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-62, Atlanta, Georgia 30333.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Styrene
CAS Numbers: 100-42-5
Date: June 2010
Profile Status: Final Draft Post-Public Comment
Route: [X] Inhalation [ ] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Graph Key: 17
Species: Human

Minimal Risk Level: 5 [ ] mg/kg/day [X] ppm

Reference: Ska B, Vyskocil A, Tardif R, et al. 2003. Effects of peak concentrations on the neurotoxicity of styrene in volunteers. Hum Exper Toxicol 22:407-415.

Experimental design: Groups of 24 healthy men (aged 20–50 years) were exposed to 1 ppm (control exposure), 24 ppm, and 24 ppm with four 15-minute exposures to peak concentrations of 49 ppm, 49 ppm, or 49 ppm with four 15-minute exposures to peak concentrations of 98 ppm for 6 hours. The subjects were exposed to each concentration with a 2-week period between each session. The subjects did not have a history of styrene exposure. At the end of the exposure session the subjects were tested for color discrimination (using the Lanthony D-15 desaturated panel), vision contrast, olfactory threshold, simple reaction time, color word stress (response time), symbol digit matching, digit span memory, and continuous tracking. The subjects were also given a questionnaire to assess mood and symptoms.

Effect noted in study and corresponding doses: No significant styrene-related alterations in performance on color discrimination, olfactory threshold, neurobehavioral tests, mood, or subjective symptoms were found.

Dose and end point used for MRL derivation:

[X] NOAEL [ ] LOAEL

A NOAEL of 49 ppm for the lack of alterations in tests of simple reaction time, choice reaction time, memory, or attention.

Uncertainty Factors used in MRL derivation:

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

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

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, because the subjects were only exposed once for 6 hours; adjusting this NOAEL from intermittent exposure to continuous exposure 0.04 ppm) may result in an overly conservative MRL.

Other additional studies or pertinent information that lend support to this MRL: Exposure to 99 ppm for 7 hours or 376 ppm for 1 hour (Stewart et al. 1968) resulted in eye irritation in experimental subjects; nasal irritation was also reported at 376 ppm. A significant inhibition of the vestibular-oculomotor system was observed in subjects exposed to 87 ppm for 1 hour (Ödkvist et al. 1982). Studies by Stewart et al. (1968) found alterations in tests of balance or coordination in subjects exposed to 376 ppm for 1 hour, but not after exposure to 99 ppm for 7 hours or 216 ppm for 1 hour; the test used in the Stewart et al. (1968) studies is probably less sensitive than those used by Ödkvist et al. (1982). No significant alterations in performance on neurobehavioral tests were observed in subjects exposed to 20 ppm for 3 hours (Seeber et al. 2004).

The available data suggest that the nervous system is the most sensitive target of styrene toxicity following acute-duration inhalation exposure. The lowest LOAEL for a relevant end point in humans is 87 ppm for vestibular impairment in subjects exposed to styrene for 1 hour (Ödkvist et al. 1982). A similar LOAEL (80 ppm) was identified for nasal effects in mice exposed to styrene for 3 days (Cruzan et al. 2001); this effect was not considered suitable as the basis of an MRL. As stated previously, mice appear to have a greater capacity than humans to generate the reactive metabolite, styrene oxide, in the nasal cavity and a lower capacity to detoxify styrene oxide (Green et al. 2001a). The identification of the nervous system as the critical target of toxicity for styrene is supported by a large number of occupational exposure studies. Delays in reaction time have been observed in workers exposed to 21.9–92 ppm (Cherry et al. 1980; Fallas et al. 1992; Gamberale et al. 1976; Jegaden et al. 1993; Mutti et al. 1984a; Tsai and Chen 1996) and vestibular effects have been observed at 18–36 ppm (Calabrese et al. 1996; Möller et al. 1990; Toppila et al. 2006).

Agency Contact (Chemical Manager): Selene Chou

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Styrene
CAS Numbers: 100-42-5
Date: June 2010
Profile Status: Final Draft Post-Public Comment
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Graph Key: 61
Species: Human

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

Reference: Benignus VA, Geller AM, Boyes WK, et al. 2005. Human neurobehavioral effects of long-term exposure to styrene: a meta-analysis. Environ Health Perspect 113:532-538.

