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 F-57, Atlanta, Georgia 30329-4027.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Toluene
CAS Numbers: 108-88-3
Date: June 2017
Profile Status: Final
Route: [X] Inhalation [ ] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Graph Key: 37
Species: Human

Minimal Risk Level: 2 [ ] mg/kg/day [X] ppm

Reference: Little CH, Georgiou GM, Shelton MJ, et al. 1999. Clinical and immunological responses in subjects sensitive to solvents. Arch Environ Health 54(1):6-14.

Experimental design: Twenty subjects (9 males, 11 females, average age 39.5 years) with a history of solvent exposure and adverse reactions to toluene (i.e., clinically sensitive to toluene) were assessed in a battery of neuropsychological tests prior to and after a 20-minute exposure to 15 ppm toluene. Methods of identification/recruitment of subjects were not reported, and a separate control group was not utilized for neuropsychological testing. The battery of tests included immediate and delayed prose memory, reaction time, letter cancellations, digit symbol, focal length, and STROOP color and color-word tasks.

Effect noted in study and corresponding doses: Statistically significant ($p<0.05$) impairments were measured in immediate and delayed prose memory (number of items recalled decreased 31%), the digit symbol test (number of correct items decreased 11%), and the letter cancellation test (percent correct decreased 5%) following a 20-minute exposure to 15 ppm toluene, compared with pre-exposure scores. A near-significant 15% increase in reaction time was also observed ($p=0.06$). No significant difference between pre- and post-exposure values was found for focal length or the STROOP tests.

Although this study is considered adequate for hazard identification and MRL derivation, the following study limitations are acknowledged: potential selection bias, lack of a separate control group for neuropsychological testing, lack of "blinding" subjects to toluene exposure, and lack of data regarding covariates/comorbid conditions. One or more of these limitations were observed in all available studies evaluating acute controlled toluene exposure in humans.

Dose and end point used for MRL derivation: 15 ppm for minimally adverse neurological effects in a susceptible population.

[ ] NOAEL [X] LOAEL

Uncertainty Factors used in MRL derivation:

[ ] 1 [X] 3 [ ] 10 (for use of a LOAEL)
An uncertainty factor of 3 was used to extrapolate from a LOAEL to a NOAEL, because the observed effects at 15 ppm are minimally adverse and expected to be reversible.
[ ] 1 [ ] 3 [ ] 10 (for extrapolation from animals to humans)
[ ] 1 [X] 3 [ ] 10 (for human variability)
The observed effects were noted in a susceptible/sensitive group of individuals; therefore, a full uncertainty factor of 10 for human toxicokinetic and toxicodynamic variability is not necessary. Using a population-based PBPK model for toluene, Mörk et al. (2014)

calculated distributions for an internal dose of toluene (Cmax in blood) for various subpopulations under various exposure and physical activity conditions, and used the ratio between the 50th percentile values and higher percentile (90, 95, or 99th) values to indicate human variability in toxicokinetic disposition of toluene (Mörk et al. 2014). The ratios were 1.2–1.8 for the general population, 1.4–2.1 for chronically-exposed workers (under various exposure scenarios), and 1.4–3.9 for acutely-exposed workers (under various exposure scenarios). This analysis indicates that the applied uncertainty factor of 3 provides adequate protection for human variability in toxicokinetic disposition of toluene, assuming equal portioning between toxicokinetic (3.3) and toxicodynamic (3.3) in the full human variability uncertainty factor.

Total uncertainty factor = 3 x 3 = 9

MRL = 15 ppm ÷ 9 = 2 ppm (7.6 mg/m^3)

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

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

Was a conversion used from intermittent to continuous exposure? No. Application of concentration x time (Cxt) adjustments (Haber's Rule) for acute exposure scenarios to volatile organic solvents like toluene has been questioned (Oshiro et al. 2011; ten Berge et al. 1986). An example of the basis of this questioning is provided by the results from studies of neurobehavior in animals acutely exposed to trichloroethylene (Bushnell 1997; Crofton and Zhao 1997). Cxt adjustments were shown to underestimate toxic effects when adjusting from relatively long acute durations to shorter durations, and to overestimate toxic effects when adjusting from relatively short acute durations to long acute durations.

Haber's Rule has been modified to reflect observations that concentration often exerts a stronger influence on acute toxicity than does time (ten Berge et al. 1986). The modification raises the concentration term to a power, (n), which is determined empirically with appropriate data (C^nxt; ten Berge et al. 1986). However, determination of the exponent (n) requires adequate concentration-duration-response data, and results from animal studies indicate that the exponent (n) can vary across neurobehavioral end points (e.g., Bushnell 1997).

No duration adjustments were made to exposure concentrations in the available neurobehavioral studies of humans exposed to controlled concentrations of toluene for times varying from 15 minutes to 8 hours, because the available data are for a variety of neurological effects (see further discussion in the next section of this worksheet), and duration adjustment by Haber's rule is likely to overestimate toxic effects when adjusting from short-term (e.g., 15-minute) to longer-term (e.g., 8-hour) exposure durations.

Estimates of brain concentration at the time of testing have been shown in animals to provide a better dose-metric for predicting acute behavioral effects of toluene than cumulative measures of exposure or Cxt adjustments. For rats exposed to varying toluene concentrations in air (1,200–2,400 ppm) and durations (22–70 minutes) and examined for signal detection behavior, effects on accuracy and response-time variables were increased with both increasing concentration and increasing duration (Bushnell et al. 2007). The use of a rat PBPK model to predict internal blood and brain concentrations of toluene as a function of time showed that estimated brain concentration at the time of testing provided a much better explanation of these performance variables than did cumulative measures of dose (AUCs for inhaled dose [ppm-hour] or brain concentration [mg-hour/L]) (Bushnell et al. 2007). Oshiro et al. (2011) tested rats in a signal detection task at various times during exposure to 0, 1,125, 1,450, or 1,660 ppm for up to

24 hours, and reported that brain toluene concentration (estimated using a rat PBPK model) at the time of testing was a better predictor of performance than Cxt adjustment. Analysis of the data also showed that the brain dose-response relationship for the response time variable at 24 hours of exposure was shifted to the right on the dose axis, compared with the relationship determined at 1 hour of exposure. This duration-induced shift of the dose response relationship indicates that extrapolation from 1- to 24-hour exposure would be confounded by an apparent development of tolerance to toluene within this acute time frame.

