. Neurosci Lett 179:162-166.

Experimental design: See worksheet for chronic inhalation MRL.

Effects noted in study and corresponding doses: See worksheet for chronic inhalation MRL.

Dose and end point used for MRL derivation: See worksheet for chronic inhalation MRL.

[ ] NOAEL [x] LOAEL

1.7 ppm

Uncertainty Factors used in MRL derivation:

[x] 10 for use of a LOAEL
[ ] 10 for extrapolation from animals to humans
[x] 10 for human variability

Modifying Factors used in MRL derivation:

[x] 3 for database deficiencies (inadequate information on low-dose immune system effects)

Was a conversion used from ppm in food or water to a mg/body weight dose? Not applicable.

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? See worksheet for chronic inhalation MRL.

Other additional studies or pertinent information which lend support to this MRL: 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 a 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 NOAEL of 10 ppm (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 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 equal 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 2 weeks). 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 longer than 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) may represent 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 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 the

24-hour AUC blood concentration-time values are very similar after 14 days, 90 days, 365 days, and 2 years of exposure (see Table A-1 below). These simulations 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 tetrachloroethylene AUC after acute-duration exposure is very similar to that after chronic exposure to the same concentration, the chronic MRL was adopted as the acute-duration MRL.

Table A-1. Predicted Effect of Exposure Duration on Human Blood Levels of Tetrachloroethylene During Continuous (24 Hours/day, 7 Days/week) Inhalation Exposure to 1.7 ppm

	Exposure duration (days)			
PBPK dose metric	14	90	365	728
Area under the blood concentration-time curve (mg-24 hour/L per ppm)	1.799	1.999	2.029	2.033

Agency Contact (Chemical Manager): Rae Benedict

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Tetrachloroethylene
CAS Number: 127-18-4
Date: June 2019
Profile Status: Final
Route: [x] Inhalation [ ] Oral
Duration: [ ] Acute [x] Intermediate [ ] Chronic
Graph Key: 128
Species: Human

Minimal Risk Level: 0.006 [ ] mg/kg/day [x] ppm

Reference: Cavalleri A; Gobba F; Paltrinieri M; et al. 1994. Perchloroethylene exposure can induce colour vision loss. Neurosci Lett 179:162-166.

Experimental design: See worksheet for chronic inhalation MRL.

Effects noted in study and corresponding doses: See worksheet for chronic inhalation MRL.

Dose and end point used for MRL derivation:

[ ] NOAEL [x] LOAEL

1.7 ppm

Uncertainty Factors used in MRL derivation:

[x] 10 for use of a LOAEL
[ ] 10 for extrapolation from animals to humans
[x] 10 for human variability

Modifying Factors used in MRL derivation:

[x] 3 for database deficiencies (inadequate information on low-dose immune system effects)

Was a conversion used from ppm in food or water to a mg/body weight dose? Not applicable.

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? See worksheet for chronic inhalation MRL.

Other additional studies or pertinent information which lend support to this MRL: 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 may be applicable to all exposure durations. A PBPK model (Chiu and Ginsberg 2011) was used to evaluate the effect of exposure duration on 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 and 24-hour AUC values are very similar after 14 days, 90 days, 365 days, and 2 years of exposure (see Table A-2). These simulations 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 tetrachloroethylene AUC after intermediate-duration exposure is the same as that after chronic exposure to the same concentration, the chronic MRL was adopted as the intermediate-duration MRLs.

Table A-2. Predicted Effect of Exposure Duration on Human Blood Levels of Tetrachloroethylene During Continuous (24 Hours/day, 7 Days/week) Inhalation Exposure to 1.7 ppm

	Exposure duration (days)			
PBPK dose metric	14	90	365	728
AUC (mg-24 hour/L per ppm)	1.799	1.999	2.029	2.033

Agency Contact (Chemical Manager): Rae Benedict

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Tetrachloroethylene
CAS Number: 127-18-4
Date: June 2019
Profile Status: Final
Route: [x] Inhalation [ ] Oral
Duration: [ ] Acute [ ] Intermediate [x] Chronic
Graph Key: 128
Species: Human

Minimal Risk Level: 0.006 [ ] mg/kg/day [x] ppm

Reference: Cavalleri A; Gobba F; Paltrinieri M; et al. 1994. Perchloroethylene exposure can induce colour vision loss. Neurosci Lett 179:162-166.

