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 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: JP-5 vapor
CAS Number: 8008-20-6
Date: March 2017
Profile Status: Final
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 23
Species: Mouse

Minimal Risk Level: 2 [ ] mg/kg/day [X] mg/m^3

Reference: Gaworski CL, MacEwen JD, Vernot EH, et al. 1984. Comparison of the subchronic inhalation toxicity of petroleum and oil shale JP-5 jet fuels. In: MacFarland HN, Holdsworth CE, MacGregor JA, et al., eds. Advances in modern environmental toxicology. Volume VI: Applied toxicology of petroleum hydrocarbons. Princeton, NJ: Princeton Scientific Publishers, 33-47.

Experimental design: Groups of approximately 35 female C57BL/6 mice were exposed by inhalation to petroleum-based JP-5 vapor at 0, 150, or 750 mg/m^3 continuously for 90 days. End points evaluated included: clinical signs, body weight (measured monthly), and histopathological examination of major tissues (adrenals, anus, bladder, brain, colon, duodenum, esophagus, gall bladder, heart, ileum, kidneys, larynx, liver, lungs and bronchi, mammary gland, mandibular lymph node, nasal cavity, ovaries, pancreas, parathyroids, pituitary, prostate, salivary gland, sciatic nerve, seminal vesicles, skin, spleen, bone-sternebrae, vertebrae or femur plus marrow, stomach, testes, thigh muscle, thymus, thyroid, trachea, and uterus).

Effect noted in study and corresponding doses: No effect on body weight gain was noted. The only remarkable finding in mice was hepatocellular fatty changes and vacuolization at 150 and 750 mg/m^3. The incidences were 8/37 (22%), 29/33 (88%), and 23/34 (68%) in the 0, 150, and 750 mg/m^3 groups, respectively.

Dose and end point used for MRL derivation:

[ ] NOAEL [X] minimal LOAEL

150 mg/m^3; hepatocellular fatty changes and vacuolization.

Uncertainty Factors used in MRL derivation:

- [x] 3 for use of a minimal LOAEL
- [x] 3 for extrapolation from animals to humans with dosimetric adjustments
- [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: A human equivalent concentration (HEC) of 150 mg/m^3 was calculated by multiplying the mouse LOAEL by the ratio of the blood:gas partition coefficients in humans and animals. Because blood:gas partition

coefficients are not measurable for a complex mixture such as JP-5, the default ratio of 1 was used (EPA 1994).

$$150 \text{ mg/m}^3 \times 1 = 150 \text{ mg/m}^3$$

Was a conversion used from intermittent to continuous exposure? Not applicable.

Other additional studies or pertinent information that lend support to this MRL: The intermediate-duration toxicity of inhaled JP-5 has been investigated in rats, mice, and dogs. In male rats, the most sensitive effect is an increase in the occurrence of hyaline droplets in the proximal renal tubules, which was observed in rats continuously exposed to ≥150 mg/m^3 JP-5 vapor (Gaworski et al. 1984). This effect, which is only observed in male rats, is due to an accumulation of alpha$_{2u}$-globulin in hyaline droplets and is not considered relevant to humans (EPA 1991a; Flamm and Lehman-McKeeman 1991; Hard et al. 1993; Swenberg 1993). No adverse effects were observed in female rats exposed to ≤750 mg/m^3 JP-5 vapor (Gaworski et al. 1984). Similar to mice, the liver appears to be the most sensitive target of toxicity in dogs; diffuse hepatocellular swelling was observed in male and female dogs continuously exposed to ≥150 mg/m^3 JP-5 vapor (Gaworski et al. 1984). The nervous system was the only other target examined in intermediate JP-5 studies. An evaluation of neurobehavioral performance in rats found increased forelimb grip strength in rats similarly exposed to 1,200 mg/m^3 JP-5 vapor (Rossi et al. 2001); no alterations in other neurobehavioral tests were found.

Studies with JP-8 have also identified the immune system as a sensitive target of toxicity; based on the similarity between JP-5 and JP-8, it is likely that the immune system will also be a relevant target of JP-5. The lowest reliable LOAEL for immunotoxicity following acute-duration inhalation exposure to JP-8 was 1,000 mg/m^3 identified in rats exposed to JP-8 vapor and aerosol 1 hour/day for 7 days (Hilgaertner et al. 2011).

