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

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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 greater than 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 30333.
MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Hydrogen Sulfide
CAS Number: 7783-06-4
Date: September 2014
Profile Status: Draft for Public Comment
Route: [x] Inhalation   [ ] Oral
Duration: [x] Acute   [ ] Intermediate   [ ] Chronic
Graph Key: 17
Species: Human

Minimal Risk Level: 0.07 [ ] mg/kg/day   [x] ppm


Experimental design: This study evaluated lung function in three male and seven female subjects with bronchial asthma requiring medication for 1–13 years; none of the subjects had severe asthma. The subjects were exposed to 2 ppm hydrogen sulfide for 30 minutes. Respiratory function in response to a histamine challenge was assessed prior to exposure and after exposure.

Effect noted in study and corresponding doses: No statistically significant changes in forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), and forced expiratory flow were noted. Airway resistance (Raw) and specific airway conductance (SGaw) did not show statistically significant changes when examined as a group. In two subjects, there were changes of over 30% in both Raw and SGaw; these changes were suggestive of bronchial obstruction. Additionally, 3 of 10 subjects complained of headaches after exposure.

Dose and end point used for MRL derivation:

[ ] NOAEL   [X] LOAEL

Uncertainty Factors used in MRL derivation:

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

The 2 ppm concentration was considered a minimally adverse effect level because the changes in airway resistance and specific airway conductance were only observed in 2 of 10 subjects. Because the study was conducted using asthmatics (who are likely to be a sensitive subpopulation) a partial uncertainty factor of 3 was used to account for human variability. An additional uncertainty factor of 3 was used for database deficiencies due to concern for the short (30-minute) exposure duration in the principal study.

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

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: No.

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

***DRAFT FOR PUBLIC COMMENT***
Other additional studies or pertinent information that lend support to this MRL: Bhambhani et al. (1996b) evaluated the acute effects of hydrogen sulfide on the physiological and hematological health of male and female volunteers exposed to 5 ppm during two 30-minute sessions of submaximal exercise (50% of maximum aerobic power). No significant changes in any parameter were noted in the women, whereas the men showed a significant decrease in muscle citrate synthetase as well as nonsignificant changes in lactate, lactate dehydrogenase, and cytochrome oxidase. Together, these changes were considered indicative of compromise of aerobic metabolism.

No respiratory or cardiovascular effects were observed in 16 male volunteers exposed by oral inhalation to hydrogen sulfide at 0.5, 2, or 5 ppm for >16 minutes while exercising (Bhambhani and Singh 1991). The end points examined included heart rate, oxygen uptake, carbon dioxide output, and blood gases. Airway resistance and conductance were not measured in this study. No significant changes in pulmonary function parameters were noted in individuals exposed to 10 ppm hydrogen sulfide for 15 minutes during exercise (Bhambhani et al. 1996a).

Respiratory distress was noted in two workers exposed to >40 ppm hydrogen sulfide for under 25 minutes (Spolyar 1951). In animals, impacts on the respiratory system such as increases in the cellularity and lactate dehydrogenase and alkaline phosphatase activity in bronchial lavage fluids have been seen at exposures as low as 10 ppm for 4 hours (Lopez et al. 1987), although without a dose-related trend.

Moderate to massive pulmonary edema was observed in rats exposed to 375 or 399 ppm for 4 hours (Prior et al. 1990). A significant dose-related decrease in lung microsomal cytochrome c oxidase activity was seen in rats following a 4 hour exposure to 50, 200, or 400 ppm hydrogen sulfide (Khan et al. 1990). Similarly, succinate oxidase activity also decreased in a dose-related fashion; although no affect was observed at the lowest dose. Cytochrome oxidase levels returned to normal by 24 hours postexposure in animals in the 200 ppm group, but not the 400 ppm group. Exposure at the two higher dose levels was also associated with complete abolition of the zymosan-induced stimulation of respiratory rates of pulmonary alveolar macrophages and there were significant decreases in the number of viable macrophages in lung lavage fluids at the highest dose (Khan et al. 1991).