Gobba F; Righi E; Fantuzzi G; et al. 1998. Two-year evolution of perchloroethylene-induced color-vision loss. Arch Environ Health 53:196-198.

Experimental design: Color vision was evaluated in 35 tetrachloroethylene-exposed workers (22 dry cleaners and 13 ironers) with an average of 106 months of exposure. Concentrations were measured in the breathing zone by personal passive samplers. The TWA concentrations for all workers ranged from 0.38 to 31.19 ppm, with mean exposures of 6.23, 7.27, and 4.80 ppm for all workers, dry cleaners, and ironers, respectively. Controls included an equal number (35) of workers without occupational exposure to solvents, and were matched for sex, age, alcohol consumption, and cigarette smoking. Color vision was evaluated by the Lanthany 15 Hue desaturated panel (D-15d) test, which is designed for early detection of acquired dyschromatopsia. The results of the test were expressed as Color Confusion Index (CCI). The subjects were reexamined 2 years later using the same test; results were reported by Gobba et al. (1998).

Effects noted in study and corresponding doses: The results of the color vision test showed a significant decrease in color vision (mainly blue-yellow range) in the dry cleaners exposed to a mean concentration of 7.3 ppm. No significant difference in color vision was found for a group of 13 ironers who experienced exposures to a lower average concentration (4.8 ppm). 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 (±standard deviation) 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 (from a geometric mean concentration of 1.67–4.35 ppm, $p<0.01$) experienced further decrements in color vision (from a mean CCI of 1.16–1.26, $p<0.01$), after controlling for age (which showed a significant association with increasing CCI), while those whose exposure had decreased (from a geometric mean concentration of 2.95–0.66 ppm) experienced no change in CCI (Gobba et al. 1998). Exposures to tetrachloroethylene were highly variable in the Cavalleri et al. (1994) study, varying by as much as 10-fold for certain job activities, and it is possible that the disturbances to color vison were more strongly related to the highest concentrations of tetrachloroethylene observed. The TWA exposure level (7.3 ppm), reported in Cavalleri et al. (1994) was selected as the exposure metric for deriving the MRL because it was the metric used in the statistical analyses that formed the basis for the association between exposure and effects on color vision. The 7.3 ppm concentration was multiplied by 8/24 hours and 5/7 days to yield an equivalent continuous exposure concentration of 1.7 ppm. This conversion assumes linear pharmacokinetics at exposures ≤7.3 ppm (Chiu and Ginsberg 2011). The

1.7 ppm concentration was considered a LOAEL for decreased color vision and was used to derive the chronic MRL.

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 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.

Dose and end point used for MRL derivation:

[ ] NOAEL [x] LOAEL

1.7 ppm, increased CCI

Uncertainty Factors used in MRL derivation:

[x] 10 for use of a LOAEL
[ ] 10 for extrapolation from animals to humans
[x] 10 for human variability

Several genetic polymorphisms in enzymes that are involved in tetrachloroethylene metabolism (e.g., GST, NAT) may contribute to variability in tetrachloroethylene toxicokinetics (Chiu and Ginsberg 2011; Spearow et al. 2017). Together with toxicodynamic uncertainty, these support a total uncertainty factor of 10 for human variability.

Modifying Factors used in MRL derivation:

[x] 3 for database deficiencies (inadequate information on low-dose immune system effects)

Was a conversion used from ppm in food or water to a mg/body weight dose? No.

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose; was a conversion used from intermittent to continuous exposure? To convert from occupational exposure to continuous exposure, the 7.3 ppm concentration was multiplied by 8/24 hours and 5/7 days to yield an equivalent continuous exposure concentration of 1.7 ppm. This conversion assumes linear pharmacokinetics at exposures ≤7.3 ppm (Chiu and Ginsberg 2011).

Other additional studies or pertinent information which lend support to this MRL: 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. There is a substantial number of studies evaluating the effects of inhaled tetrachloroethylene in occupationally exposed individuals, particularly those engaged in dry cleaning activities. More recent studies have also examined residential populations living in buildings that also housed dry cleaning facilities or in buildings

in close proximity to such facilities. The human epidemiological studies (especially Cavalleri et al. 1994; Echeverria et al. 1995; Gobba et al. 1998; Schneiber et al. 2002; Seeber 1989; Storm et al. 2011), 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-, intermediate-, and chronic-duration exposures to tetrachloroethylene.