Agency Contacts (Chemical Managers): John Risher and Obaid Faroon

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: JP-8 vapor
CAS Number: 8008-20-6
Date: March 2017
Profile Status: Final
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 31
Species: Rat

Minimal Risk Level: 3 [ ] mg/kg/day [X] mg/m^3

Reference: Ritchie GD, Rossi J, Nordholm AF, et al. 2001. Effects of repeated exposure to JP-8 jet fuel vapor on learning of simple and difficult operant tasks by rats. J Toxicol Environ Health, Part A 64: 385-415.

Experimental design: Groups of male Sprague-Dawley rats (16/group) were exposed whole-body to 0, 500, or 1,000 mg/m^3 JP-8 fuel vapors 6 hours/day, 5 days/week for 6 weeks. Sixty-five days after exposure termination, the rats underwent simple and difficult operant tasks (lever acquisition, fixed ratio, lever spatial reversal, stimulus reversal, and incremental repeated acquisition in order of increasing difficulty). After the neurobehavioral testing, 4 rats/group were killed and the brains were dissected and processed for determination of neurotransmitters and their metabolites.

Effect noted in study and corresponding doses: Exposure to 1,000 mg/m^3 JP-8 fuel vapors induced significant deficits in acquisition or performance of the two most difficult tasks, but not in the simple learning tasks compared to rats in the low-exposure group. Learning/performance of complex tasks in the low-exposure group generally exceeded performance of control rats, while learning by high-exposure rats was almost always inferior to control rats, suggesting possible neurobehavioral hormesis. Neurochemical analyses showed significantly increased levels of dopamine in the cerebral cortex and DOPAC (major dopamine metabolite) in the brainstem for as long as 180 days post-exposure in both exposed groups relative to controls. This could have resulted from solvent-induced reductions in cyclic guanosine monophosphate (GMP) that is involved in signal transduction in specific brain regions.

Dose and end point used for MRL derivation:

[X] NOAEL [ ] LOAEL

The MRL is based on a NOAEL of 500 mg/m^3 and LOAEL of 1,000 mg/m^3 for neurotoxicity.

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[X] 3 for extrapolation from animals to humans with dosimetric adjustments
[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: A $NOAEL_{HEC}$ of 89 mg/m^3 was calculated by multiplying the $NOAEL_{ADJ}$ by the ratio of the blood:gas partition coefficients in humans and animals. Because blood:gas partition coefficients are not measurable for a complex mixture such as JP-8, the default ratio of 1 was used (EPA 1994).

$$89 \text{ mg/m}^3 \times 1 = 89 \text{ mg/m}^3$$

Was a conversion used from intermittent to continuous exposure? The NOAEL of 500 mg/m^3 was adjusted for intermittent exposure:

$$NOAEL_{ADJ} = 500 \text{ mg/m}^3 \times 6 \text{ hours}/24 \text{ hours} \times 5 \text{ days}/7 \text{ days} = 89 \text{ mg/m}^3$$

Other additional studies or pertinent information that lend support to this MRL: Two studies have examined the systemic toxicity of JP-8 following intermediate-duration inhalation exposure. Mattie et al. (1991) reported an increase in hyaline nephropathy in male rats continuously exposed to ≥500 mg/m^3 JP-8 vapor for 90 days. No other effects were observed in the male rats and no effects were observed in the female rats; the highest concentration tested was 1,000 mg/m^3. In contrast, Hanas et al. (2010) reported a number of adverse effects in male rats exposed to JP-8 vapor 6 hours/day for 91 days. At 250 mg/m^3 proximal tubular damage was observed in the kidneys; enlarged alveolar capillaries, myocardial scarring, reduction in fat cells/globules in bone marrow, and dilated sinusoids and fatty hepatocytes were observed at 500 mg/m^3. Interpretation of the results of the Hanas et al. (2010) study is limited by the small number of animals tested (3/group). The renal effects observed in the Mattie et al. (1991) and Hanas et al. (2010) studies are characteristic of $alpha_{2u}$-globulin nephropathy, which is not considered a relevant effect in humans (EPA 1991a; Flamm and Lehman-McKeeman 1991; Hard et al. 1993; Swenberg 1993).

