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 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 chemical-induced end point 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 Environmental Medicine, 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 Environmental Medicine, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-32, Atlanta, Georgia 30333.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: 1,1,1-Trichloroethane
CAS Number: 71-55-6
Date: February 2006
Profile Status: Final Draft Post-Public Comment
Route: [X] Inhalation [ ] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Graph Key: 35
Species: Human

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

Reference: Mackay CJ, Campbell L, Samuel AM, et al. 1987. Behavioral changes during exposure to 1,1,1-trichloroethane: Time-course and relationship to blood solvent levels. Am J Ind Med 11:223-240.

Experimental design: Twelve male volunteers participated in the experiment. Exposures were to 0, 175, or 350 ppm of 1,1,1-trichloroethane for 3.5 hours. Each volunteer was exposed to all three exposure concentrations in a balanced design, with a minimum of 2 weeks between exposures for any one individual. Test performance was assessed immediately before entering the exposure chamber and 20, 60, 120, and 180 minutes after entry. Tests were conducted for three psychomotor tasks (simple reaction time, choice reaction time, and tracking ability) and two cognitive tasks (syntactic reasoning and concentration). Volunteers also completed a stress-arousal checklist as part of the test battery. Blood levels of 1,1,1-trichloroethane were measured after 0, 20, 60, 120, and 180 minutes of exposure. Statistical analysis of variance to determine the main effects of exposure and duration was performed for the various tests, but pairwise statistical comparisons were not made.

Effects noted in study and corresponding doses: The tests for simple reaction time, choice reaction time and tracking ability all showed impaired psychomotor performance in volunteers exposed to 1,1,1-trichloroethane concentrations of 175 and 350 ppm. Effects were detected as soon as 20 minutes after the start of exposure at both concentrations. The test for simple reaction time appeared to be the most sensitive, exhibiting a 10–15% increase over baseline values. Observed performance changes correlated with 1,1,1-trichloroethane absolute blood levels. Performance in the cognitive tasks was not adversely affected by exposure, and neither was the self-reported mood of the volunteers. None of the subjects complained of headache, discomfort, or nausea.

Dose and end point used for MRL derivation: 175 ppm; decreased performance in psychomotor tests.

[ ] NOAEL [X] LOAEL

Although the LOAEL of 175 ppm in the critical study of Mackay et al. (1987) was associated with only a 3.5-hour exposure period, the acute-duration inhalation MRL is intended to be protective of a continuous acute-duration exposure. Data reported by Nolan et al. (1984) and Mackay et al. (1987) indicate that blood levels of 1,1,1-trichloroethane approach steady state during 2 hours of continuous inhalation exposure in humans. Neurobehavioral performance was correlated with 1,1,1-trichloroethane blood levels and there was little additional change in most measures of neurobehavioral performance as exposure duration increased from 2 to 3 hours (Mackay et al. 1987). Therefore, the LOAEL of 175 ppm was not adjusted for exposure duration.

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

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:

Other additional studies or pertinent information which lend support to this MRL: Gamberale and Hultengren (1973) observed psychophysiological test performance deficits in human subjects exposed to 250, 350, 450, and 550 ppm of 1,1,1-trichloroethane in consecutive 30-minute periods. All tasks tested were affected, including simple reaction time, choice reaction time, and tests for manual dexterity and perceptual speed. Statistically significant deficits were found as early as exposure period #2, during which the exposure concentration was 350 ppm. Muttray et al. (1999, 2000) found EEG changes consistent with increased drowsiness and slight irritant nasal responses in volunteers exposed to 200 ppm. In contrast, no psychomotor effects were seen in human volunteers exposed to 1,1,1-trichloroethane vapors at concentrations of 400-450 ppm for 4 hours once or twice in a 24-hour period (Salvini et al. 1971; Savolainen et al. 1981). Laine et al. (1996) found no consistent, statistically significant effects on electroencephalogram, visual evoked potential, or equilibrium in a group of 9 healthy male volunteers exposed to a constant 200 ppm of 1,1,1-trichloroethane vapors for 3 hours, followed by a 40-minute lunch break and a 40-minute afternoon exposure. A conservative approach was followed in the selection of Mackay et al. (1987) as the critical study for derivation of an acute-duration inhalation MRL because it identified the lowest LOAEL for psychomotor effects in humans following acute-duration inhalation exposure to 1,1,1-trichloroethane and was supported by results of Gamberale and Hultengren (1973) and Muttray et al. (1999, 2000). The choice of critical effect (neurological changes) is supported by animal studies, although exposure levels eliciting neurobehavioral and neurophysiological effects were much higher than those eliciting psychomotor effects in humans. For example, increased motor activity was observed in mice exposed to 1,250 ppm of 1,1,1-trichloroethane for 30 minutes (Bowen and Balster 1996). A 4-hour exposure of mice to 2,064 ppm resulted in impaired swimming behavior (DeCeaurriz et al. 1983). Dow Chemical Co. (1990b) reported 1,1,1-trichloroethane-induced alterations in flash evoked potential, somatosensory evoked potential, and electroencephalogram in rats exposed to 1,000 ppm for 6 hours per day on 4 consecutive days.