Storm et al. (2011) recruited adults and children living in New York City buildings with or without colocated dry cleaners for a larger study of visual acuity and contrast sensitivity. There were a number of differences between the exposed and referent groups with respect to education, race/ethnicity, and income. The exposed subjects were stratified into low and high exposure (<100 or >100 μg/m^3 tetrachloroethylene) groups based on 24-hour air samples; exhaled air and blood were also analyzed for tetrachloroethylene. Geometric mean indoor air concentrations of 0.00046, 0.0018, or 0.050 ppm tetrachloroethylene were reported for the referent, low, and high exposure groups of children (n=56, 39, and 11, respectively); for adult participants, the respective concentrations were 0.00043, 0.0017, or 0.070 ppm (n=49, 43, and 12, respectively). Visual acuity testing was limited to far distance visual contrast only, and the response was scored as either perfect or less than perfect. In children, a higher concentration of tetrachloroethylene in indoor air was associated with a higher odds of achieving less than the maximum score (in the poorer performing eye) at a spatial frequency of 12 cycles per degree of visual arc; the effect remained after adjustment for race, ethnicity, and age (adjusted OR of 2.64; 95% CI 1.41–5.52). Visual contrast sensitivity of adults was not associated with measures of tetrachloroethylene exposure. Due to the limitations of this study, including the use of an insensitive vision test and differences between exposed and referent populations that were not accounted for, this study is not considered to be a candidate for MRL derivation.

Schreiber et al. (2002) evaluated a group of residents (n=17) and a group of daycare workers (n=9), each of whom was exposed to tetrachloroethylene for an average of 4 or 5.8 years, respectively, originating from a dry cleaner that was co-located with the residence or daycare. Age- and sex-matched controls without exposure consisted of New York State Department of Health (NYSDOH) employees. Visual acuity, color discrimination, and contrast sensitivity were assessed in these groups; investigators involved in vision testing were not blinded to the exposure status. Ambient and personal air monitoring results suggested mean concentrations of about 0.11 ppm among the residents and about 0.3 ppm among the daycare workers. In both groups, significant ($p<0.001$) decreases in visual contrast sensitivity were observed when compared with the unexposed referent groups. Due to limitations of this study, including small sample size (17 exposed and 17 controls), selection bias in choice of referent population (NYSDOH employees), and vision testing by investigators not blinded to exposure status, it was not selected for use in MRL derivation.

Altmann et al. (1995) evaluated neurobehavioral effects of tetrachloroethylene in 14 persons living above or next to dry cleaning facilities for 1–30 years compared with 23 unexposed controls. The median concentrations of tetrachloroethylene were 0.2 and 0.003 ppm in the apartments of exposed and control subjects, respectively; blood concentrations measured in the examination room (not in the apartments) were 17.8±46.9 μg/L (mean±standard deviation) in exposed subjects and below the 0.5 μg/L detection limit in controls. A neurological test battery, including pattern reversal visual-evoked potentials, continuous performance test, hand-eye coordination, finger tapping, simple reaction time, and visual memory, was administered to both groups. No significant differences between the groups were observed when the unadjusted test results were compared (Altmann et al. 1995). However, when results were analyzed using multivariate analysis to adjust for age, gender, and education, response times in the continuous performance test and simple reaction time were increased ($p<0.05$), and a smaller number of stimuli were identified correctly by the exposed subjects ($p<0.05$) relative to 23 controls. Limitations of this study include its small sample size and differences in educational level between the exposed and referent groups.

Performance on neurobehavioral tests was also assessed in a study of 65 dry cleaning workers exposed to tetrachloroethylene for at least 1 year (Echeverria et al. 1995). The workers were grouped into low, medium, or high exposure categories based on job title and years of employment. Exposure estimates for the three categories were based on air concentrations measured in the breathing zone of clerks, pressers, and operators (8-hour TWA concentrations were 11.2, 23.2, and 40.8 ppm, respectively). Neurobehavioral tests that measured short-term memory for visual designs showed deficits in the high-exposure group (40.8 ppm) relative to the low-exposure group (11.2 ppm). After adjustment for potential confounding, scores for pattern recognition, pattern memory, and visual reproduction were significantly reduced (4, 7, and 14%, respectively; $p<0.01$) in the high-exposure group compared with the low-exposure group. Echeverria et al. (1995) also described four cases referred for neuropsychologic assessment of possible tetrachloroethylene encephalopathy. The subjects performed below expectation on tasks assessing memory, motor, visuospatial, and executive functions, with milder attentional deficits.