As discussed in Section 3.4.5, none of the available human PBPK models for toluene contain a brain compartment or have the ability to estimate brain concentrations of toluene. The lack of human data for kinetics of toluene in brain tissue impedes the development of such a model. Such a model could be used to compare results across available acute exposure studies of human neurobehavior, based on estimates of brain concentrations at the time of testing.

Other additional studies or pertinent information that lend support to this MRL: The critical effect of acute inhalation exposure to toluene is on the central nervous system. Multiple studies report subtle neurological effects in healthy individuals following acute exposure to concentrations in the 75–300 ppm range with durations ranging from 20 minutes to 8 hours (Andersen et al. 1983; Baelum et al. 1985; Dick et al. 1984; Echeverria et al. 1991; Gamberale and Hultengren 1972; Kobald et al. 2015; Rahill et al. 1996; von Oettingen et al. 1942). Effects include increased subjective complaints (e.g., headache, sleepiness, dizziness) following exposure to 100 ppm for 6 or 6.5 hours (Andersen et al. 1983; Baelum et al. 1985) or 200 ppm for 3 or 8 hours (von Oettingen et al. 1942), and impairments in psychomotor tests following exposure to 75 or 150 ppm toluene for 7 hours (Echeverria et al. 1991), 100 ppm for 6–8 hours (Dick et al. 1984; Rahill et al. 1996), 200 ppm for 40 minutes (Kobald et al. 2015), and 300 ppm for 20 minutes (Gamberale and Hultengren 1972).

No adverse, dose-related effects have been observed in healthy individuals acutely exposed to 40–50 ppm toluene for 2–6 hours (Andersen et al. 1983; Lammers et al. 2005a; Muttray et al. 2005; Osterberg et al. 2000, 2003). Therefore, a NOAEL of 40 ppm from Anderson et al. (1983) was considered as the basis for the acute MRL, and previously was used as the point of departure (POD) for the acute inhalation MRL (ATSDR, 2000).

However, recent studies indicate that individuals clinically sensitive to toluene experienced subtle neurological effects at lower concentrations in the 15–48 ppm range (Little et al. 1999; Orbaek et al. 1998; Osterberg et al. 2003). In addition to the altered performance in psychomotor tasks observed in individuals clinically sensitive to toluene reported by Little et al. (1999), individuals with multiple chemical sensitivity (MCS) or toxic encephalopathy had significantly higher self-reported scores of fatigue (headache, drowsiness, decreased concentration) during exposure to increasing toluene concentrations over 2 hours (0 ppm [20 minutes], 3 ppm [10 minutes], 6 ppm [10 minutes], 12 ppm [20 minutes], 24 ppm [10 minutes], 48 ppm [20 minutes], and 0 ppm [10 minutes]), compared with healthy referents (Orbaek et al. 1998; Osterberg et al. 2003). During these studies, psychomotor tests were performed before exposure and during the 12- and 48-ppm exposure periods. Both healthy referents and individuals with multiple chemical sensitivity showed increased response time in the reaction-time test (visual stimuli) following exposure, compared with pre-exposure scores (Osterberg et al. 2003). However, the increase was not dose-related in healthy individuals, and exposure-related impairments were not observed in the reaction time-inhibition test (with auditory alarm) or digit symbol test in either group (Osterberg et al. 2003). In a separate study, there were no observed psychomotor impairments in exposed individuals with toxic encephalopathy or healthy referents using the same protocol (Osterberg et al. 2000). A LOAEL of 48 ppm for the studies conducted by Orbaek et al. (1998) and Osterberg et al. (2003) was determined for susceptible individuals based on increased self-reported fatigue. A NOAEL could not be determined, as fatigue scores were not reported at individual exposure concentrations.

Rationale for Selection of Key Study: Both the previously used study in healthy subjects by Andersen et al. (1983) and the study in subjects with MCS by Little et al. (1999) were considered as key studies for the derivation of the acute inhalation MRL. The previous ATSDR profile (ATSDR 2000) derived an acute inhalation MRL of 1 ppm based on the NOAEL of 40 ppm in healthy individuals; however, that derivation utilized a CxT adjustment. As discussed above, this adjustment for continuous exposure is no longer considered appropriate for acute toluene exposure. Thus, use of a POD of 40 ppm (NOAEL for neurological effects in healthy individuals) and an uncertainty factor of 10 (to protect for susceptible populations, which may differ from healthy populations due to toxicodynamic or toxicokinetic variability) would result in an acute inhalation MRL of 4 ppm. However, ATSDR prefers to use data from a susceptible population to better estimate the risk of acute toluene exposure, rather than using a default uncertainty factor of 10 with data from healthy individuals to account for susceptible populations. Therefore, the Little et al. (1999) study in subjects with MCS was selected as the key study and considered the most health-protective option based on the available data.

