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: Parathion
CAS Numbers: 56-38-2
Date: January 2017
Profile Status: Final
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 9
Species: Rat

Minimal Risk Level: 20 [ ] mg/kg/day [X] ng/m^3

Reference: NIOSH. 1974. Inhalation and oral toxicity 13 studies of ethyl parathion administered acutely and subacutely to the rat and dog. National Institute of Occupational Safety and Health Report No. 00134578. Aberdeen Proving Ground, MD: Edgewood Arsenal, Toxicology Division.

Experimental design: Groups of male rats (20/group) were exposed whole-body to 0, 0.01, 0.1, or 0.74 mg parathion aerosol/m^3 7 hours/day, 5 days/week for 6 weeks. It should be noted that since the rats were not prevented from grooming themselves, ingestion of some amount of parathion may have occurred. Blood samples obtained from 71 rats were assayed for red blood cell and plasma cholinesterase and served as baseline controls. Ten rats per exposure group and control group were sacrificed at various times during the exposure period and during a 6-week post-exposure period to collect blood samples. The rats were observed for clinical signs and were weighed before blood sampling and sacrifice.

Effect noted in study and corresponding doses: No clinical signs were seen in rats exposed to 0.01 or 0.1 mg parathion/m^3. Some rats in the high-concentration group showed signs of parathion toxicity, including tremors and ataxia. Blood collected from the high-dose group after the last exposure showed no significant alteration in hematocrit. Body weight was not significantly altered by exposure to parathion. In the low-exposure group, red blood cell AChE activity was maximally decreased by approximately 30% on exposure weeks 4 and 5; no data were available for week 3. On exposure week 6, red blood cell AChE activity in the low-exposure group had recovered to 97.3% of control levels. In the mid-exposure group, the maximum decrease in red blood cell AChE was 43% and occurred on week 1. During the rest of the exposure period, red blood cell cholinesterase activity was 60–70% of pretest levels, suggesting that a steady state had been achieved. Red blood cell AChE activity during the first and second week of the post-exposure period was 82 and 84.4% of controls, indicating that recovery was in progress. In the high-exposure group, red blood cell AChE activity achieved its maximal depression on week 5 of exposure, reaching 15% of controls. In general, enzyme activities recovered during the 6-week post-dosing period. Changes in plasma cholinesterase activity paralleled red blood cell changes, recovered faster and exceeded control levels by week 1 or 2 post-exposure. Since the exposure level of 0.1 mg parathion/m^3 induced a level of depression of red blood cell AChE activity that appeared to achieve steady state at approximately 60–70% of controls during exposure, and no clinical signs were observed at this exposure level, 0.1 mg/m^3 constitutes a less serious LOAEL for neurological effects in rats; the exposure concentration of 0.01 mg parathion/m^3 is a NOAEL.

Since only means without deviation parameters were reported for red blood cell AChE values, dose-responses using benchmark dose approaches cannot be constructed to estimate points of departure from the rat data. Therefore, a NOAEL/LOAEL approach will be used and the NOAEL of 0.01 mg parathion/m^3 for red blood cell AChE in rats is the point of departure for MRL derivation.

Exposure concentration and end point used for MRL derivation: 0.01 mg/m^3; NOAEL for neurological effects (red blood cell AChE inhibition).

[X] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

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

Was a conversion 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 dose could not be determined because the study did not provide information regarding information about particle size.

Was a conversion used from intermittent to continuous exposure? Yes (7 hours/24 hours) x (5 days/7 days).