Performance on neurobehavioral tests was assessed in 101 dry cleaning workers exposed to tetrachloroethylene for 11–12 years (Seeber 1989). The workers were grouped into low or high exposure categories based on job title and room air measurements at each work location (TWA concentration of 12 or 54 ppm). Low- and high-exposure groups had significantly impaired perceptual function, attention, and intellectual function compared to a population of 84 controls, when evaluated by a battery of psychological tests and questionnaires. The workers were exposed on average 12 and 11 years in the low- and high-exposure groups, respectively (as reported by EPA 2012a). The study showed statistically significant differences, indicative of impairment, between exposed and control groups in test scores for neurological signs, emotional lability, perceptual speed, delayed reactions, digit reproduction, cancellation d2 (fault corrected performance), and digit symbol, after controlling for gender, age, and intelligence. Among these tests, only scores for perceptual speed, delayed reactions, and digit reproduction exhibited monotonic dose-response relationships; for the other tests, the scores were worse in the low-exposure group than in the high-exposure group.

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 of tetrachloroethylene (Friberg et al. 1953; Goldberg et al. 1964; NTP 1986; Rowe et al. 1952). Rats exposed to 3,000 ppm tetrachloroethylene became anesthetized in several hours, while those exposed to 6,000 ppm were anesthetized in minutes (Rowe et al. 1952). Anesthesia was observed in mice within 2.5 minutes of breathing air containing 6,800 ppm tetrachloroethylene (Friberg et al. 1953). Mice inhaling tetrachloroethylene for 4 hours showed signs of anesthesia at a concentration of 2,328 ppm (NTP 1986). Rats became ataxic following exposure to 2,300 ppm for 4 hours (Goldberg et al. 1964). Dyspnea, hypoactivity, hyperactivity, anesthesia, and ataxia were noted in mice and rats exposed to 1,750 ppm for 6 hours/day, 5 days/week for 2 weeks; these effects were not seen at lower concentrations (up to 875 ppm) (NTP 1986). 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), and neurobehavioral tests (Oshiro et al. 2008; Savolainen et al. 1977), as well as brain chemistry (Karlsson et al. 1987; Kyrklund et al. 1988; Rosengren et al. 1986; Wang et al. 1993) in laboratory rodents or gerbils. Male Long-Evans rats exposed for 1.5 hours to concentrations of 250, 500, or 1,000 ppm exhibited reduced amplitude of visual evoked potentials at all exposure concentrations (Boyes et al. 2009). Albee et al. (1991) reported electrophysiological changes including altered shape, reduced amplitude, and decreased latency of flash-evoked potentials; decreased latency of somatosensory evoked potentials; and EEG changes in male rats exposed to tetrachloroethylene at 800 ppm 4 hours/day for 4 days. Similar findings were observed when male F344 rats were exposed 6 hours/day for 4 days to 800 ppm tetrachloroethylene as a pilot study in preparation for a subchronic study (Mattsson et al. 1998). Impairment of sustained attention was observed in male Long-Evans rats exposed for 1 hour to concentrations ≥500 ppm tetrachloroethylene (Oshiro et al. 2008). Open-field behavior (ambulation) was

elevated in groups of 10 male rats exposed to 200 ppm tetrachloroethylene of unspecified purity for 6 hours/day for 4 days (Savolainen et al. 1977). Ambulation was significantly increased 1 hour, but not 17 hours, after the last exposure (Savolainen et al. 1977).

In addition, brain chemistry has been altered in laboratory rodents or gerbils exposed to tetrachloroethylene (Karlsson et al. 1987; Kyrklund et al. 1984, 1988; Rosengren et al. 1986; Wang et al. 1993). Gerbils exposed to 320 ppm continuously for 3 months followed by a 4-month exposure-free period had changes in levels of S-100 protein, a marker for astrocytes as well as other cells in the peripheral nervous system and skin (Rosengren et al. 1986). Rats exposed to 320 ppm continuously for 30 days had changes in brain cholesterol, lipids, and polyunsaturated fatty acids (Kyrklund et al. 1988). Changes in the fatty acid composition of the brain were also observed in rats continuously exposed to tetrachloroethylene at 320 ppm for 90 days (Kyrklund et al. 1990). Gerbils exposed to 60 or 320 ppm had decreased DNA content in portions of the cerebrum (Karlsson et al. 1987; Rosengren et al. 1986). Gerbils exposed to 120 ppm continuously for 12 months had altered phospholipid content (phosphatidylethanolamine) in the cerebral cortex and hippocampus (Kyrklund et al. 1984). In rats exposed to 600 ppm tetrachloroethylene continuously for 4 weeks, cytoskeletal elements of neuronal cells (neurofilament 68 kD polypeptide) were significantly reduced in the frontal cerebral cortex, hippocampus, and brainstem; after 12 weeks at this concentration, a cytosolic marker (glial S-100) and cytoskeletal elements of glial cells (glial fibrillary acid protein) were also significantly reduced in all three brain regions (Wang et al. 1993).