Agency Contact (Chemical Manager): Henry Abadin, M.S.P.H.; Daphne Moffett, Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: 1,1,1-Trichloroethane
CAS Number: 71-55-6
Date: February 2006
Profile Status: Final Draft Post-Public Comment
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 122
Species: Gerbil

Minimal Risk Level: 0.7 [ ] mg/kg/day [X] ppm

Reference: Rosengren LE, Aurell A, Kjellstrand P, et al. 1985. Astrogliosis in the cerebral cortex of gerbils after long-term exposure to 1,1,1-trichloroethane. Scand J Work Environ Health 11:447-456.

Experimental design: Groups of Mongolian gerbils (four/sex) were exposed to 70, 210, or 1,000 ppm of 1,1,1-trichloroethane vapor (cleaning grade, containing 5% dioxane-free stabilizers) continuously for 3 months. Each exposure group was paired with a control group consisting of eight sex-matched littermates of the test group. At the end of the exposure period, all animals were held for 4 months prior to sacrifice. Upon sacrifice, brains were weighed and prepared for analyses for the astroglial proteins S-100 and glial fibrillary acid (GFA) protein, both of which are biomarkers for astrogliosis.

Effects noted in study and corresponding doses: Levels of GFA protein in the sensorimotor cerebral cortex were significantly increased in gerbils exposed to 210 or 1,000 ppm of 1,1,1-trichloroethane, but not those exposed to 70 ppm. Levels of S-100 were not affected by treatment. Total protein levels were also unaffected by treatment. Brain weight was significantly reduced in gerbils exposed to 1,000 ppm.

Dose and end point used for MRL derivation: 70 ppm; biochemical changes (increased GFA protein) in the brain indicative of neuronal damage.

[X] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

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

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:

NOAEL = 70 ppm

For a continuous exposure study, $NOAEL_{ADJ}$ = NOAEL:

$NOAEL_{ADJ}$ = 70 ppm

For a gas:extra respiratory effect, $NOAEL_{HEC} = NOAEL_{ADJ} \times L_A/L_H$, where L_A/L_H is the ratio of blood/gas partition coefficients in animals and humans. A blood/gas partition coefficient is not available for 1,1,1-trichloroethane in gerbils so the default value of $L_A/L_H = 1$ is used:

$NOAEL_{HEC} = 70 \text{ ppm} \times 1 = 70 \text{ ppm}$

The final MRL was calculated to be 0.7 ppm by dividing the concentration of 70 ppm by the uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Intermediate-duration inhalation MRL = 70 ÷ 100 = 0.7 ppm

Other additional studies or pertinent information which lend support to this MRL: The choice of neurological effects as the critical end point of 1,1,1-trichloroethane toxicity is supported by both human and animal studies, which identified the nervous system as a particularly sensitive target of 1,1,1-trichloroethane toxicity following short-term exposures. For example, Gamberale and Hultengren (1973) observed psychophysiological test performance deficits in human subjects exposed to 250, 350, 450, and 550 ppm of 1,1,1-trichloroethane in consecutive 30-minute periods. Mackay et al. (1987) reported psychomotor deficits in human subjects exposed to 175 or 350 ppm of 1,1,1-trichloroethane for 3.5 hours. Increased motor activity was observed in mice exposed to 1,250 ppm of 1,1,1-trichloroethane for 30 minutes (Bowen and Balster 1996). A 4-hour exposure of mice to 2,064 ppm resulted in impaired swimming behavior (DeCeaurriz et al. 1983). Dow Chemical Co. (1990b) reported 1,1,1-trichloroethane-induced alterations in flash evoked potential, somatosensory evoked potential, and electroencephalogram in rats exposed to 1,000 ppm for 6 hours/day on 4 consecutive days. Mattsson et al. (1993) noted decreased forelimb grip strength in rats exposed to 2,000 ppm of 1,1,1-trichloroethane, 6 hours/day, 5 days/week for 13 weeks.