There is some controversy in the medical community regarding the underlying etiology of the symptoms observed in MSC patients. Reviews published in the last decade show varied findings, concluding that: (1) MCS is predominantly a physiological condition (CHRC 2007; De Luca et al. 2011; Genuis 2010, 2013); (2) available data are inadequate to determine the relative contributions of physiological and psychological factors (NICNAS 2010; Spencer and Shur, 2008); or (3) MCS is primarily psychological or a sociological belief system (Boyd et al. 2012; Das-Munshi et al. 2006; Hetherington and Battershill 2013). Proposed etiologies include the initiation of a hypersensitive immune state by exposure to exogenous toxic exposures (toxicant-induced loss of tolerance); respiratory/neurogenic inflammation; neurochemical, endocrine, or receptor-mediated sensitization; altered metabolic capacity; behavioral conditioning; psychological conditions; or some combination thereof (CHRC 2007; De Luca et al. 2010, 2011; Genuis 2013; NICNAS 2010). While the etiological basis of MCS is still unknown, the exclusion of studies evaluating MCS subjects (who are extensively recognized and discussed in the literature) would be dismissing a potentially sensitive subgroup during the human health risk analysis for toluene. Therefore, despite a lack of understanding of the mechanistic underpinnings of MCS, ATSDR considers the MCS test subjects in Little et al. (1999) as a group of individuals with potentially increased sensitivity to chemical exposures, including exposure to toluene. It is important to note that the test subjects with MCS are not experiencing unique effects not observed in the healthy population; rather, they are experiencing neurological deficits commonly associated with toluene exposure in healthy individuals, but at lower exposure levels. Therefore, the study by Little et al. (1999) was selected as the key study in order to protect this sensitive subpopulation. Since data are inadequate to determine if subjects with MCS are the *most* sensitive subpopulation, a partial uncertainty factor of 3 was used to account for other potentially susceptible populations, as well as human variability in toxicokinetic disposition of toluene.

Agency Contacts (Chemical Manager): Jessilyn Taylor

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Toluene
CAS Numbers: 108-88-3
Date: June 2017
Profile Status: Final
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Graph Key: 229–230, 238
Species: Human

Minimal Risk Level: 1 [ ] mg/kg/day [X] ppm

References: Schäper M, Demes P, Zupanic M, et al. 2003. Occupational toluene exposure and auditory function: results from a follow-up study. Ann Occup Hygiene 47(6):493-502.

Schäper M, Demes P, Kiesswetter E, et al. 2004. Colour vision and occupational toluene exposure: results of repeated examinations. Toxicol Lett 151(1):193-202.

Schäper M, Seeber A, van Thriel, C. 2008. The effects of toluene plus noise on hearing thresholds: an evaluation based on repeated measurements in the German printing industry. Int J Occup Med Environ Health 21(3):191-200.

Seeber A, Schäper M, Zupanic M, et al. 2004. Toluene exposure below 50 ppm and cognitive function: a follow-up study with four repeated measurements in rotogravure printing plants. Int Arch Occup Environ Health 77(1):1-9.

Seeber A, Demes P, Kiesswetter E, et al. 2005. Changes of neurobehavioral and sensory functions due to toluene exposure below 50 ppm? Environ Toxicol Pharmacol 19(3):635-643.

Zupanic M, Demes P, Seeber A. 2002. Psychomotor performance and subjective symptoms at low level toluene exposure. Occup Environ Med 59(4):263-268.

Experimental design: A series of studies by the same group of investigators assessed subjective neurological symptoms, performance on psychomotor tasks, color vision, and hearing in groups of German photogravure printers employed for an average duration of 13.5 years (Schäper et al. 2003, 2004, 2008; Seeber et al. 2004, 2005; Zupanic et al. 2002). These studies compared neurological end points in workers with high exposure to toluene (printers, n=106–181) with workers with low exposure to toluene (end-processors, n=86–152). Current toluene air exposure levels for printers and end-processors were 24.6–26 and 3–3.5 ppm, respectively (measured twice yearly from 1996 to 2001). Historical exposure levels for printers prior to 1995 and prior to 1975 were 40 and 140 ppm, respectively. Historical exposure levels for end-processors prior to 1995 and prior to 1975 were 5 and 40 ppm, respectively. Using job history and current exposure and historical exposure levels, individual TWA exposure levels were calculated. The average TWA levels for printers and end-processors were calculated to be 45 and 10 ppm for subjects included in analyses by Schäper et al. (2003, 2008), 45 and 9 ppm for subjects included in analyses by Seeber et al. (2004, 2005) and Zupanic et al. (2002), and 43 and 9 ppm for subjects included in analyses by Schäper et al. (2004).

Effect noted in study and corresponding doses: Schäper et al. (2003, 2008) did not find any statistically significant differences in audiometric readings from four readings over 5 years in 181 printers, compared with 152 end-processors. Schäper et al. (2004) did not find any differences in color vision assessed

4 times over 5 years in 154 printers, compared with 124 end-processors. Seeber et al. (2004, 2005) and Zupanic et al. (2002) did not find any increase in subjective neurological complaints or decreased performance in psychomotor tasks in 106–154 printers, compared with 86–124 end-processors.

Dose and end point used for MRL derivation: 45 ppm for neurological effects

[X] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

[ ] 1 [ ] 3 [ ] 10 (for use of a LOAEL)
[ ] 1 [ ] 3 [ ] 10 (for extrapolation from animals to humans)
[ ] 1 [ ] 3 [X] 10 (for human variability). The analysis by (Mörk et al. 2014) provides evidence that the uncertainty factor of 10 for human toxicokinetic and toxicodynamic variability provides adequate protection for human variability in toxicokinetic disposition of toluene, assuming equal portioning between toxicokinetic variability (3.3) and toxicodynamic variability (3.3) (see discussion in the acute inhalation MRL worksheet).

MRL = 45 ppm x 5 days/7 days x 8 hours/24 hours ÷ 10 = 1 ppm (3.8 mg/m^3)

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

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

Was a conversion used from intermittent to continuous exposure? The exposure concentration was adjusted to continuous exposure basis as shown above.