Other additional studies or pertinent information that lend support to this MRL: A 6-week inhalation study in dogs also established a NOAEL of 0.01 mg/m^3 for red blood cell AChE activity (NIOSH 1974). In that study, male beagle dogs (6/group) were exposed to parathion aerosol at concentrations of 0, 0.001, 0.01, or 0.2 mg/m^3 7 hours/day, 5 days/week for 6 weeks and were held for an additional 6-week post-exposure period. Blood samples obtained from the dogs at various times during the exposure and post-exposure periods were assayed for red blood cell AChE and plasma cholinesterase. Blood samples were taken pre-exposure so that each dog served as its own control. No clinical signs were observed in the dogs. Exposure to parathion did not affect body weight gain in the dogs. No significant effects on levels of red blood cell AChE activity were observed at the low-exposure level. Exposure to 0.01 mg parathion/m^3 reduced red blood cell AChE activity by 21% by the end of the second week of exposure, but levels recovered to 14% of pre-exposure values by the third week of exposure and to 100% of pretest levels during the remaining of the exposure period. In the high-exposure group, red blood cell AChE activity was reduced between 26 and 46% during the first 5 weeks of exposure and inhibition reached a maximum of 41% of pre-exposure levels on week 6 of exposure. Slow recovery was evident during the post-exposure period. Plasma cholinesterase activity was inhibited to a greater extent during the exposure period, but seemed to recover faster during the post-exposure period. Based on the fact that red blood cell AChE activity was depressed over 20% (21%) only on week 2 of exposure in the 0.01 mg/m^3 group, this exposure level is considered a NOAEL for neurological effects in dogs in an intermediate-duration study; the LOAEL is 0.2 mg/parathion/m^3.

Agency Contacts (Chemical Managers): Sam Keith

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Parathion
CAS Numbers: 56-38-2
Date: January 2017
Profile Status: Final
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 50
Species: Human

Minimal Risk Level: 0.009 [X] mg/kg/day [ ] mg/m^3

Reference: Rider JA, Moeller HC, Puletti EJ, et al. 1969. Toxicity of parathion, systox, octamethyl pyrophosphoramide, and methyl parathion in man. Toxicol Appl Pharmacol 14(3):603-611.

Experimental design: Five male volunteers* were administered 3, 4.5, 6, or 7.5 mg parathion/day in a capsule (0.04, 0.06, 0.09, and 0.11 mg/kg/day, assuming 70 kg body weight) for approximately 30 days; two additional subjects served as controls. In a pretest period of 30 days, blood was collected to establish baseline levels of plasma cholinesterase and red blood cell AChE. The subjects were also monitored during a post-test period of about 30 days. At the beginning of the pretest period, routine blood counts, urinalysis, and prothrombin time were performed, and these were repeated at the end of each test period.

Effect noted in study and corresponding doses: Doses of 0.04 or 0.06 mg parathion/kg/day did not affect the levels of either enzyme. Administration of 0.09 mg parathion/kg/day caused a slight depression of plasma cholinesterase (data not provided). Doses of 0.11 mg parathion/kg/day induced a 27% decrease in the plasma enzyme in one subject on day 4. On day 9, two subjects showed 36 and 32% inhibition of the plasma enzyme. On day 16, the levels of plasma cholinesterase in these two subjects were 50 and 52% of pretest levels and parathion dosing was discontinued. In the other three subjects, plasma cholinesterase levels were 97, 82, and 69% of pretest levels. On day 16, the mean levels of plasma cholinesterase in the five exposed subjects was reduced by 28% from the control value. On day 23, plasma cholinesterase activity in a third exposed subject was 54% of his pretest level and dosing was also discontinued. Therefore, of the five dosed subjects, three had the treatment discontinued by day 23 (two on day 16 and one on day 23). In the two subjects who received parathion during 35 days, the lowest plasma cholinesterase levels were 86 and 78% of their pretest values.

Red blood cell AChE activity in the three subjects who discontinued parathion dosing achieved maximal inhibition levels of 63, 78, and 86% of pretest levels. In the two subjects who completed the test period, there was no significant effect on red blood cell AChE activity. By the end of the post-test period, both enzymes had returned to pretest levels. No information was provided regarding blood counts, urinalysis, or prothrombin test results. Based on a >20% inhibition of red blood cell AChE activity in two out of five subjects for 16 days, the dose of 0.11 mg parathion/kg/day is a LOAEL for neurological effects; the next lower dose, 0.09 mg parathion/kg/day, is a NOAEL.