Agency Contact (Chemical Manager): Rae Benedict

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Tetrachloroethylene
CAS Number: 127-18-4
Date: June 2019
Profile Status: Final
Route: [ ] Inhalation [x] Oral
Duration: [x] Acute [ ] Intermediate [ ] Chronic
Graph Key: 128(see Figure 3-1)
Species: Human

Minimal Risk Level: 0.008 [x] mg/kg/day [ ] ppm

Reference: Cavalleri A; Gobba F; Paltrinieri M; et al. 1994. Perchloroethylene exposure can induce colour vision loss. Neurosci Lett 179:162-166.

Gobba F; Righi E; Fantuzzi G; et al. 1998. Two-year evolution of perchloroethylene-induced color-vision loss. Arch Environ Health 53:196-198.

Experimental design: See worksheet for chronic-duration inhalation MRL.

Effects noted in study and corresponding doses: See worksheet for chronic-duration inhalation MRL.

Dose and end point used for MRL derivation:

[ ] NOAEL [x] LOAEL

2.3 mg/kg/day, increased Color Confusion Index (CCI), estimated by route-to-route extrapolation from continuous-equivalent inhalation exposure concentration of 1.7 ppm.

Uncertainty Factors used in MRL derivation:

[x] 10 for use of a LOAEL
[ ] 10 for extrapolation from animals to humans
[x] 10 for human variability

Modifying Factors used in MRL derivation:

[x] 3 for database deficiencies (inadequate information on low-dose immune system effects)

Was a conversion used from ppm in food or water to a mg/body weight dose? Not applicable.

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? See worksheet for chronic-duration inhalation MRL.

Other additional studies or pertinent information which lend support to this 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]). Among human and animal studies identifying neurological or neurobehavioral effects after acute-duration oral exposure, the lowest effect level was identified by Fredrikkson et al. (1993). 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. Other acute-duration studies evaluating neurological responses used doses at least 10-fold higher. In addition, the LOAEL of 5 mg/kg/day identified in mice is similar to the POD of 2.3 mg/kg/day for the chronic oral MRL. Given the lack of suitable acute-duration oral data, and the observation that neurobehavioral effect levels for acute-duration exposure in humans are similar to those for chronic-duration exposure, the acute oral MRL was set equal to the chronic oral MRL.

Agency Contact (Chemical Manager): Rae Benedict

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Tetrachloroethylene
CAS Number: 127-18-4
Date: June 2019
Profile Status: Final
Route: [ ] Inhalation [x] Oral
Duration: [ ] Acute [x] Intermediate [ ] Chronic
Graph Key: 128 (see Figure 3-1)
Species: Human

Minimal Risk Level: 0.008 [x] mg/kg/day [ ] ppm

Reference: Cavalleri A; Gobba F; Paltrinieri M; et al. 1994. Perchloroethylene exposure can induce colour vision loss. Neurosci Lett 179:162-166.

Gobba F; Righi E; Fantuzzi G; et al. 1998. Two-year evolution of perchloroethylene-induced color-vision loss. Arch Environ Health 53:196-198.

Experimental design: See worksheet for chronic-duration inhalation MRL.

Effects noted in study and corresponding doses: See worksheet for chronic-duration inhalation MRL.

Dose and end point used for MRL derivation:

[ ] NOAEL [x] LOAEL

2.3 mg/kg/day, increased Color Confusion Index (CCI), estimated by route-to-route extrapolation from continuous- equivalent inhalation exposure concentration of 1.7 ppm.

Uncertainty Factors used in MRL derivation:

[x] 10 for use of a LOAEL
[ ] 10 for extrapolation from animals to humans
[x] 10 for human variability

Modifying Factors used in MRL derivation:

[x] 3 for database deficiencies (inadequate information on low-dose immune system effects)

Was a conversion used from ppm in food or water to a mg/body weight dose? Not applicable.