Agency Contact (Chemical Manager): Selene Chou
MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Hydrogen Sulfide
CAS Number: 7783-06-4
Date: September 2014
Profile Status: Draft for Public Comment
Route: [x] Inhalation   [ ] Oral
Duration: [ ] Acute   [x] Intermediate   [ ] Chronic
Graph Key: 41
Species: Rat

Minimal Risk Level: 0.02   [ ] mg/kg/day  [x] ppm


Experimental design: Groups of male Sprague Dawley rats (12/group) were exposed to 0, 10, 30, or 80 ppm hydrogen sulfide 6 hours/day, 7 days/week for 10 weeks. Parameters used to assess toxicity were limited to extensive histopathological examination of the nasal cavity (six transverse sections examined via light microscopy; transverse sections form a series of circumferential slices [labeled levels 1–6], which allow for a thorough evaluation of all major structures and mucosae of the nasal cavity).

Effect noted in study and corresponding doses: Nasal lesions occurred only in the olfactory mucosa in rats exposed to 30 or 80 ppm and consisted of multifocal, bilaterally symmetrical olfactory neuron loss and basal cell hyperplasia affecting the lining of the dorsal medial meatus and the dorsal and medial regions of the ethmoid recess. The severity of the olfactory lesions was scored as 1 mild, 2 moderate, or 3 severe. For the olfactory neuron loss, the mild, moderate, or severe severity scores corresponded to 26–50, 51–75, and 76–100%, respectively, reduction in the normal thickness of the olfactory neuron layer. For the basal cell hyperplasia, mild, moderate, or severe severity scores corresponded to 1–33, 34–67, or 68–100% of the normal thickness of the olfactory neuron cell layer replaced by basal cells. No olfactory lesions were observed in the controls or rats exposed to 10 ppm. At 30 ppm, olfactory neuron loss was observed at nasal levels 4 (11/12, severity 1.4) and 5 (9/12, severity 1.1) and basal cell hyperplasia was observed at nasal levels 4 (10/12, severity 1.8) and 5 (11/12, severity 1.3). At 80 ppm, olfactory neuron loss was observed at levels 3 (8/8, severity 2.4), 4 (12/12, severity 2.4), 5 (11/12, severity 1.5), and 6 (5/12, severity 1.2-incidence not statistically significant) and basal cell hyperplasia was observed at nasal levels 4 (12/12, severity 1.2), 5 (11/12, severity 1.3), and 6 (6/12, severity 1.0).

Dose and end point used for MRL derivation: Two approaches were considered for the derivation of the MRL: the traditional NOAEL/LOAEL approach and the benchmark dose (BMD) modeling approach. For the NOAEL/LOAEL approach, the MRL would be derived using the NOAEL of 10 ppm and LOAEL of 30 ppm for olfactory neuron loss and basal cell hyperplasia in the nasal olfactory epithelium. Two data sets were considered for BMD modeling: olfactory neuron loss and basal cell hyperplasia. Incidence data were reported for nasal section levels 3 (olfactory neuron loss only) through 6. Because the highest incidence of lesions in the 30 ppm group was found in level 4, these data were used for the BMD analyses. The incidence data are reported in Table A-1.
Table A-1. Incidence of Olfactory Neuron Loss and Basal Cell Hyperplasia Observed in the Nasal Cavity of Male Rats Exposed to Hydrogen Sulfide for 10 Weeks

<table>
<thead>
<tr>
<th>Concentration (ppm)</th>
<th>Incidence of olfactory neuron loss</th>
<th>Incidence of basal cell hyperplasia</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0/12</td>
<td>0/12</td>
</tr>
<tr>
<td>10</td>
<td>0/12</td>
<td>0/12</td>
</tr>
<tr>
<td>30</td>
<td>11/12</td>
<td>10/12</td>
</tr>
<tr>
<td>80</td>
<td>12/12</td>
<td>12/12</td>
</tr>
</tbody>
</table>

Source: Brenneman et al. (2000)

The steepness of the dose-response curve for both lesion types (in particular the lack of intermediate response levels) precludes BMD modeling. Therefore, the NOAEL/LOAEL approach was selected for MRL derivation.