Other additional studies or pertinent information that lend support to this MRL: Twenty-four human occupational studies evaluating neurological end points following exposure predominately or exclusively to toluene were considered for deriving the chronic inhalation MRL (see Table A-1). Numerous studies identified subtle neurological effects following occupational exposure to toluene at concentration estimates ranging from 50 to 140 ppm, including subjective neurological symptoms, altered performance on neurobehavioral and psychomotor tasks, impaired color vision, and hearing loss (Abbate et al. 1993; Boey et al. 1997; Foo et al. 1990; Kang et al. 2005; Matsushita et al. 1975; Murata et al. 1993; Neubert et al. 2001; Nordling Nilson et al. 2010; Orbaek and Nise 1989; Ukai et al. 1993; Vrca 1995, 1996, 1997b; Yin t al. 1987; Zavalic et al. 1998a, 1998b, 1998c). Several occupational studies identify NOAELs for these effects in the range of 20–46 ppm toluene (Chouanière et al. 2002; Gericke et al. 2001; Kang et al. 2005; Nakatsuka et al. 1992; Neubert et al. 2001; Schäper et al. 2003, 2004, 2008; Seeber et al. 2004, 2005; Ukai et al. 1993; Zavalic et al. 1998a, 1998c; Zupanic et al. 2002). One outlier study reported that no increases in subjective symptoms or changed performance on psychomotor tasks were found in printers exposed to 9–83 ppm and laboratory workers exposed to 184–467 ppm when analyzed together, compared with unexposed referents (Deschamps et al. 2001). However, the findings for the two groups were not reported separately. The NOAEL for this study was set at the average of the midpoints of the exposure ranges for the two groups of workers (midpoint factory, 46 ppm; midpoint laboratory, 325.5; average, 185.75 ppm). Studies that evaluated only subjective end points (Ukai et al. 1993; Yin et al. 1987) were not considered for deriving the chronic inhalation MRL.

Table A-1. Chronic Occupational Studies Considered for Deriving the Chronic Inhalation MRL

Study author/date	Neurological end point(s) evaluated (altered end points at LOAEL are in bold)	NOAEL	LOAEL
Abbate et al. 1993	**BAEPs**		97
Boey et al. 1997	Logical memory, **digit span, visual reproduction, Benton visual retention test, trail making test, symbol digit modality test, grooved pegboard test**, and finger tapping test		90.9
Chouanière et al. 2002	Subjective symptoms, simple reaction time, symbol digit substitution, digit span forwards and backwards, pattern memory test, associate learning and recall	27	
Deschamps et al. 2001	Subjective symptoms, vocabulary test, simple reaction time, digit symbol, digit span forwards and backwards, continuous tracking, color word vigilance, and switching attention test	186[a]	
Foo et al. 1990	**Benton visual retention, visual reproduction, trail making, grooved peg board, digit span, digit symbol,** finger tapping, and simple reaction time		88
Gericke et al. 2001	Subjective symptoms, assessment of color vision (test used was not specified), and a battery of psychomotor tests (immediate visual memory, digit span forward and backward, and digit symbol)	24	
Kang et al. 2005	**Finger tapping, selective attention,** digit span forward and backward, symbol digit, and simple reaction time tests	20	75
Matsushita et al. 1975	**Subjective symptoms, tendon reflexes, grasping power**, and tapping tempo		84
Murata et al. 1993	**Nerve conduction** (EKG, median nerve)		83
Nakatsuka et al. 1992	Color vision (Lanthony's new color test and Ishihara's color/vision test)	46	
Neubert et al. 2001	Subjective symptoms, digit span forward/backward, visuomotor performance, visual memory, self-rating of feelings, bisensory vigilance, **flicker fusion frequency**, and personality dispositions	33	75
Orbaek and Nise 1989; Nordling Nilson et al. 2010	Initial: **Subjective symptoms** and psychometric tests including verbal, logical inductive, spatial memory, perceptual, and psychomotor tests 20-year follow-up: Subjective symptoms and psychometric tests including verbal, logical inductive (**reasoning**), spatial memory (**associative learning**), perceptual, psychomotor tests, trail-making test, STROOP test, and memory tests		140
Schäper et al. 2003, 2008[b]	Audiometry (two reports of the same study)	45	
Schäper et al. 2004[b]	Color vision (Lanthony desaturated panel D-15d, Ishihara plates)	43	
Seeber et al. 2004, 2005[b]	Subjective symptoms, symbol digit substitution, switching attention, and memory span (initial study 2004; follow-up analysis of the same data in 2005)	45	
Vrca 1995, 1997[b]	**VEPs**		50
Vrca et al. 1996	**BAEPs**		50

Table A-1. Chronic Occupational Studies Considered for Deriving the Chronic Inhalation MRL

Study author/date	Neurological end point(s) evaluated (altered end points at LOAEL are in bold)	NOAEL	LOAEL
Zavalic 1998a, 1998c	**Color vision** (Lanthony D-15 desaturated test; Verriest's classification of color vision loss)	35	156
Zavalic 1998b	**Color vision** (Lanthony D-15 desaturated test; Verriest's classification of color vision loss)		120
Zupanic et al. 2002[b]	Subjective symptoms, manual dexterity: steadiness, line tracing, aiming, tapping, and peg board	45	

[a]Two toluene-exposed groups were described by Deschamps et al. (2001): 36 factory workers (9–83 ppm) and 36 laboratory workers (184–467 ppm). No average exposure levels were reported, and the two groups were analyzed together. Therefore, the NOAEL was set at the average of the midpoints of the exposed ranges (midpoint factory, 46 ppm; midpoint laboratory, 325.5; average, 185.75 ppm).
[b]Studies selected for derivation of the chronic MRL.

BAEP = brainstem auditory evoked potential; LOAEL = lowest-observed-adverse-effect level; MRL = minimal risk level; NOAEL = no-observed-adverse-effect level; VEP = visual-evoked potential

After reviewing all available studies, the series of six recent studies in German rotogravure printers reporting NOAELs of 43–45 ppm for hearing loss (Schäper et al. 2003, 2008), color vision (Schäper et al. 2004), and psychomotor function (Seeber et al. 2004, 2005; Zupanic et al. 2002) were selected to support a POD of 45 ppm. This POD NOAEL value is lower than all LOAEL values in Table A-1 and is consistent with the mean and median NOAEL values from all studies summarized in Table A-1 (50 and 43 ppm, respectively).