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? See worksheet for chronic-duration inhalation MRL.

Other additional studies or pertinent information which lend support to this MRL: 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. An intermediate-duration 8-week study by Chen et al. (2002) identified a LOAEL of 5 mg/kg/day (adjusted to equivalent continuous dose of 3.6 mg/kg/day based on administration on 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 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 virtually identical 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.

It should be noted that the lowest effect levels for acute- or intermediate-duration oral exposure to tetrachloroethylene were from rat and mouse studies of drinking water exposures examining immune stimulation. Seo et al. (2008a, 2012) observed enhancement of antigen-stimulated allergic responses in rats and mice exposed to estimated doses of 0, 0.0009, or 0.09 mg/kg/day (rats) and 0, 0.0025, or 0.26 mg/kg/day (mice) tetrachloroethylene administered in drinking water for 2 or 4 weeks. Little support for the observed enhancement of allergic response has been shown in other animal studies of tetrachloroethylene exposure, and few human data pertaining to immune system effects of tetrachloroethylene are available. The studies by Seo et al. (2008a, 2012) were considered for MRL derivation. However, the evidence for enhanced allergic responses after oral tetrachloroethylene exposure is limited to studies from a single laboratory using small numbers of animals (4–6 per group) and uncertain dose estimates, and support for immune system perturbation in animals or humans exposed to tetrachloroethylene is lacking. Furthermore, the effects reported by Seo and coworkers (enhanced passive and active cutaneous anaphylaxis, increased histamine release, etc.) are of uncertain toxicological and human health relevance, as it is unclear when these responses can be considered adverse. Due to the lack of supporting evidence for immune system perturbation, unclear relevance of the enhanced allergic response to humans, and uncertainty regarding when such an effect is considered adverse, these studies were not used for oral MRL derivation.

Agency Contact (Chemical Manager): Rae Benedict

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Tetrachloroethylene
CAS Number: 127-18-4
Date: June 2019
Profile Status: Final
Route: [ ] Inhalation [x] Oral
Duration: [ ] Acute [ ] Intermediate [x] Chronic
Graph Key: 128 (see Figure 3-1)
Species: Human

Minimal Risk Level: 0.008 [x] mg/kg/day [ ] ppm

Reference: Cavalleri A; Gobba F; Paltrinieri M; et al. 1994. Perchloroethylene exposure can induce colour vision loss. Neurosci Lett 179:162-166.

Gobba F; Righi E; Fantuzzi G; et al. 1998. Two-year evolution of perchloroethylene-induced color-vision loss. Arch Environ Health 53:196-198.

Experimental design: See worksheet for chronic-duration inhalation MRL.

Effects noted in study and corresponding doses: See worksheet for chronic-duration inhalation MRL.

Dose and end point used for MRL derivation:

[ ] NOAEL [x] LOAEL

2.3 mg/kg/day, increased Color Confusion Index (CCI), estimated by route-to-route extrapolation from continuous-equivalent inhalation exposure concentration of 1.7 ppm. The internal dose metric chosen for route-to-route extrapolation was the 24-hour AUC of the tetrachloroethylene blood concentration-time curve. 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). In addition, Chiu and Ginsberg (2011) showed that alternative dose metrics (based on metabolites) yielded minimal differences in route-to-route extrapolation (within 1.4-fold of the extrapolation based on blood AUC). 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.

Uncertainty Factors used in MRL derivation:

[x] 10 for use of a LOAEL
[ ] 10 for extrapolation from animals to humans
[x] 10 for human variability

Modifying Factors used in MRL derivation:

[x] 3 for database deficiencies (inadequate information on low-dose immune system effects)

Was a conversion used from ppm in food or water to a mg/body weight dose? Not applicable.

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? See worksheet for chronic-duration inhalation MRL.

Other additional studies or pertinent information which lend support to this MRL: 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 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 by route-to-route extrapolation from the chronic-duration inhalation MRL using the PBPK model.

Agency Contact (Chemical Manager): Rae Benedict

APPENDIX B. USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public, especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Relevance to Public Health

This chapter provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions:

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The chapter covers end points in the same order that they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, and dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this chapter.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal Risk Levels (MRLs) for noncancer end points (if derived) and the end points from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Chapter 3 Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, ATSDR has derived MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

MRLs should help physicians and public health officials determine the safety of a community living near a hazardous substance emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2, "Relevance to Public Health," contains basic information known about the substance. Other sections such as Chapter 3 Section 3.9, "Interactions with Other Substances," and Section 3.10, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables.