Experimental design: Benignus et al. (2005) used data from occupational exposure studies examining color vision impairment (Campagna et al. 1996; Eguchi et al. 1995; Gobba et al. 1991; Gong et al. 2002; Kishi et al. 2001) and delays in choice reaction time (Jegaden et al. 1993; Mutti et al. 1984a; Triebig et al. 1989; Tsai and Chen 1996). Average styrene exposure concentrations for each study were estimated from individual data reported in the papers; for studies reporting individual data as urinary mandelic acid levels, standardized methods for converting to styrene exposure levels were used. Cumulative styrene exposure was estimated by multiplying exposure level by length of employment. A common metric of effect magnitude (percentage of baseline) was calculated for the different neurological effects.

Effect noted in study and corresponding doses: A significant linear relationship between choice reaction time and cumulative styrene exposure was found; cumulative exposure accounted for 91% of the variance in reaction time. Similarly, a significant relationship between CCI and cumulative styrene exposure was found, with cumulative exposure accounting for 35% of the variance in CCI. Using the regression equations for these two effects, the investigators estimated that exposure to 150 ppm for 8 work-years would result in a 50% increase in choice reaction time and a 17% increase in CCI score; exposure to 20 ppm for 8 work-years would result in a 6.5% increase in choice reaction time and a 2.23% increase in CCI score. As discussed in Benignus et al. (2005), a 7% decrease in reaction time would prevent 58,000–70,000 injuries per year from automobile accidents. The investigators also noted that CCI increases with age, and the rate of increase is about 10% per 13 years of age; thus, a 2.23% decrease in color perception would be roughly equivalent to 2.9 additional years of age. Based on this analysis, 20 ppm is considered a LOAEL for neurological effects.

Dose and end point used for MRL derivation:

[ ] NOAEL [X] LOAEL

A minimal LOAEL of 20 ppm in the Benignus et al. (2005) meta-analysis was selected as the point of departure for the chronic-duration inhalation MRL. The LOAEL was classified as a minimal LOAEL based on the findings of Triebig et al. (2001) that alterations in color vision were reversible and the workers were not aware of any changes in color vision.

Uncertainty Factors used in MRL derivation: 30

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

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

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? Yes.

$LOAEL_{ADJ}$ = 20 ppm x 8 hours/24 hours x 5 days/7 days
$LOAEL_{ADJ}$ = 4.8 ppm

Other additional studies or pertinent information that lend support to this MRL: A large number of occupational exposure studies have examined the toxicity of styrene; however, most of these studies have focused on the potential neurotoxicity of styrene, which appears to be the most sensitive effect. Two common limitations of the occupational exposure studies are: (1) the range of current styrene levels for the workers is typically large and it is difficult to ascribe the observed effects to the mean or median exposure level and (2) historical exposure to higher styrene levels are not adequately taken into consideration. The use of urinary levels of mandelic acid, phenylglyoxylic acid, or mandelic acid plus phenylglyoxylic acid levels as biomarkers for styrene exposure eliminates another common limitation of styrene occupational exposure studies, which is poor characterization of styrene exposure levels due to the lack of personal air samples and the workers' use of respirators with or without canisters.

A variety of neurological effects have been reported in workers at reinforced plastic manufacturing facilities, including decreased color discrimination, slowed reaction time, impaired performance on other neurobehavioral tests, permanent hearing threshold shifts, vestibular effects, altered nerve conduction velocity, and increases in subjective symptoms. A summary of the results of studies for some of these neurological effects is presented in Table A-1 (more details regarding these studies and other studies of neurological effects in styrene workers are presented in Table 3-2). An alteration in color discrimination is one of the more consistently found neurological effects; it may also be one of the more sensitive effects. Color discrimination was typically measured using the Lanthony desaturated panel D-15 test in which the subjects were asked to arrange 15 painted caps in a line with definite chromatic sequence; the TCDS and CCI are used to quantitatively analyze the results. LOAEL values of 6–93 ppm have been identified; however, these LOAELs often reflect the mean exposure level or the lower end of the range of exposure levels. Other neurological effects that have been frequently found include alterations in performance on neurobehavioral tests, particularly reaction time, in workers exposed to ≥21 ppm; vestibular alterations at ≥18 ppm; and increased frequency of clinical symptoms (e.g., tiredness and headaches in workers exposed to ≥6 ppm). Hearing loss and alterations in nerve conduction velocity have also been reported in some studies, but the finding is not consistent across studies.