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APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: 1,1,1-Trichloroethane
CAS Number: 71-55-6
Date: February 2006
Profile Status: Final Draft Post-Public Comment
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 23
Species: Mouse

Minimal Risk Level: 20 [X] mg/kg/day [ ] ppm

Reference: NTP. 2000. Technical report on the toxicity studies of 1,1,1-trichloroethane (CAS No. 71-55-6) administered in microcapsules in feed to F344/N rats and B6C3F1 mice. National Toxicology Program. (41) NIH 004402.

Experimental design: Groups of male and female B6C3F1 mice (10 per group) were fed diets containing 0 (untreated feed); 0 (microcapsule vehicle in feed); 5,000; 10,000; 20,000; 40,000; or 80,000 ppm of microencapsulated 1,1,1-trichloroethane (99% pure) 7 days/week for 13 weeks. Average daily doses calculated by the researchers were 850; 1,750; 3,500; 7,370; and 15,000 mg/kg in male mice; and 1,340; 2,820; 5,600; 11,125; and 23,000 mg/kg in female mice. Clinical signs and body weights were recorded weekly. Food consumption was determined every 3–4 days. Water consumption was not reported. Vaginal cytology and sperm motility evaluations were performed on all mice in the vehicle control and the three highest dose groups of mice. At necropsy, all mice were subjected to gross pathological examinations, and the heart, lungs, thymus, liver, right kidney, and right testis were weighed. Mice in untreated and vehicle control and high-dose groups were subjected to complete histopathologic examinations.

Effects noted in study and corresponding doses: There were no exposure-related deaths and no indications of treatment-related clinical or histopathological effects. Food consumption was slightly increased in 1,1,1-trichloroethane-treated groups, relative to untreated and vehicle controls. However, final mean body weight and mean body weight gain of all treatment groups of male and female mice were lower than those of respective vehicle controls (see Table A-1). The final mean body weights in the 5,000; 10,000; 20,000; 40,000; and 80,000 ppm groups were 91, 91, 88, 90, and 85% (males) and 97, 93, 89, 88, and 84% (females) of the respective vehicle control means. As demonstrated in Table A-1, the treatment-related effects on final mean body weight and body weight gain reached the level of statistical significance in all treated groups of male mice and ≥20,000-ppm female mice, relative to vehicle controls. The 10,000-ppm group of female mice exhibited a significantly lower mean body weight gain, but not final mean body weight, relative to vehicle controls. NTP (2000) estimated the dose of 10,000 ppm (1,750 and 2,820 mg/kg/day in male and female mice, respectively) to represent a NOAEL. According to ATSDR policy, a treatment-related change in body weight ≥10% (relative to controls) may be considered to represent an adverse effect. Therefore, the 20,000 ppm (3,500 and 5,600 mg/kg/day in males and females, respectively) level is considered to represent a LOAEL for decreased mean terminal body weight (≥10% lower than control values).

Table A-1. Body Weight Data for Mice Administered 1,1,1-Trichloroethane in the Diet for 13 Weeks

	Males			Females		
Dose (ppm)	Final mean body weight (g)	Mean weight gain (g) (±SE)	Percent[a]	Final mean body weight (g)	Mean weight gain (g) (±SE)	Percent[a]
Untreated control	35.4±0.8	12.8±0.5		28.8±0.9	10.1±0.8	
Vehicle control	36.9±0.7	13.7±0.5		29.3±0.8	11.2±0.8	
5,000	33.6±0.7[b]	11.2±0.5[b,d]	91	28.4±0.6	9.6±0.7	97
10,000	33.7±0.6[b]	10.8±0.5[b,c]	91	27.2±0.8	8.7±0.6[b,d]	93
20,000	32.7±0.5[b,c]	9.9±0.4[b,c]	88	26.0±0.8[b,c]	7.5±0.7[b,c]	89
40,000	33.1±0.5[b,c]	10.0±0.3[b,c]	90	25.8±0.7[b,c]	7.2±0.6[b,c]	88
80,000	31.3±0.4[b,c]	8.7±0.3[b,c]	85	24.5±0.5[b,c]	6.2±0.5[b,c]	84

[a]Percent final mean body weight relative to vehicle control
[b]Significantly different ($p \leq 0.01$) from the vehicle control group
[c]Significantly different ($p \leq 0.01$) from the untreated control group
[d]Significantly different ($p \leq 0.05$) from the untreated control group