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, MRLs to humans for noncancer end points, and EPA's estimated range associated with an upper- bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 3-1 and Figure 3-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See Sample LSE Table 3-1 (page B-6)

(1) Route of Exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Tables 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures.

(2) Exposure Period. Three exposure periods—acute (less than 15 days), intermediate (15–364 days), and chronic (365 days or more)—are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Health Effect. The major categories of health effects included in LSE tables and figures include death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) Key to Figure. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the two "18r" data points in sample Figure 3-1).

(5) Species. The test species, whether animal or human, are identified in this column. Chapter 2, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 3.4, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequency/Duration. The duration of the study and the weekly and daily exposure regimens are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to “Chemical x” via inhalation for 6 hours/day, 5 days/week, for 13 weeks. For a more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Nitschke et al. 1981).

(7) System. This column further defines the systemic effects. These systems include respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, one systemic effect (respiratory) was investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no adverse effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system, which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused an adverse health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less Serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

(10) Reference. The complete reference citation is given in Chapter 9 of the profile.

(11) CEL. A CEL is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

(12) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates that the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Sample Figure 3-1 (page B-7)

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure Period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the acute and intermediate exposure periods are illustrated.

(14) Health Effect. These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

(15) Levels of Exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16) NOAEL. In this example, the open circle designated 18r identifies a NOAEL critical end point in the rat upon which an intermediate inhalation exposure MRL is based. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17) CEL. Key number 38m is one of three studies for which CELs were derived. The diamond symbol refers to a CEL for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18) Estimated Upper-Bound Human Cancer Risk Levels. This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

(19) Key to LSE Figure. The Key explains the abbreviations and symbols used in the figure.

SAMPLE

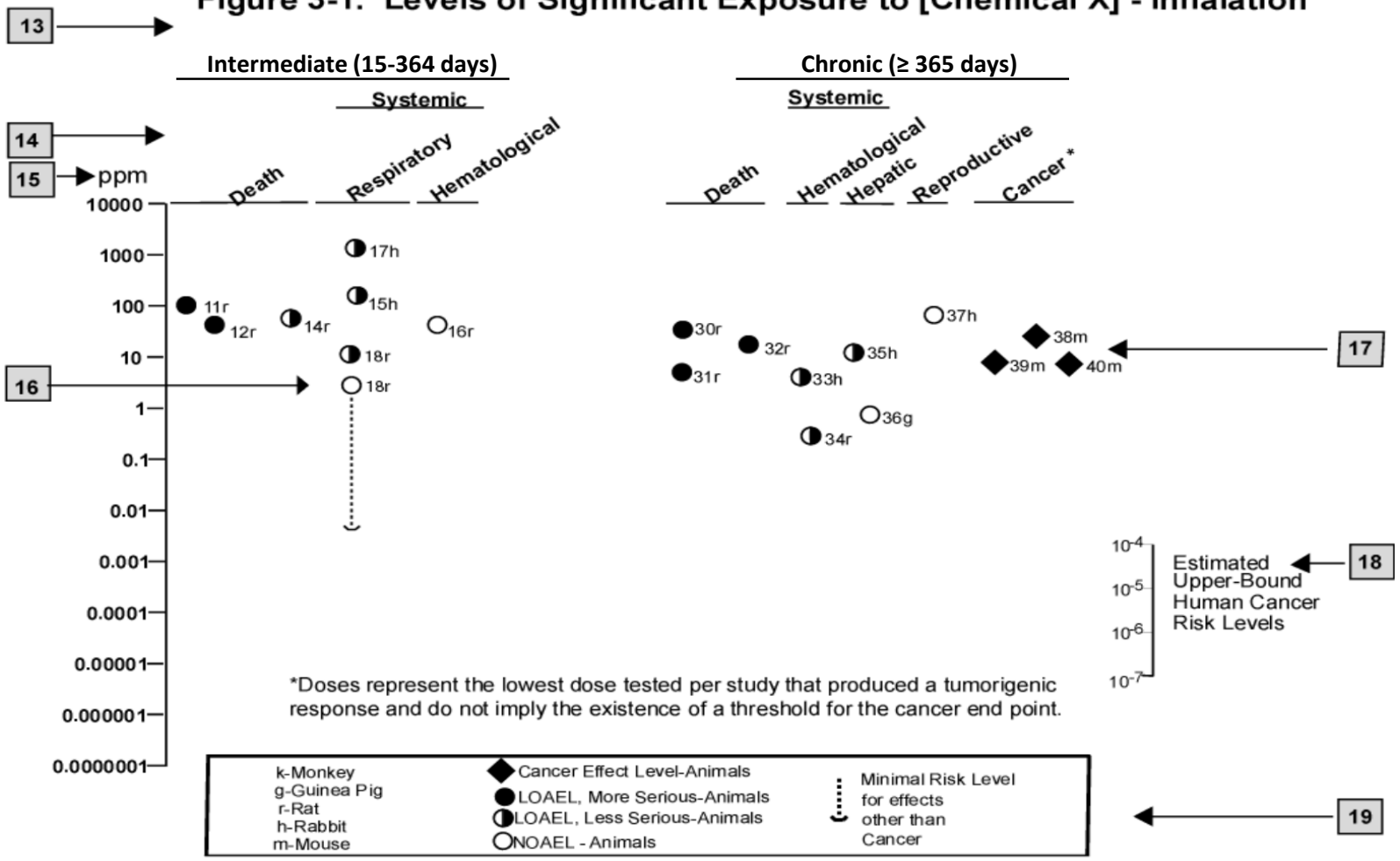
1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
2 → INTERMEDIATE EXPOSURE							
	5	6	7	8	9		10
3 → Systemic	↓	↓	↓	↓	↓		↓
18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
4 → CHRONIC EXPOSURE							
Cancer					11		
					↓		
38	Rat	18 mo 5 d/wk 7 hr/d			20	(CEL, multiple organs)	Wong et al. 1982
39	Rat	89–104 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, nasal tumors)	NTP 1982
40	Mouse	79–103 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, hemangiosarcomas)	NTP 1982