Table A-1. Results of Selected Human Neurotoxicity Studies

Result	Reference	NOAEL (ppm)	LOAEL (ppm)
Decreased color discrimination	Chia et al. (1994)		6
	Kishi et al. (2001)	4	10
	Gong et al. (2002)		10
	Gobba et al. (1991)		16
	Triebig et al. 2001		20
	Iregren et al. (2005)		22
	Fallas et al. (1992)		24.3
	Campagna et al. (1996)		265
	Eguchi et al. (1995)	8	93
Neurological symptoms	Flodin et al. (1989)	6	
	Edling et al. (1993)	8.6	
	Checkoway et al. (1992)	10.8	18.9
	Cherry et al. 1980		92
Vestibular effects	Möller et al. (1990)		18
	Toppila et al. (2006)		24.8
	Calabrese et al. (1996)		36
Reaction time	Edling et al. (1993)	8.6	21.9
	Tsai and Chen (1996)		21.9
	Jegaden et al. (1993)		22.68
	Fallas et al. (1992)		24.3
	Mutti et al. (1984a)		25
	Gamberale et al. (1976)		4,755
	Cherry et al. (1980)		92

Non-neurological effects observed in styrene workers include obstructive lung effects (Chmielewski and Renke 1975), mild hematological alterations (Checkoway and Williams 1982; Stengel et al. 1990; Thiess and Friedheim 1978), and impaired immune response to concanavalin (Somorowská et al. 1999; Tulinska et al. 2000). Although exposure levels were not reported in all of these studies, effects were typically observed at styrene concentrations of >20 ppm. Clinical chemistry studies did not find alterations indicative of impaired liver (Härkönen et al. 1984; Hotz et al. 1980; Lorimer et al. 1978; Thiess and Friedheim 1978) or kidney (Verplanke and Herber 1998; Viau et al. 1987; Vyskocil et al. 1989) function in workers exposed to ≥24 ppm.

Chronic-duration studies in laboratory animals identify the nasal olfactory epithelium as the most sensitive end point. Atrophic and/or degenerative changes were observed in rats exposed to 50 ppm styrene 6 hours/day, 5 days/week for 104 weeks (Cruzan et al. 1998) and respiratory metaplasia in the nasal olfactory epithelium were observed in mice exposed to 20 ppm 6 hours/day, 5 days/week for 98–104 weeks (Cruzan et al. 2001). As noted previously, mice do not appear to be a good model for potential respiratory effects in humans.

In addition to the studies included in the Benignus et al. (2005) meta-analysis, a LOAEL of 20 ppm is supported by a color discrimination study conducted by Triebig et al. (2001). In this study, significant

increases in CCI values were observed in styrene workers with urinary mandelic acid plus phenylglyoxylic acid levels of ≥472 mg/g creatinine (approximately 20 ppm air styrene concentration), when compared to >95th percentile age-dependent reference CCI values. An advantage of the Triebig et al. (2001) study is that individual exposure and CCI data were reported, which diminishes the problem of ascribing an observed effect to the mean or median concentration and the study addresses the issue of biological relevance because the CCI scores were compared to the 95th percentile of age-dependent reference values rather than values in the control group.

In comparisons between styrene workers and a control group employed at the same facility without styrene exposure, Triebig et al. (2001) found no significant differences in CCI scores between workers and controls when the tests were conducted on a Monday morning, but CCI scores were significantly different when measured on a Thursday afternoon. Within the styrene-exposed workers, CCI scores on Monday morning and Thursday afternoon were not significantly different. After a 4-week nonexposure period, the CCI scores were significantly reduced in the styrene workers. After styrene exposure levels were lowered, no difference between workers and controls was observed on Monday morning or Thursday afternoon. However, among styrene workers, there were significant differences between Monday morning and Thursday afternoon measurements and between Monday morning and post-vacation levels. These findings provide suggestive evidence that the alterations in color discrimination were reversible.