The previous draft used a POD based on a LOAEL of 35 ppm for color vision impairment in the studies by Zavalic et al. (1998a, 1998c). The current evaluation of this study arrives at a different LOAEL determination. In Zavalic et al. (1998a), the color confusion index (CCI) was statistically significantly increased by 14% in 32 printers exposed to geometric mean toluene concentrations of 156 ppm, respectively, when compared with 83 unexposed controls on Monday morning prior to their work shift. However, the CCI in 41 shoemakers exposed to geometric mean toluene concentrations of 35 ppm were not significantly elevated when compared with controls. When alcohol consumers were excluded, the CCI in 27 shoemakers and 10 printers was significantly increased by 4 and 11%, respectively, compared with 36 controls. When adjusted for age and alcohol consumption, CCIs were significantly higher in both shoemakers and printers (adjusted mean CCI values were not reported). Individual adjusted CCIs were significantly correlated with individual exposure estimates (air, blood, or urine) in printers, but not shoemakers. In Zavalic et al. (1998c), further analysis of color vision loss in these groups of workers demonstrated that total dychromatopsia (combined incidence of blue-yellow and red-green color confusion [dyschromatopsia type II] and just blue-yellow color confusion [dyschromatopsia III]) was significantly increased in printers, but not shoemakers, compared with unexposed workers. Dyschromatopsia type I (red-green color confusion only) was not observed in any exposed or unexposed workers Zavalic et al. 1998c). Taken together, these studies indicate a clear LOAEL of 156 ppm for color vision loss in printers, based on increased CCIs significantly associated with individual estimates of toluene exposure and increased prevalence of dyschromatopia. A NOAEL of 35 ppm was identified, as it is unclear if the statistically significant findings for increased CCI in the small sample of non-alcohol consuming workers or adjusted CCIs in all workers represents an adverse effect, especially since the magnitude of change was small and individual CCIs in this group were not associated with toluene exposure estimates in the air, blood, or urine. This interpretation of findings is consistent with the

interpretation in the most recent Integrated Risk Information System (IRIS) document (EPA 2005a), which considers the lower exposure level to be a NOAEL for color vision impairment.

Agency Contacts (Chemical Manager): Jessilyn Taylor

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Toluene
CAS Numbers: 108-88-3
Date: June 2017
Profile Status: Final
Route: [ ] Inhalation [X] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Graph Key: 18
Species: Rat

Minimal Risk Level: 0.8 [X] mg/kg [ ] ppm

Reference: Dyer RS, Bercegeay MS, Mayo LM. 1988. Acute exposures to p-xylene and toluene alter visual information processing. Neurotoxicol Teratol 10:147-153.

Experimental design: Male Long-Evans rats (12/group) were administered doses of toluene in corn oil of 0, 250, 500, and 1,000 mg/kg by gavage. FEP tests were administered 45 minutes later as a test of the ability of the nervous system to process visual information. In another study (time-course), toluene was administered to male Long-Evans rats (16/group) at doses of 0 and 500 mg/kg by gavage, and FEP tests were performed 4, 8, 16, and 30 hours later.

Effect noted in study and corresponding doses: The amplitude of the N3 peak of the FEP was significantly decreased ($p<0.05$) by toluene exposure at all doses. The magnitude of this decrease in peak amplitude was not dose-related. In the time course study, 500 mg/kg also decreased the amplitude of the FEP; at this dose, little change in magnitude of peak N3 depression had occurred 8 hours post-treatment; by 16 hours, recovery was complete.

Dose and end point used for MRL derivation: 250 mg/kg for neurological effects

[ ] NOAEL [X] LOAEL

Uncertainty Factors used in MRL derivation:

[ ] 1 [X] 3 [ ] 10 (for use of a LOAEL)
[ ] 1 [ ] 3 [X] 10 (for extrapolation from animals to humans)
[ ] 1 [ ] 3 [X] 10 (for human variability)

MRL = 250 mg/kg/day ÷ 300 = 0.8 mg/kg/day

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

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

Was a conversion used from intermittent to continuous exposure? No.

Other additional studies or pertinent information that lend support to this MRL: Human data suitable for deriving an acute oral MRL for toluene are not available.

Only a limited number of acute-exposure rat studies have evaluated neurological end points in addition to the study by Dyer et al. (1988) and all of them evaluated higher doses. These studies report transient increases in motor activity following single oral doses of 650–5,220 mg/kg (Gordon et al. 2007, 2010; MacPhail et al. 2012; Mehta et al. 1998), abnormal gait following single oral doses of 3,915–5,220 mg/kg (Mehta et al. 1998), and ototoxicity following exposure to 780 mg/kg/day, 5 days/week for 2 weeks (Gagnaire and Langlais 2005). Additionally, numerous acute-duration animal inhalation studies have reported neurological effects from toluene (see Table 3-1 for complete list). Human inhalation studies have focused on the central nervous system as the critical toxicity target for acute-duration toluene exposure (Andersen et al. 1983; Baelum et al. 1985; Dick et al. 1984; Echeverria et al. 1989; Gamberale and Hultengren 1972; Rahill et al. 1996; von Oettingen et al. 1942).

An additional study that lends support to the MRL is a developmental study that reported altered cortical cell proliferation and migration in offspring following exposure of pregnant rats to gavage doses of 0 or 650 mg/kg/day toluene in corn oil on GDs 6–19 (Gospe and Zhou 2000). Cortical cell density was significantly decreased by 12.5% in all layers of the cerebral cortex in toluene-exposed pups on PND 21, compared with controls. The greatest decrease (26.8%) was observed in layer IV. Decreased density was attributed to altered neurogenesis, as neurons labeled with BrdU from injections on GDs 13–21 were decreased in numbers and exhibited altered migration patterns.

Agency Contacts (Chemical Manager): Jessilyn Taylor

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Toluene
CAS Numbers: 108-88-3
Date: June 2017
Profile Status: Final
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 45-47
Species: Mouse

Minimal Risk Level: 0.2 [X] mg/kg/day [ ] ppm

References: Hsieh GC, Sharma RP, Parker RD. 1989. Immunotoxicological evaluation of toluene exposure via drinking water in mice. Environ Res 49:93-103.

Hsieh GC, Parker RD, Sharma RP, et al. 1990a. Subclinical effects of groundwater contaminants. III. Effects of repeated oral exposure to combinations of benzene and toluene on immunologic responses in mice. Arch Toxicol 64:320-328.