A 6-week study conducted by Rossi et al. (2001) also evaluated the neurotoxicity of JP-8 in rats exposed for 6 weeks. An alteration in a novel appetitive stimulus test was observed in rats exposed to 1,000 mg/m^3 JP-8 vapor; the investigators suggested that this test quantified dopamine system sensitization in the rat. No other alterations in neurobehavioral tests were found. Studies by Fechter et al. (2012) and Guthrie et al. (2014, 2015) evaluated the potential of JP-8 to damage the auditory system. No significant alterations in auditory function was observed in rats exposed to 1,500 mg/m^3 JP-8 vapor for 4 weeks (Fechter et al. 2012); however, if the rats were also exposed to non-damaging noise, there was damage to the auditory function. Central auditory processing dysfunction was observed in rats exposed to 1,000 mg/m^3 JP-8 vapor for 4 weeks; however, no damage to peripheral auditory function, including damage to cochlear hair cells, was observed (Guthrie et al. 2014, 2015).

In addition to these studies, three University of Arizona studies have reported edema and inflammation of the terminal bronchioles in rats exposed 1 hour/day for 28 or 56 days to JP-8 aerosols and vapors (Hays et al. 1995; Pfaff et al. 1995, 1996). Hays et al. (1995) also found increased lung epithelial permeability and alveolar permeability. None of the three studies measured the vapor component of the test atmosphere (see Section 3.2.1 for a discussion of these studies).

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APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: JP-8
CAS Number: 8008-20-6
Date: March 2017
Profile Status: Final
Route: [ ] Inhalation [X] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Graph Key: 11
Species: Mouse

Minimal Risk Level: 3 [X] mg/kg/day [ ] mg/m^3

Reference: Keil D, Dudley A, EuDaly JG, et al. 2004. Immunological and hematological effects observed in B6C3F1 mice exposed to JP-8 jet fuel for 14 days. J Toxicol Environ Health Part A 67:1109-1129.

Experimental design: The study examined the effects of JP-8 fuel on humoral and cell-mediated and hematological parameters in female B6C3F1 mice. Groups of mice (4–6/group) were administered doses of JP-8 fuel ranging from 250 to 2,000 mg/kg/day by gavage in olive oil for 14 days. End points monitored included body weight; weight of the liver, kidneys, spleen, and thymus; spleen and thymus cellularity; lymphocyte proliferation; natural killer (NK) cell activity; antibody plaque-forming cells assay; splenic and thymic CD4/CD8 subpopulations; and bone marrow cellularity and colony-forming units.

Effect noted in study and corresponding doses: There were no clinical signs during the study. There was a trend for increase in body weight gain, but there was no statistical significance. Relative kidney weight was not affected, but liver weight was significantly increased at ≥1,000 mg/kg/day (23%). Significant hematological alterations included decreases in hemoglobin levels, hematocrit levels, and red blood cell counts and increases in mean corpuscular volume at 2,500 mg/kg/day; mean corpuscular volume was also increased at 1,500 and 2,000 mg/kg/day. All of these changes were ≤7% relative to controls and probably of no toxicological significance. There were no significant changes in peripheral blood differential count. An increase in colony forming units was observed in the bone marrow of mice administered 2,000 mg/kg/day, but there were no alterations in bone marrow cellularity. A significant decrease in cellularity was observed in the thymus at 2,000 mg/kg/day; no alterations were observed in the spleen. No significant alterations in mitogen-induced T or B cell proliferation or alterations in NK activity were observed. In response to sheep red blood cells (SRBCs), there were significant suppression of IgM antibody production (when assessed using antibody plague-forming cell response) at doses ≥500 mg/kg/day. However, there were no significant alterations in serum levels of anti-SRBC IgM when measured by ELISA or hemagglutination. In the spleen, there were no alterations in the percentage of individual T-cell phenotypes or the ratio of CD4+ to CD8+ cells; however, decreases in $CD4^-/CD8^-$ cells were observed at 1,000 and 2,000 mg/kg/day. In contrast, there were significant decreases in the absolute values of $CD8^+$, $CD4^+$, and $CD4^+/CD8^+$ T-cell subpopulations in the thymus in mice administered 2,000 mg/kg/day.

Dose and end point used for MRL derivation:

[X] NOAEL [ ] LOAEL

The MRL is based on a NOAEL of 250 mg/kg/day and LOAEL of 500 mg/kg/day for an impaired response to SRBCs.