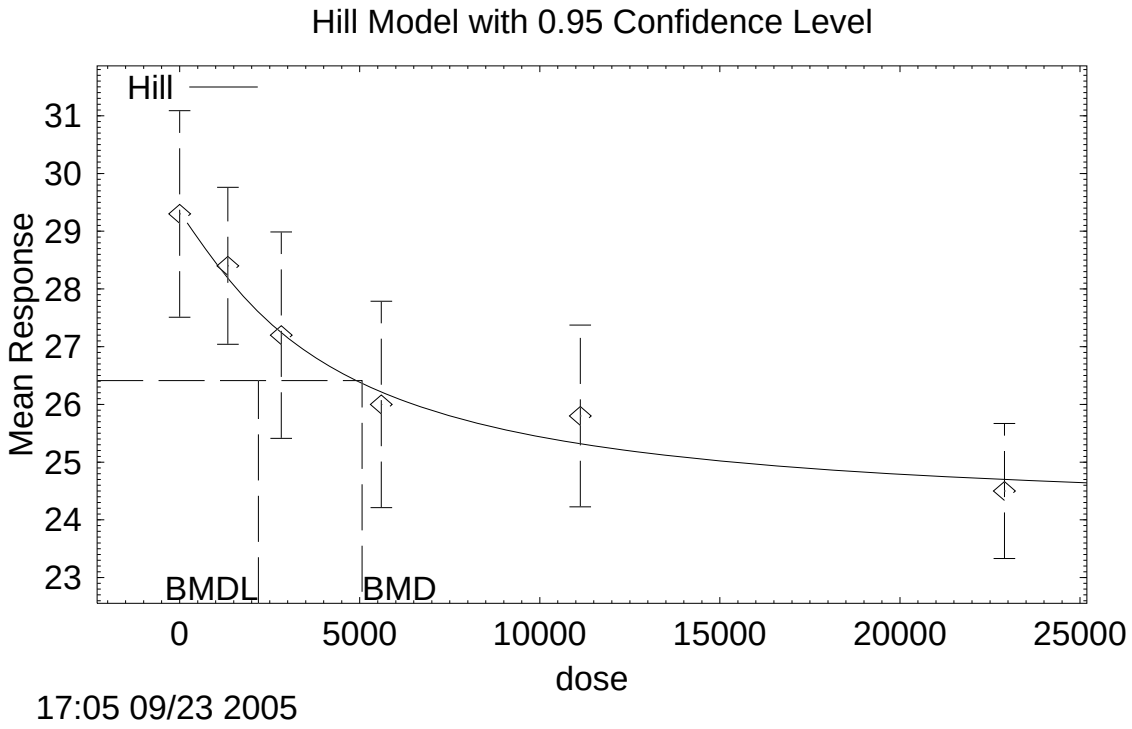
Source: NTP 2000

Dose and end point used for MRL derivation: 2,185 mg/kg/day ($BMDL_{10}$) for treatment-related decreased terminal body weight in female mice.

All continuous data models in the EPA Benchmark Dose Software (version 1.3.2) were fit to the terminal body weight data for male and female mice in the NTP (2000) study. A 10% change in mean terminal body weight relative to the control mean was selected as the benchmark response (BMR) level. A 10% change in body weight is the minimal level of change generally considered to be biologically significant, according to EPA benchmark dose guidance (EPA 2000).

Based on the goodness-of-fit statistic, male mouse data were not adequately fit by any of the continuous data models. An adequate fit was obtained for the female mouse data using the Hill model ($p=0.68$; EPA benchmark dose guidance recommends a p-value ≥ 0.1), which yielded BMD and $BMDL_{10}$ values of 5,064 and 2,185 mg/kg/day, respectively (see Figure A-1 for a plot of the predicted and observed means).

Figure A-1. Hill Model Plot of the Observed and Predicted Terminal Mean Body Weights (in Grams) of Female Mice Given Diets Containing Encapsulated 1,1,1-Trichloroethane 7 Days/Week for 13 Weeks at Concentrations Resulting in Estimated Doses of 0 (Vehicle Controls); 1,340; 2,820; 5,600; 11,125; or 23,000 mg/kg/day (NTP 2000)



[ ] NOAEL [ ] LOAEL [X] Benchmark

Uncertainty Factors used in MRL derivation:

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

Was a conversion used from ppm in food or water to a mg/body weight dose? No, the study authors provided the calculated doses.

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose:

Other additional studies or pertinent information which lend support to this MRL: Decreased body weight appears to be a sensitive effect in other subchronic and chronic studies by oral or inhalation routes of exposure, either in the absence of other signs of toxicity (Adams et al. 1950; Bruckner et al. 2001; Prendergast et al. 1967) or at doses causing minimal liver lesions (Calhoun et al. 1981; Quast et al. 1978, 1988).