Uncertainty Factors used in MRL derivation:

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

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

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

\[ \text{NOAEL}_{ADJ} = 10 \text{ ppm} \times 6 \text{ hours/24 hours} \times 7 \text{ days/7 days} = 2.5 \text{ ppm} \]

The human equivalent concentration (HEC) was calculated using the following equation (EPA 1994b) for category 1 gases:

\[ \text{NOAEL}_{HEC} = \text{NOAEL}_{ADJ} \times \text{RDG}_{RET} \]

The regional gas dose ratio for the extrathoracic region (\( \text{RGD}_{RET} \)) of 0.184 was calculated using the following equation:

\[ \text{RGD}_{ET} = \frac{\left( \frac{V_E}{SA_{ET}} \right)_{\text{rat}}}{\left( \frac{V_E}{SA_{ET}} \right)_{\text{human}}} \]

Where:

- \( V_E \) is the minute volume and \( SA_{ET} \) is the surface area of the extrathoracic (ET) region of the respiratory tract.

Minute volume (\( V_E \))

Human: 13.8 L/minute (EPA 1994b)
Rat: 0.190 L/minute; calculated using the following EPA equation:

$$\ln(V_e) = b_0 + b_1 \ln(BW)$$

For rats, $b_0$ equals -0.578 and $b_1$ equals 0.821.

Because limited body weight data were reported in the study, a reference body weight of 0.267 kg (EPA 1988) was used.

EPA (1994b) rat and human respiratory surface area reference values:

- Extrathoracic: 15.0 cm$^2$ (rat), 200 cm$^2$ (human)

$$\text{NOAEL}_{\text{HEC}} = \text{NOAEL (ADJ)} \times \text{RGDR} = 2.5 \text{ ppm} \times 0.184 = 0.46 \text{ ppm}$$

The dosimetric model typically used to estimate a concentration for humans that would be equivalent to the exposure concentration in rats takes into account species differences in the surface area of the upper respiratory tract and inhalation rates. However, the model does not take into consideration that a larger portion of the rat nasal cavity is lined with olfactory epithelium compared to humans (50% in rats compared to 10% in humans) and differences in air flow patterns. A computational fluid dynamics model of the rat nasal epithelium developed for hydrogen sulfide (Moulin et al. 2002; Schroeter et al. 2006a, 2006b) found strong correlations between the amount of hydrogen sulfide reaching the olfactory tissue and the severity of the lesions (Moulin et al. 2002) and between hydrogen sulfide flux (uptake by the olfactory tissue) and the lesion incidence (Schroeter et al. 2006a). Using data generated from hydrogen sulfide uptake simulations in the human nasal passage at exposure levels of 1–50 ppm, Schroeter et al. (2006a) derived regression equations for predicting the maximum and 99th percentile flux values in the human olfactory region. However, data for the uptake simulations in the human nasal passage were based on a model reconstructed from MRI images from one male individual and did not take into account the potential individual variability in parameters. Schroeter et al. (2010) noted that there is considerable variation in nasal anatomy that could affect airflow patterns and dosimetry of inhaled gases. No actual measurements of gas delivery or absorption across nasal membranes were made; the simulations of a single computer model were used by Schroeter et al. (2006a) to predict HECs. When Schroeter et al. (2010) used the same male subject and a different computer model to simulate gas uptake, the average airflux was 14% lower than estimated by Schroeter et al. (2006a). Using MRI data for three adults and two children, Schroeter et al. (2010) concluded that normal variations in nasal anatomy, breathing rate, and air flow distribution were not likely to result in large variations in olfactory wall mass flux of hydrogen sulfide; however, the investigators recommended additional research on the influence of interindividual variability in absorption and pharmacodynamics effects of hydrogen sulfide in the nasal tissues to olfactory dose. Based on these uncertainties in the computational fluid dynamics model to predict a HEC, ATSDR estimated the NOAEL$\_\text{HEC}$ using the dosimetric model, which adjusts for surface area and breathing rate differences between rats and humans.