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APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Styrene
CAS Numbers: 100-42-5
Date: June 2010
Profile Status: Final Draft Post-Public Comment
Route: [ ] Inhalation [X] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Graph Key: 3
Species: Rat

Minimal Risk Level: 0.1 [X] mg/kg/day [ ] ppm

Reference: Husain R, Srivastava SP, Seth PK. 1985. Some behavioral effects of early styrene intoxication in experimental animals. Arch Toxicol 57:53-55.

Experimental design: Groups of 15 male Wistar rats were administered by gavage 0, 100, or 200 mg/kg/day styrene in ground nut oil for 14 consecutive days. Spontaneous motor activity for a period of 10 minutes was measured 24 hours after the last dose. After baseline activity was measured, the rats received an intraperitoneal injection of 2.5 mg/kg amphetamine, and amphetamine-induced spontaneous motor activity was measured. Two days after exposure termination, acquisition training was initiated using a Cook's pole climbing apparatus. Learning was assessed by measuring the number of times the rat climbed the pole after the conditioned stimulus to avoid the foot-shock unconditioned stimulus. The rats were tested for 4 days. Noradrenaline, dopamine, and serotonin levels were measured in seven regions of the brain in six rats/group killed after the acquisition training.

Effect noted in study and corresponding doses: No overt signs of toxicity were observed. No significant alterations in locomotor activity were observed with or without amphetamine induction. Significantly greater increases in percent avoidance response (indicative of impaired learning) were observed at 100 and 200 mg/kg/day; no difference was found between the two styrene groups. The effects were observed on test days 3 and 4. Significant increases in the level of serotonin in the hypothalamus (70%), hippocampus (51%), and midbrain (29%) were observed at 200 mg/kg/day. Styrene did not affect brain noradrenaline and dopamine levels.

Dose and end point used for MRL derivation:

[ ] NOAEL [X] LOAEL

A LOAEL of 100 mg/kg/day for impaired learning

Uncertainty Factors used in MRL derivation:

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

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

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? Not applicable.

Other additional studies or pertinent information that lend support to this MRL: A limited number of studies have examined the acute toxicity of orally-administered styrene; these studies have examined potential neurotoxicity and developmental toxicity. No developmental effects were observed in rats administered a single dose of 300 mg/kg on gestational day 11 (Daston et al. 1991) or administered 300 mg/kg/day (administered as two daily doses of 150 mg/kg) on gestational days 6–15 (Murray et al. 1978). Impaired learning was observed in rats administered via gavage 100 or 200 mg/kg/day for 14 days (Husain et al. 1985); increases in serotonin levels in the hypothalamus, hippocampus, and midbrain were also observed at 200 mg/kg/day. In another study, increases in dopamine receptor binding was observed in rats administered a single gavage dose of 200 mg/kg (Agrawal et al. 1982).

Although there is a limited acute toxicity database, longer-term oral studies support the selection of neurotoxicity as the principal effect. The lowest LOAEL identified for a systemic effect is 400 mg/kg/day for Heinz body formation in dogs administered styrene by gavage for 561 days (Quast et al. 1979); the identified NOAEL was 200 mg/kg/day. Decreased spermatozoa counts were observed in adult rats administered 400 mg/kg 6 days/week for 60 days (Srivastava et al. 1989), young rats exposed via lactation on postnatal days 1–21 (maternal dose of 400 mg/kg/day) (Srivastava et al. 1992a), and young rats administered 200 mg/kg 6 days/week on postnatal days 1–61 (Srivastava et al. 1992b); the NOAELs identified in these three studies were 200, 200, and 100 mg/kg, respectively. Marked degeneration of the seminiferous tubules was also observed in the adult rats administered 400 mg/kg (Srivastava et al. 1989). Impaired learning was also observed in rats administered 500 mg/kg 5 days/week for 8 weeks (Bushnell 1994); a NOAEL was not identified in this study. The extensive inhalation toxicity database for styrene also supports the selection of neurotoxicity as the most sensitive target of toxicity; both the acute- and chronic-duration inhalation MRLs are based on neurological effects in humans. Neurological effects observed in chronically exposed styrene workers include decreased color discrimination, slowed reaction time, increased prevalence of neurological symptoms, and ototoxicity (hearing and vestibular effects).