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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 chemical 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 are 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 harmful 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 a harmful 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

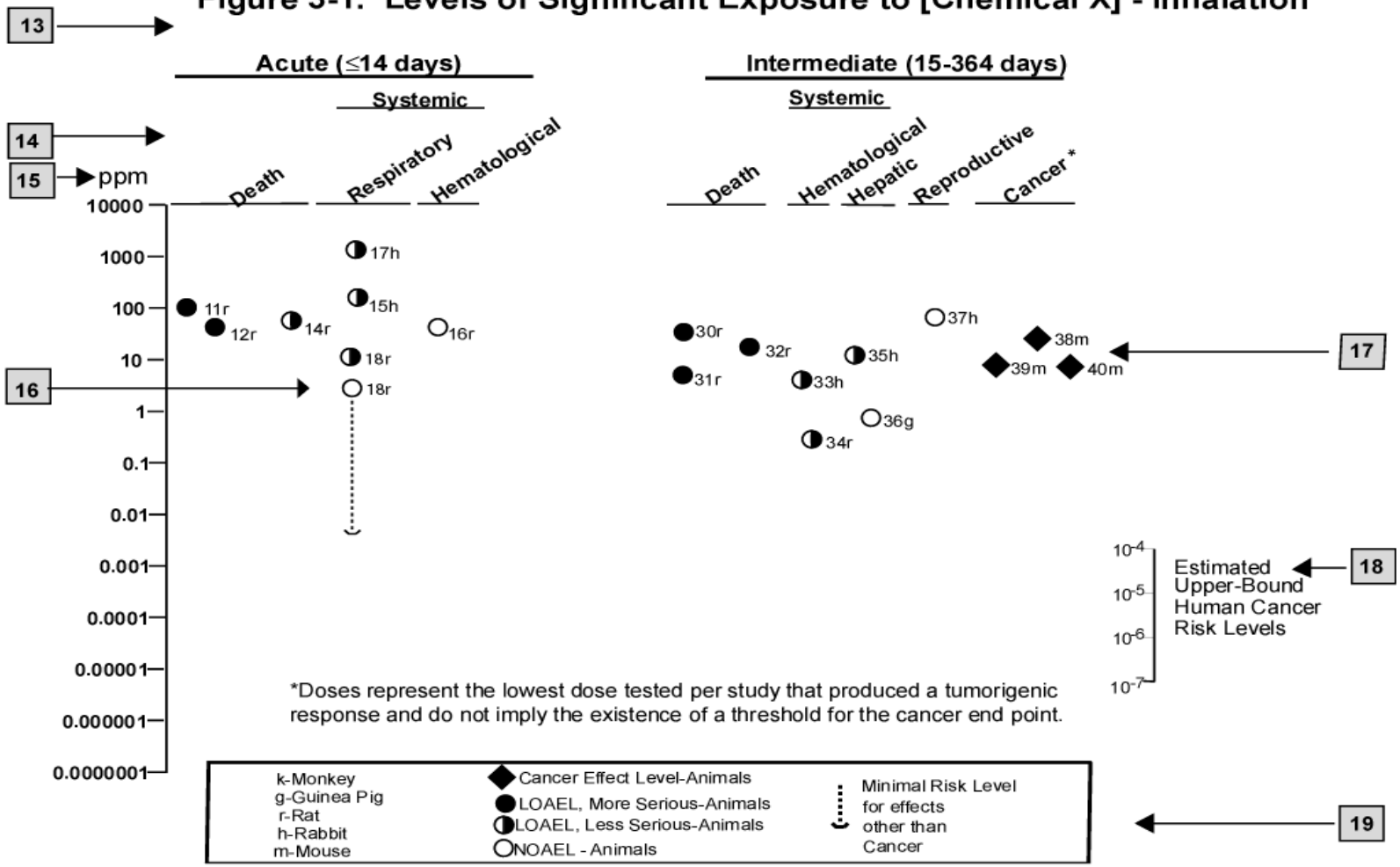
1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

	Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	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	benchmark dose
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
CL	ceiling limit value
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

APPENDIX C

DOT/UN/NA/IMCO	Department of Transportation/United Nations/North America/International 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	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
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
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
RfC	reference concentration
RfD	reference dose
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
SGPT	serum glutamic pyruvic transaminase
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
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

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APPENDIX D. INDEX

APPENDIX D. INDEX