**Was a conversion used from intermittent to continuous exposure?** The NOAEL was adjusted for intermittent exposure (6 hours/day, 7 days/week)

**Other additional studies or pertinent information that lend support to this MRL:** Intermediate-duration animal studies support the identification of the respiratory tract and nervous system as sensitive targets. Studies conducted by CIIT (1983b, 1983c) did not find significant alterations in the nasal turbinates of Sprague-Dawley or Fischer-344 (F-344) rats exposed to 80 ppm or less hydrogen sulfide 6 hours/day, 5 days/week for 13 weeks. Inflammation of the squamous portion of the nasal mucosa was observed in mice exposed to 80 ppm hydrogen sulfide, 6 hours/day, 5 days/week for 13 weeks (CIIT 1983a); the NOAEL for this effect is 30 ppm. However, a re-examination of the histological specimens from this...
study (Dorman et al. 2004) revealed a statistically significant increase in the incidence of olfactory neuron loss in Sprague-Dawley rats, F-344 rats, and B6C3F1 mice exposed to 30 or 80 ppm; no lesions were observed at 10 ppm. In addition, increases in the incidence of bronchiolar epithelial hyperplasia and hypertrophy were observed in female Sprague-Dawley rats exposed to 30 or 80 ppm and male Sprague-Dawley and F-344 rats exposed to 80 ppm. The sensitivity of the olfactory epithelium has also been confirmed by acute-duration studies. Degeneration of the olfactory epithelium was observed in rats exposed to 400 ppm hydrogen sulfide for 4 hours (Lopez et al. 1988b), rats exposed to 200 ppm for 3 hours (Brenneman et al. 2002), and rats exposed to 80 ppm, 3 hours/day for 5 days (Brenneman et al. 2002). Additionally, data collected using a computational fluid dynamics model of the rat nasal epithelium (Moulin et al. 2002) suggest that the olfactory epithelium is more sensitive than the nasal respiratory epithelium despite the higher hydrogen sulfide flux (a surrogate for dose) to the regions lined with respiratory epithelium compared to regions lined with olfactory epithelium. Within the areas of the nose lined with olfactory epithelium, a high correlation between predicted hydrogen sulfide flux and the incidence of olfactory lesion was found.

The neurotoxicity of hydrogen sulfide in mature animals following intermediate-duration exposure has been assessed in studies examining brain weight, neurological function (posture, gait, tone of facial muscles, and pupillary reflexes), and histopathology; neurobehavioral performance has not been adequately assessed in longer duration studies. A 5% decrease in absolute brain weight was observed in Sprague-Dawley rats exposed to 80 ppm hydrogen sulfide 6 hours/day, 5 days/week for 13 weeks; no alterations were observed at 30 ppm (CIIT 1983c). No alterations in histopathology or neurological function were observed in these rats (CIIT 1983c) or in similarly exposed F-344 rats (CIIT 1983b) or B6C3F1 mice (CIIT 1983a). Neurodevelopmental toxicity studies have found some alterations that are suggestive of neurotoxicity. The suggestive findings in the offspring of rats exposed for 7 hours/day on gestational day 5 through postnatal day 21 include alterations in the architecture and growth characteristics of Purkinje cell dendritic fields at 20 ppm (Hannah and Roth 1991), decreases in norepinephrine and increases in serotonin in the frontal cortex at 20 ppm (Skrajny et al. 1992), and decreases in brain amino acid levels at 75 ppm (Hannah et al. 1989, 1990). However, no alterations in neurobehavioral performance (assessed via motor activity, passive avoidance, acoustic startle, and functional observation battery), delays in development (pinnae detachment, surface righting, incisor eruption, negative geotaxis, and eyelid detachment), or neuropathology were observed in the offspring of rats exposed 6 hours/day, 7 days/week for 2 weeks prior to mating, during mating, on gestation days 5–19, and on postnatal days 5–18 (Dorman et al. 2000). These data suggest that exposures of 20–80 ppm may result in subclinical alterations in neurochemistry and neuroanatomy.

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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, and 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.

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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 the 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.

***DRAFT FOR PUBLIC COMMENT***
LEGEND

(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").
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.

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

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.

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.

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.

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

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/m³ or ppm and oral exposure is reported in mg/kg/day.

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).