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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

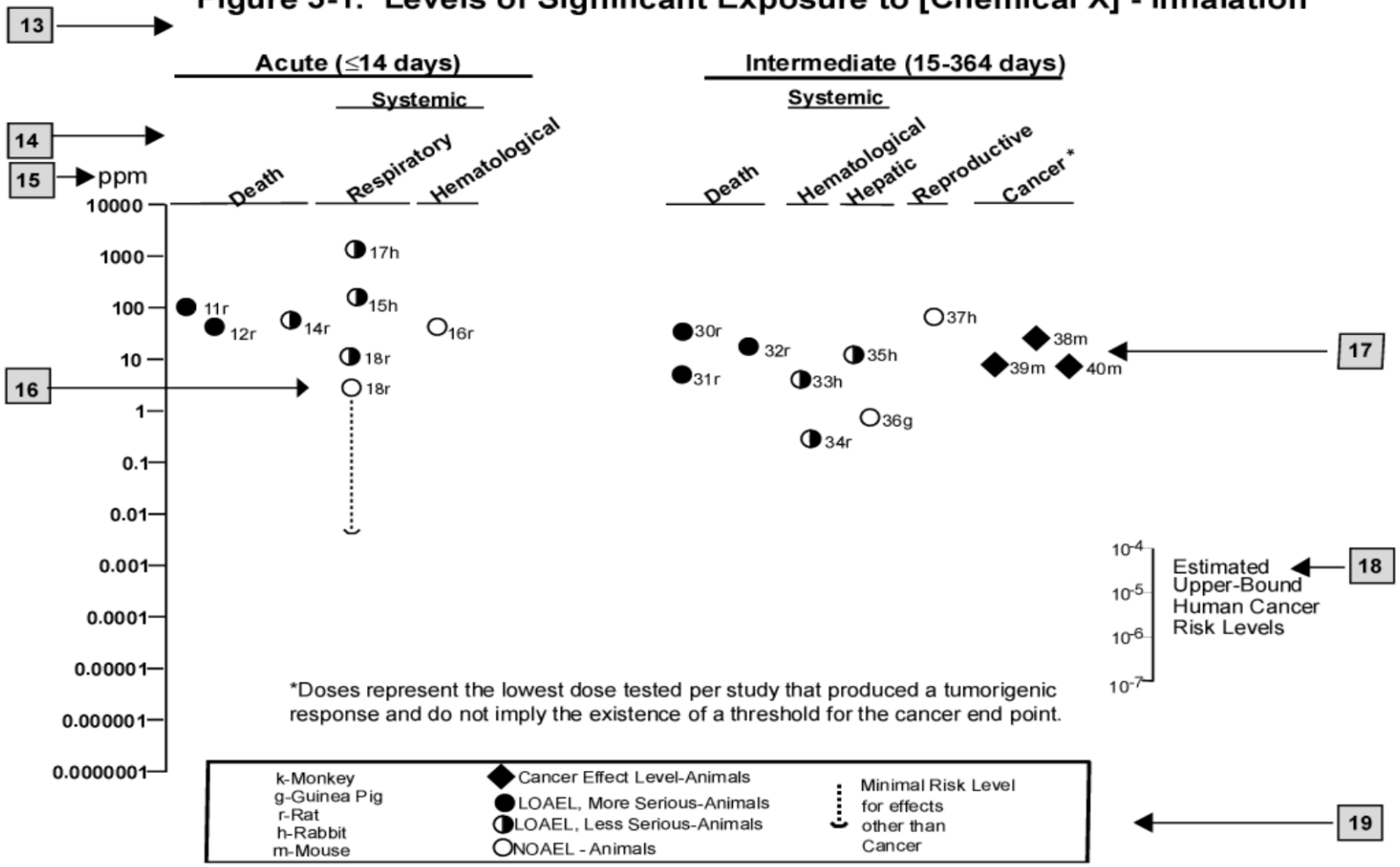
1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

	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/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
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
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	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

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