Hsieh GC, Sharma RP, Parker RD. 1991. Hypothalamic-pituitary-adrenocortical axis activity and immune function after oral exposure to benzene and toluene. Immunopharmacol 21:23-31.

Experimental design: A series of studies evaluated immune end points in male CD-1 mice (5/group) administered toluene in their drinking water for 28 days at concentrations of 0, 5, 22, or 105 mg/kg/day (Hsieh et al. 1989, 1991) or 0, 22, or 84 mg/kg/day (Hsieh et al. 1990a). In Hsieh et al. (1989, 1990a), rats were weighed, sacrificed, and examined for gross pathological lesions at 28 days. Spleen and thymus were weighed and hematology was performed. Spleens were assessed for cellularity, and splenocytes were used in *in vitro* immune assays (mitogen-stimulated lymphocyte proliferation, mixed lymphocyte reaction, IL-2 production assay, and antibody PFC response). Hsieh et al. (1990a) also measured the *in vitro* cell-mediated cytolysis response. In Hsieh et al. (1991), immune function was only assessed using the IL-2 assay in cultured splenocytes. A level of $p<0.05$ was considered statistically significant unless otherwise stated.

Effect noted in study and corresponding doses: In Hsieh et al. (1989), significantly decreased thymus weight and significantly depressed immune responses were observed in all *in vitro* immune assays at 105 mg/kg/day, compared with control. IL-2 production and mitogen-stimulated lymphocyte proliferation were also significantly decreased at 22 mg/kg/day compared with control. In Hsieh et al. (1990a), significantly depressed immune responses were observed in the PFC assay and mixed lymphocyte reaction at 84 mg/kg/day. The mixed lymphocyte reaction was also significantly depressed at 22 mg/kg/day. In Hsieh et al. (1991), the IL-2 production assay was significantly depressed at 105 mg/kg/day. Taken together, these studies consistently reported diminished immune responses in multiple *in vitro* immune assays following *in vivo* exposure to 84–105 mg/kg/day in drinking water for 28 days, compared with controls. A couple of immune assays were altered at 22 mg/kg/day, but findings were not consistent between the three Hsieh studies. Additionally, the antibody PFC assay was significantly altered at 84 and 105 mg/kg/day, but not at 22 mg/kg/day (Hsieh et al. 1989, 1990a). The PFC *in vitro* assay is considered the most predictive assay of impaired immune function (Luster et al. 1992). Collectively, results from these studies support a NOAEL of 22 mg/kg/day for immune effects.

Dose and end point used for MRL derivation: 22 mg/kg/day for immune depression

[X] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

[ ] 1 [ ] 3 [ ] 10 (for use of a LOAEL)
[ ] 1 [ ] 3 [X] 10 (for extrapolation from animals to humans)
[ ] 1 [ ] 3 [X] 10 (for human variability)

MRL = 22 mg/kg/day ÷ 100 = 0.2 mg/kg/day

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Yes. The study authors calculated that exposure to 0, 17, 80, and 405 mg/L in drinking water for 28 days was equivalent to toluene doses of 0, 5, 22, and 105 mg/kg/day, respectively, over this period based on water consumption (Hsieh et al. 1989). These equivalent doses were used for the Hsieh et al. (1991) study. Toluene concentration in Hsieh et al. (1990a) was reported to be 0, 80, or 325 mg/L in drinking water. The equivalent dose for the 80 mg/L group from previous studies was adopted for the 1990a study (22 mg/kg/day). Using the conversion factor from the high-dose group from Hsieh et al. (1989) (1 mg/L = 0.259 mg/kg/day), the equivalent dose for the 325 mg/L group was calculated to be 84 mg/kg/day.

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

Was a conversion used from intermittent to continuous exposure? No.

Other additional studies or pertinent information that lend support to this MRL: Human data suitable for deriving an intermediate oral MRL for toluene are not available.

No other intermediate-duration oral studies evaluating immune function were located. In an acute oral study, Burns et al. (1994) reported that exposure to 600 mg/kg/day via gavage for 14 days did not diminish immune response in *in vitro* immune assays or decrease host resistance to *Listeria monocytogenes, S. pneumoniae, Plasmodium yoelii*, B16F10 melanoma, or PYB6 fibrosarcoma in female mice, compared with controls. The EPA (2005) discounted immune effects as a critical effect for the IRIS RfD due to the absence of immune effects in the Burns et al. (1994) study and apparent conflicting evidence for toluene immunotoxicity in animals. However, exposure was under different conditions (gavage versus drinking water) and for a shorter duration (14 days versus 28 days) in the Hseih et al. studies than in the Burns et al. (1994) study. The sex and strain also differed between the studies (B6C3F1 versus CD-1; females versus males). Therefore, the lack of observed effects in the Burns et al. (1994) study may not represent conflicting evidence; rather, it may be due to the shorter duration, different exposure conditions, and/or differences between sexes or strains.

In animal inhalation studies, evidence for toluene effects on the immune system include the finding of decreased resistance to mortality from respiratory infection by *S. zooepidemicus* in a study of mice exposed for 3 hours to toluene concentrations as low as 2.5 ppm, but not 1 ppm (Aranyi et al. 1985).

Hepatic, renal, and neurological effects were also considered as bases of the intermediate-duration oral MRL. However, the PODs for hepatic, renal, and neurological effects (see Table A-2) are all higher than the selected POD for immune effects. Additionally, findings for increased liver and kidney weight were not consistent between studies, nor were they associated with histopathological changes.