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

<table>
<thead>
<tr>
<th>Key to figure</th>
<th>Exposure frequency/duration</th>
<th>Species</th>
<th>System</th>
<th>NOAEL (ppm)</th>
<th>LOAEL (effect)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>INTERMEDIATE EXPOSURE</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>9</td>
<td></td>
<td></td>
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<tr>
<td>Systemic</td>
<td>↓</td>
<td>↓</td>
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<tr>
<td>18</td>
<td>Rat</td>
<td>13 wk</td>
<td>Resp</td>
<td>3&lt;sup&gt;b&lt;/sup&gt;</td>
<td>10 (hyperplasia)</td>
<td>Nitschke et al. 1981</td>
</tr>
<tr>
<td></td>
<td>5 d/wk</td>
<td>6 hr/d</td>
<td></td>
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<tr>
<td>CHRONIC EXPOSURE</td>
<td></td>
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</tr>
<tr>
<td>Cancer</td>
<td></td>
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</tr>
<tr>
<td>38</td>
<td>Rat</td>
<td>18 mo</td>
<td>5 d/wk</td>
<td>20 (CEL, multiple organs)</td>
<td>Wong et al. 1982</td>
<td></td>
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<tr>
<td></td>
<td>7 hr/d</td>
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<tr>
<td>39</td>
<td>Rat</td>
<td>89–104 wk</td>
<td>5 d/wk</td>
<td>10 (CEL, lung tumors, nasal tumors)</td>
<td>NTP 1982</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6 hr/d</td>
<td></td>
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<tr>
<td>40</td>
<td>Mouse</td>
<td>79–103 wk</td>
<td>5 d/wk</td>
<td>10 (CEL, lung tumors, hemangiosarcomas)</td>
<td>NTP 1982</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6 hr/d</td>
<td></td>
<td></td>
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</tbody>
</table>

<sup>a</sup> The number corresponds to entries in Figure 3-1.

<sup>b</sup> Used to derive an intermediate inhalation Minimal Risk Level (MRL) of $5 \times 10^{-3}$ ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).
Figure 3-1. Levels of Significant Exposure to [Chemical X] - Inhalation

Acute (≤14 days) Systemic

Death
Respiratory
Hematological

Intermediate (15-364 days) Systemic

Death
Hematological
Hepatic
Reproductive
Cancer

*Doses represent the lowest dose tested per study that produced a tumorigenic response and do not imply the existence of a threshold for the cancer end point.

- k-Monkey
- g-Guinea Pig
- r-Rat
- h-Rabbit
- m-Mouse

- Cancer Effect Level - Animals
- LOAEL, More Serious - Animals
- LOAEL, Less Serious - Animals
- NOAEL - Animals