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 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: The available data on the acute-toxicity of JP-8 primarily focused on immunotoxicity. Altered immune function (response to SRBCs) was observed in mice administered 1,000 mg/kg/day JP-8 for 7 days (Dudley et al. 2001) or 500 mg/kg/day for 14 days (Keil et al. 2004; Peden-Adams et al. 2001). At higher doses, decreases in thymus weight and cellularity were observed (Dudley et al. 2001). Impaired immune response was also observed in the offspring of mice administered 1,000 mg/kg/day on GDs 6–15 (Keil et al. 2003). In another developmental toxicity study (Cooper and Mattie 1996), a decrease in fetal body weight was observed at a dose (1,000 mg/kg/day) that also resulted in decreased maternal weight gain and mortality.

Although the acute-duration studies did not examine the potential for systemic toxicity, intermediate-duration JP-8 oral studies suggest that systemic effects such as liver toxicity would occur at higher doses than the LOAEL for immunotoxicity (Mattie et al. 1995, 2000).

Agency Contacts (Chemical Managers): John Risher and Obaid Faroon

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: JP-8
CAS Number: 8008-20-6
Date: March 2017
Profile Status: Final
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 28
Species: Rat

Minimal Risk Level: 0.3 [X] mg/kg/day [ ] mg/m^3

Reference: Mattie DR, Cooper JR, Sterner TR, et al. 2001. Developmental neurobehavioral effects on JP-8 jet fuel on pups from female Sprague-Dawley rats exposed by oral gavage. Wright-Patterson, AFB: OH: Air Force Research Laboratory. 22. ARFL-HE-WP-TR-2001-0186. ADA428272.

Experimental design: The study examined neurobehavioral parameters in pups from rats exposed to JP-8 fuel for a total of 21 weeks (90 days followed by cohabitation, gestation, delivery, and lactation). Groups of rats (35/groups) were administered 0, 325, 750, or 1,500 mg/kg neat JP-8 fuel by gavage. Litters were standardized to four male and four female pups on PND 4. Pup weights were recorded on PNDs 1, 4, 14, 21, and 90. Male pups were checked for descent of testes on PND 21 or 22. Female pups were checked for vaginal opening on PND 30. The following neurobehavioral tests were conducted: surface righting (beginning PND 4), negative geotaxis (beginning PND 5), swimming development (PNDs 6–20), and water maze (PNDs 70 and 77)

Effect noted in study and corresponding doses: The results showed a significant alteration in the total score for the swimming development test at ≥325 mg/kg/day on PND 8 and at 750 and 1,500 mg/kg/day on PND 14; however, no significant alterations in total score were observed on PNDs 10, 12, 16, 18, or 20. The alterations in the total scores were primarily due to swimming direction scores; significant decreases in direction scores were observed on PND 6 (750 and 1,500 mg/kg/day), PND 8 (≥325 mg/kg/day), and PND 14 (750 and 1,500 mg/kg/day); no alterations in angle of head or limb usage scores were observed at any time point. No significant alterations in surface righting (tested on PND 4), negative geotaxis (tested on PND 5), or water maze performance (tested on PNDs 70 and 77) were observed. The investigators suggested that the results in the swimming development test were indicative of a possible developmental delay in motor coordination; however, the delay did not affect motor ability at later ages.

Dose and end point used for MRL derivation:

[ ] NOAEL [X] LOAEL

The MRL is based on a LOAEL of 325 mg/kg/day for neurodevelopmental effects.

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: Two studies have evaluated the intermediate-duration oral toxicity of JP-8 (Mattie et al. 1995, 2000). Administration of 750 mg/kg/day resulted in increases in serum ALT and AST activities in male rats, stomach hyperplasia in male and female rats, hypoglycemia in male rats, perianal dermatitis in male rats, and hyaline droplet formation in the kidneys of male rats; perianal dermatitis was also observed in female rats at 1,500 mg/kg/day. The third study in the intermediate-duration database was the Mattie et al. (2001) developmental study, which was the basis of the MRL.