Table A-2. Animals Studies Considered for Deriving the Intermediate-Duration Oral MRL

Study	End point(s) evaluated	Significant effects at LOAEL	NOAEL	LOAEL
Immuno/lymphoreticular effects				
NTP 1990; 13 weeks; F344 rats 0, 312, 650, 1,250, 2,500, and 5,000 mg/kg/day via gavage (5 days/week)	Spleen and thymus weight and histology (0, 2,500, and 5,000 mg/kg/day groups only)	All 5,000 mg/kg/day mice died within 1 week, so the NOAEL was set at 2,500 mg/kg/day	2,500	–
Hsieh et al. 1989[a]; 28 days; CD-1 male mice 0, 5, 22, and 105 mg/kg/day via drinking water	Immune assays (PFC assay, mixed lymphocyte response, mitogen stimulation, IL-2 immune response); spleen and thymus weight and gross pathology	Decreased thymus weight, depressed immune response in all assays (mitogen-stimulated lymphocyte proliferation and IL-2 immunity were also depressed at 22 mg/kg/day)	22 (males)	105 (males)
Hsieh et al. 1990a[a]; 28 days; CD-1 male mice 0, 22, and 84 mg/kg/day via drinking water	Immune assays (PFC assay, mixed lymphocyte culture, mitogen stimulation, IL-2 immune response, cell-mediated cytotoxicity); spleen and thymus weight and gross pathology	Depressed immune response in PFC assay and mixed lymphocyte culture (mixed lymphocyte culture was also depressed at 22 mg/kg/day)	22 (males)	84 (males)
Hsieh et al. 1991[a]; 28 days; CD-1 male mice 0, 5, 22, and 105 mg/kg/day via drinking water	IL-2 immune response assay	Depressed IL-2 immune response	22 (males)	105 (males)
NTP 1990; 13 weeks; B6C3F1 mice 0, 312, 650, 1,250, 2,500, and 5,000 mg/kg/day via gavage (5 days/week)	Spleen and thymus weight and histology (0, 2,500, and 5,000 mg/kg/day groups only)	All 5000 mg/kg/day mice died within 1 week, so the NOAEL was set at 2,500 mg/kg/day	2,500	–
Hepatic effects				
NTP 1990; 13 weeks; F344 rats 0, 312, 650, 1,250, 2,500, and 5,000 mg/kg/day via gavage (5 days/week)	Liver weight, histology, clinical chemistry	Increased absolute and relative liver weight	312 M 625 (females)	625 M 1,250 (females)
Wolf et al. 1956; 6 months; Wistar rats 0, 118, 354, and 590 mg/kg/day via gavage (5 days/week)	Liver weight, histology	No adverse-effect level determined for liver end points	590 (females)	–
Hsieh et al. 1989; 28 days; CD-1 male mice 0, 5, 22, and 105 mg/kg/day via drinking water	Liver weight, gross pathology	Increased liver weight	22 (males)	105 (males)

Table A-2. Animals Studies Considered for Deriving the Intermediate-Duration Oral MRL

Study	End point(s) evaluated	Significant effects at LOAEL	NOAEL	LOAEL
Hsieh et al. 1990a; 28 days; CD-1 male mice 0, 22, and 84 mg/kg/day via drinking water	Liver weight, gross pathology	No adverse-effect level determined for liver end points	84 M	–
NTP 1990[b]; 13 weeks; B6C3F1 mice 0, 312, 650, 1,250, 2,500, and 5,000 mg/kg/day via gavage (5 days/week)	Liver weight, histology, clinical chemistry	Increased absolute (females) and relative (males and females) liver weight	625 (males) – (females)	1,250 (males) 312 (females)
Renal effects				
NTP 1990[a]; 13 weeks; F344 rats 0, 312, 650, 1,250, 2,500, and 5,000 mg/kg/day via gavage (5 days/week)	Kidney weight, histology, clinical chemistry, urinalysis	Increased absolute and relative kidney weight (increased urinary bladder hemorrhage at higher doses)	312 (males) 625 (females)	625 (males) 1,250 (females)
Wolf et al. 1956; 6 months; Wistar rats 0, 118, 354, and 590 mg/kg/day via gavage (5 days/week)	Kidney weight, gross morphology	No adverse-effect level determined for kidney effects	590 (females)	–
Hsieh et al. 1989; 28 days; CD-1 male mice 0, 5, 22, and 105 mg/kg/day via drinking water	Kidney weight, gross pathology	No adverse-effect level determined for kidney effects	105 (males)	–
Hsieh et al. 1990a; 28 days; CD-1 male mice 0, 22, and 84 mg/kg/day via drinking water	Kidney weight, gross pathology	No adverse-effect level determined for kidney effects	84 (males)	–
NTP 1990; 13 weeks; B6C3F1 mice 0, 312, 650, 1,250, 2,500, and 5,000 mg/kg/day via gavage (5 days/week)	Kidney weight, histology, clinical chemistry, urinalysis	All 5000 mg/kg/day mice died within 1 week, so the NOAEL was set at 2,500 mg/kg/day	2,500	–
Neurological effects				
NTP 1990; 13 weeks; F344 rats 0, 312, 650, 1,250, 2,500, and 5,000 mg/kg/day via gavage (5 days/week)	Brain weight, histology, clinical signs	Brain necrosis in hippocampus and cerebellum (increased absolute brain weight and clinical signs of neurotoxicity at 2,500 mg/kg/day)	625 (males)	1,250 (males)
NTP 1990; 13 weeks; B6C3F1 mice 0, 312, 650, 1,250, 2,500, and 5,000 mg/kg/day via gavage (5 days/week)	Brain weight, histology, clinical signs	Increased absolute brain weight (males); clinical signs of neurotoxicity at 2,500 mg/kg/day (males and females)	625 (males) 1,250 (females)	1,250 (males)

Table A-2. Animals Studies Considered for Deriving the Intermediate-Duration Oral MRL

Study	End point(s) evaluated	Significant effects at LOAEL	NOAEL	LOAEL
Developmental effects				
Kostas and Hotchin 1981; GDs 0–21 and PNDs 0–55; Nya:NYLAR mice 0, 4, 21, and 106 mg/kg/day via drinking water	Neonatal survival, growth and development; surface righting, startle reflex, rotarod performance, and open-field activity	Increased open-field activity (lack of habituation)	21	106

[a]Studies and end points selected for deriving the intermediate-duration oral MRL.