- Minimal Risk Level for effects other than Cancer

10^-7
10^-6
10^-5
10^-4

Estimated Upper-Bound Human Cancer Risk Levels
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### APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
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<tbody>
<tr>
<td>ACGIH</td>
<td>American Conference of Governmental Industrial Hygienists</td>
</tr>
<tr>
<td>ACOEM</td>
<td>American College of Occupational and Environmental Medicine</td>
</tr>
<tr>
<td>ADI</td>
<td>acceptable daily intake</td>
</tr>
<tr>
<td>ADME</td>
<td>absorption, distribution, metabolism, and excretion</td>
</tr>
<tr>
<td>AED</td>
<td>atomic emission detection</td>
</tr>
<tr>
<td>AFID</td>
<td>alkali flame ionization detector</td>
</tr>
<tr>
<td>AFOSH</td>
<td>Air Force Office of Safety and Health</td>
</tr>
<tr>
<td>ALT</td>
<td>alanine aminotransferase</td>
</tr>
<tr>
<td>AML</td>
<td>acute myeloid leukemia</td>
</tr>
<tr>
<td>AOAC</td>
<td>Association of Official Analytical Chemists</td>
</tr>
<tr>
<td>AOEC</td>
<td>Association of Occupational and Environmental Clinics</td>
</tr>
<tr>
<td>AP</td>
<td>alkaline phosphatase</td>
</tr>
<tr>
<td>APHA</td>
<td>American Public Health Association</td>
</tr>
<tr>
<td>AST</td>
<td>aspartate aminotransferase</td>
</tr>
<tr>
<td>atm</td>
<td>atmosphere</td>
</tr>
<tr>
<td>ATSDR</td>
<td>Agency for Toxic Substances and Disease Registry</td>
</tr>
<tr>
<td>AWQC</td>
<td>Ambient Water Quality Criteria</td>
</tr>
<tr>
<td>BAT</td>
<td>best available technology</td>
</tr>
<tr>
<td>BCF</td>
<td>bioconcentration factor</td>
</tr>
<tr>
<td>BEI</td>
<td>Biological Exposure Index</td>
</tr>
<tr>
<td>BMD/C</td>
<td>benchmark dose or benchmark concentration</td>
</tr>
<tr>
<td>BMDX</td>
<td>dose that produces a X% change in response rate of an adverse effect</td>
</tr>
<tr>
<td>BMDEX</td>
<td>95% lower confidence limit on the BMDX</td>
</tr>
<tr>
<td>BMDS</td>
<td>Benchmark Dose Software</td>
</tr>
<tr>
<td>BMR</td>
<td>benchmark response</td>
</tr>
<tr>
<td>BSC</td>
<td>Board of Scientific Counselors</td>
</tr>
<tr>
<td>C</td>
<td>centigrade</td>
</tr>
<tr>
<td>CAA</td>
<td>Clean Air Act</td>
</tr>
<tr>
<td>CAG</td>
<td>Cancer Assessment Group of the U.S. Environmental Protection Agency</td>
</tr>
<tr>
<td>CAS</td>
<td>Chemical Abstract Services</td>
</tr>
<tr>
<td>CDC</td>
<td>Centers for Disease Control and Prevention</td>
</tr>
<tr>
<td>CEL</td>
<td>cancer effect level</td>
</tr>
<tr>
<td>CELDS</td>
<td>Computer-Environmental Legislative Data System</td>
</tr>
<tr>
<td>CERCLA</td>
<td>Comprehensive Environmental Response, Compensation, and Liability Act</td>
</tr>
<tr>
<td>CFR</td>
<td>Code of Federal Regulations</td>
</tr>
<tr>
<td>Ci</td>
<td>curie</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>CL</td>
<td>ceiling limit value</td>
</tr>
<tr>
<td>CLP</td>
<td>Contract Laboratory Program</td>
</tr>
<tr>
<td>cm</td>
<td>centimeter</td>
</tr>
<tr>
<td>CML</td>
<td>chronic myeloid leukemia</td>
</tr>
<tr>
<td>CPSC</td>
<td>Consumer Products Safety Commission</td>
</tr>
<tr>
<td>CWA</td>
<td>Clean Water Act</td>
</tr>
<tr>
<td>DHEW</td>
<td>Department of Health, Education, and Welfare</td>
</tr>
<tr>
<td>DHHS</td>
<td>Department of Health and Human Services</td>
</tr>
<tr>
<td>DNA</td>
<td>deoxyribonucleic acid</td>
</tr>
<tr>
<td>DOD</td>
<td>Department of Defense</td>
</tr>
<tr>
<td>DOE</td>
<td>Department of Energy</td>
</tr>
<tr>
<td>DOL</td>
<td>Department of Labor</td>
</tr>
</tbody>
</table>
DOT Department of Transportation
DOT/UN/ Department of Transportation/United Nations/
NA/IMDG 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
F₁ 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
Koc organic carbon partition coefficient
Kow octanol-water partition coefficient
L liter
LC liquid chromatography
L₅₀ lethal concentration, 50% kill
L₅₀ lethal concentration, low
LD₅₀ lethal dose, 50% kill
LD₅₀ lethal dose, low
LDH lactic dehydrogenase
LH luteinizing hormone
LOAEL lowest-observed-adverse-effect level
LSE Levels of Significant Exposure
LT₅₀ 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
NOSHTIC 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
TD50 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

`q₁`
cancer slope factor

`−`
negative

`+`
positive

`(+)`
weakly positive result

`(−)`
weakly negative result
APPENDIX D. INDEX

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