Acute-duration oral studies suggest that the immune system is also a sensitive target of JP-8 toxicity; however, this end point has not been investigated following intermediate-duration exposure. The lowest LOAEL for immune effects identified in oral exposure studies was 500 mg/kg/day for an impaired response to SRBCs (Keil et al. 2004). Since the LOAEL for neurodevelopmental is similar to this LOAEL, the intermediate MRL should be protective for potential immune 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 in LSE tables and figures include death, systemic, immunological and lymphoreticular, 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

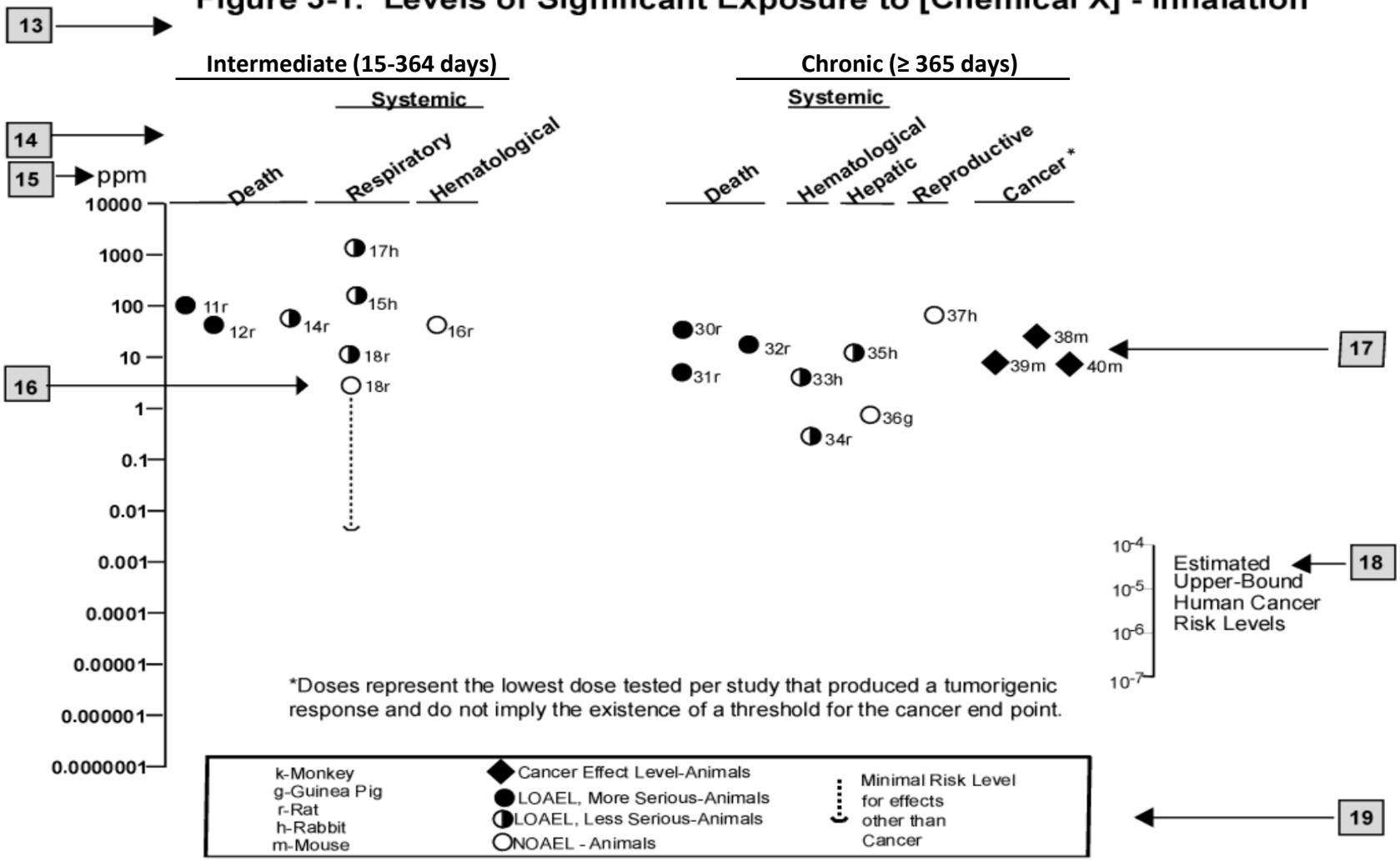
Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
INTERMEDIATE EXPOSURE							
Systemic							
18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
CHRONIC EXPOSURE							
Cancer							
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

[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

APPENDIX C

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