GD = gestation day; IL-2 = interleukin-2; LOAEL = lowest-observed-adverse-effect level; MRL = minimal risk level; NOAEL = no-observed-adverse-effect level; NTP = National Toxicology Program; PFC = plaque-forming cell; PND = postnatal day

Impaired neurodevelopment following pre- and postnatal exposure to toluene, as evidenced by altered open-field behavior in offspring, was also considered as basis of the intermediate-duration oral MRL. Pups exposed to 106 mg/kg/day, but not 4 or 21 mg/kg/day, on GDs 0–21 and PNDs 0–55 demonstrated impaired habituation compared with controls (Kostas and Hotchin 1981). The POD of 21 mg/kg/day is comparable to the immune effects POD of 22 mg/kg/day. However, no other neurodevelopmental oral studies were located to support this finding. Therefore, the series of three studies by Hsieh et al. (1989, 1990b, 1991) demonstrating that consistent immune suppression was determined to be a better selection for a critical effect. While not selected as the basis of the MRL, this study does support the use of a NOAEL of 22 mg/kg/day as the POD.

In the previous draft (ATSDR, 2000), the basis of the intermediate-duration oral MRL was a minimally adverse LOAEL of 5 mg/kg/day for increased brain levels of norepinephrine, dopamine, and serotonin (Hsieh et al. 1990b). As mentioned in the 2000 draft, it is unclear how (or if) these effects relate to neurobehavioral changes. Additionally, alterations in neurotransmitters, and their precursors, are inconsistent between brain regions and do not increase with increasing dose. For the majority of findings, increased neurotransmitter levels in mice exposed to 5, 22, or 105 mg/kg/day for 28 days were the highest in the 22 mg/kg/day group. Since neurotransmitter levels were only evaluated at one time point, it is also unknown if these changes are transient. Due to the lack of dose response, lack of information on persistence of changes, and unclear association with neurobehavior, it cannot be determined if these changes are adverse. Therefore, a NOAEL/LOAEL call was not made for the neurological effects in this study. This interpretation is consistent with the interpretation by EPA (2005): "the changes in neurotransmitter levels have not been correlated with behavioral, neuropsychological, or neuroanatomical changes and were not considered further [for deriving RfD]".

Agency Contacts (Chemical Manager): Jessilyn Taylor

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

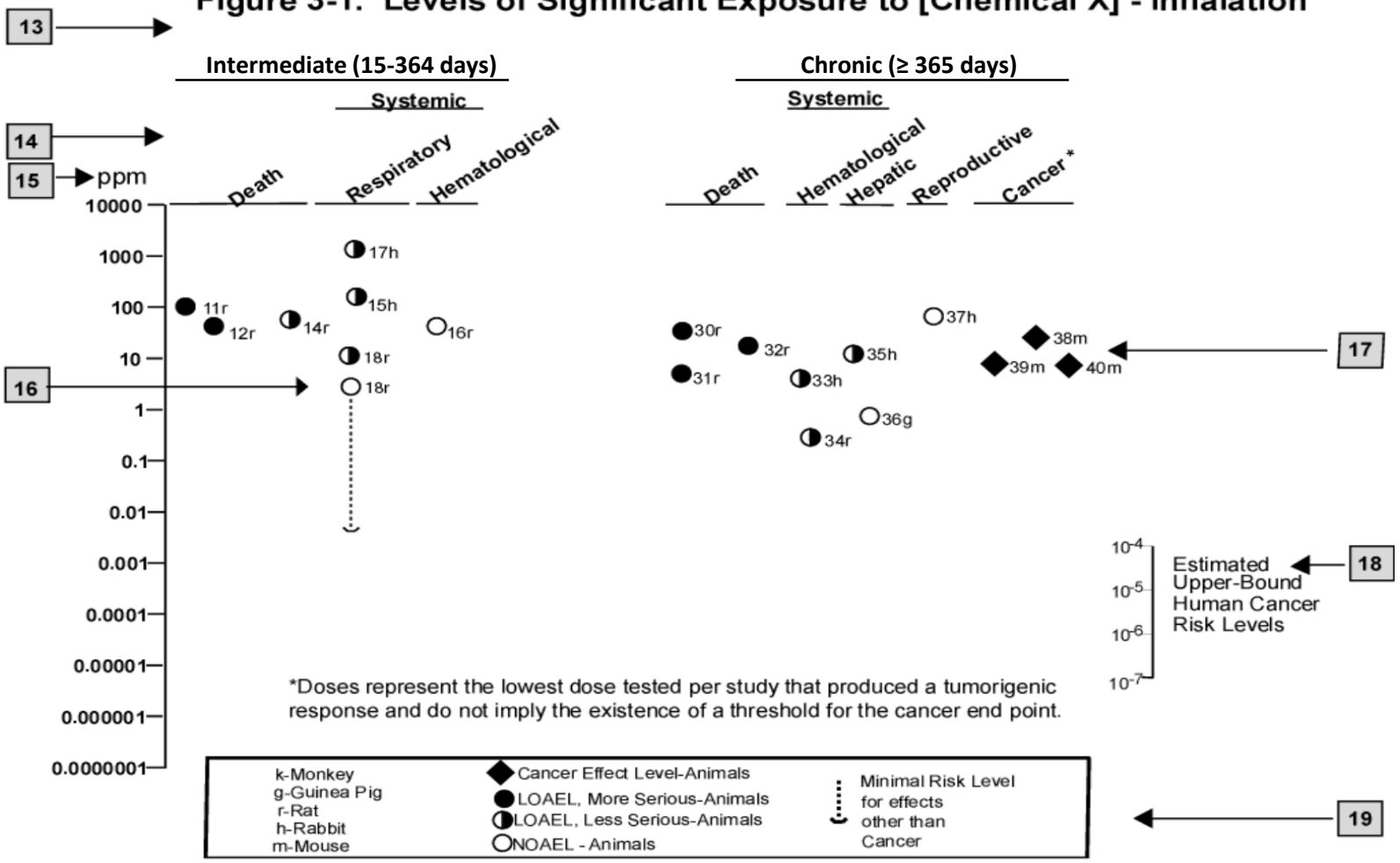
1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

	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	↓	↓	↓	↓	↓		↓
4 →	18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
	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 $5x10^{-3}$ 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