12 → [a] The number corresponds to entries in Figure 3-1.
[b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5×10^{-3} ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

SAMPLE

Figure 3-1. Levels of Significant Exposure to [Chemical X] - Inhalation



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APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
APHA	American Public Health Association
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	best available technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BMD/C	benchmark dose or benchmark concentration
BMD_X	dose that produces a X% change in response rate of an adverse effect
$BMDL_X$	95% lower confidence limit on the BMD_X
BMDS	Benchmark Dose Software
BMR	benchmark response
BSC	Board of Scientific Counselors
C	centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor
DOT	Department of Transportation

DOT/UN/ NA/IMDG	Department of Transportation/United Nations/ North America/Intergovernmental Maritime Dangerous Goods Code
DWEL	drinking water exposure level
ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F_1	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
FR	Federal Register
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
ILO	International Labor Organization
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	kilokilogram; 1 kilokilogram is equivalent to 1,000 kilograms and 1 metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
MA	*trans*,*trans*-muconic acid
MAL	maximum allowable level
mCi	millicurie
MCL	maximum contaminant level

MCLG	maximum contaminant level goal
MF	modifying factor
MFO	mixed function oxidase
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
mt	metric ton
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCEH	National Center for Environmental Health
NCI	National Cancer Institute
ND	not detected
NFPA	National Fire Protection Association
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OR	odds ratio
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OTS	Office of Toxic Substances

OW	Office of Water
OWRS	Office of Water Regulations and Standards, EPA
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
PEL-C	permissible exposure limit-ceiling value
pg	picogram
PHS	Public Health Service
PID	photo ionization detector
pmol	picomole
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	pretreatment standards for new sources
RBC	red blood cell
REL	recommended exposure level/limit
REL-C	recommended exposure level-ceiling value
RfC	reference concentration (inhalation)
RfD	reference dose (oral)
RNA	ribonucleic acid
RQ	reportable quantity
RTECS	Registry of Toxic Effects of Chemical Substances
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SGOT	serum glutamic oxaloacetic transaminase (same as aspartate aminotransferase or AST)
SGPT	serum glutamic pyruvic transaminase (same as alanine aminotransferase or ALT)
SIC	standard industrial classification
SIM	selected ion monitoring
SMCL	secondary maximum contaminant level
SMR	standardized mortality ratio
SNARL	suggested no adverse response level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short term exposure limit
STORET	Storage and Retrieval
TD_{50}	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TLV-C	threshold limit value-ceiling value
TOC	total organic carbon
TPQ	threshold planning quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey
VOC	volatile organic compound
WBC	white blood cell

WHO	World Health Organization
>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result