Benchmark dose analysis cannot be performed because the data were not presented as means plus or minus a measure of dispersion. The intermediate-duration oral MRL for parathion is derived by dividing the NOAEL of 0.09 mg parathion/kg/day by an uncertainty factor of 10 (to account for human variability); this yields an MRL of 0.009 mg parathion/kg/day (9 µg/kg/day).

Dose and end point used for MRL derivation: 0.09 mg/kg/day; NOAEL for neurological effects (inhibition of red blood cell AChE activity).

[X] NOAEL [ ] LOAEL

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? No.

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

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

Other additional studies or pertinent information that lend support to this MRL: Edson (1964) identified a NOAEL of 0.1 mg parathion/kg/day (the highest dose tested) for red blood cell AChE activity in female volunteers administered the pesticide orally for 6 weeks. The available intermediate-duration oral studies in animals suggest that significant inhibition (>20%) of red blood cell AChE occurs with repeated doses ≥0.1 mg parathion/kg/day. In a study in dogs, red blood cell AChE activity was depressed approximately 25% with doses of 0.047 mg parathion/kg/day for 12 weeks, but appeared to increase to near 90% of pretest values on week 16 of exposure (Frawley and Fuyat 1957). Another study in dogs showed that a constant inhibition of the enzyme of >20% could be achieved only with repeated doses of 0.5 mg parathion/kg/day (NIOSH 1974). Two studies in rats dosed for several weeks identified LOAELs of 0.1 mg parathion/kg/day for red blood cell AChE; the NOAELs were 0.024 and 0.05 mg parathion/kg/day (Ivens et al. 1998; NIOSH 1974).

*Note: ATSDR endorses the highest ethical standards in conducting human dosing studies. Thus, it should be noted that the Rider et al. (1969) study raises ethical concerns about human subjects' protection and would not be approved today based on the current human subject protection regulations (HHS 2009). The participants in the study were prisoners in San Quentin State prison and the California Medical Facility in Vacaville, raising questions about their ability to make a truly voluntary and uncoerced decision whether or not to participate in the study. The study report provides no detailed information regarding consent procedures other than to state that the participants were volunteers. ATSDR believes that the use of the study is consistent with the recommendations by the NRC (2004).

> Recommendation 7-2 states that: "*The cholinesterase inhibition studies that already have been submitted to EPA, if determined to be scientifically valid and justified for EPA's regulatory purposes, may be considered for use in risk assessment and standard setting if they were not unethically conducted (see Recommendation 5-7.)*"
>
> Recommendation 5-7 states that: "*EPA should accept scientifically valid studies conducted before its new rules are implemented unless there is clear and convincing evidence that the conduct of those studies was fundamentally unethical (e.g., the studies were intended to seriously harm participants or failed to obtain informed consent.)*"

Although there is limited information about the consent procedures used in this study, the information that is provided about the participants being volunteers suggests that there is no clear and convincing evidence that the conduct of this study was fundamentally unethical.

> Recommendation 4-1 further states that: *"EPA should consider a human dosing study intended to reduce the interspecies uncertainty factor (for example, a study of a biomarker such as cholinesterase inhibition) as conferring a societal benefit only if it was designed and conducted in a manner that would improve the scientific accuracy of EPA's extrapolation from animal to human data."*

As discussed above, the available intermediate-duration oral studies suggest that in humans, rats, and dogs, significant inhibition (>20%) of red blood cell AChE activity occurs with repeated doses ≥0.1 mg parathion/kg/day. The human study by Rider et al. provides a basis for an MRL that improves the accuracy of the value based on the animal data alone, and eliminates the interspecies uncertainty factor. Any human dosing study must have a useful purpose and convey a benefit to participants and/or society (NRC 2004). ATSDR believes that the Rider et al. (1969) study provides a benefit to society in that the data provide the basis for a health guidance value (i.e., MRL) that can be used to protect exposed populations to parathion.

Agency Contacts (Chemical Managers): Sam Keith

This page is intentionally blank.

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

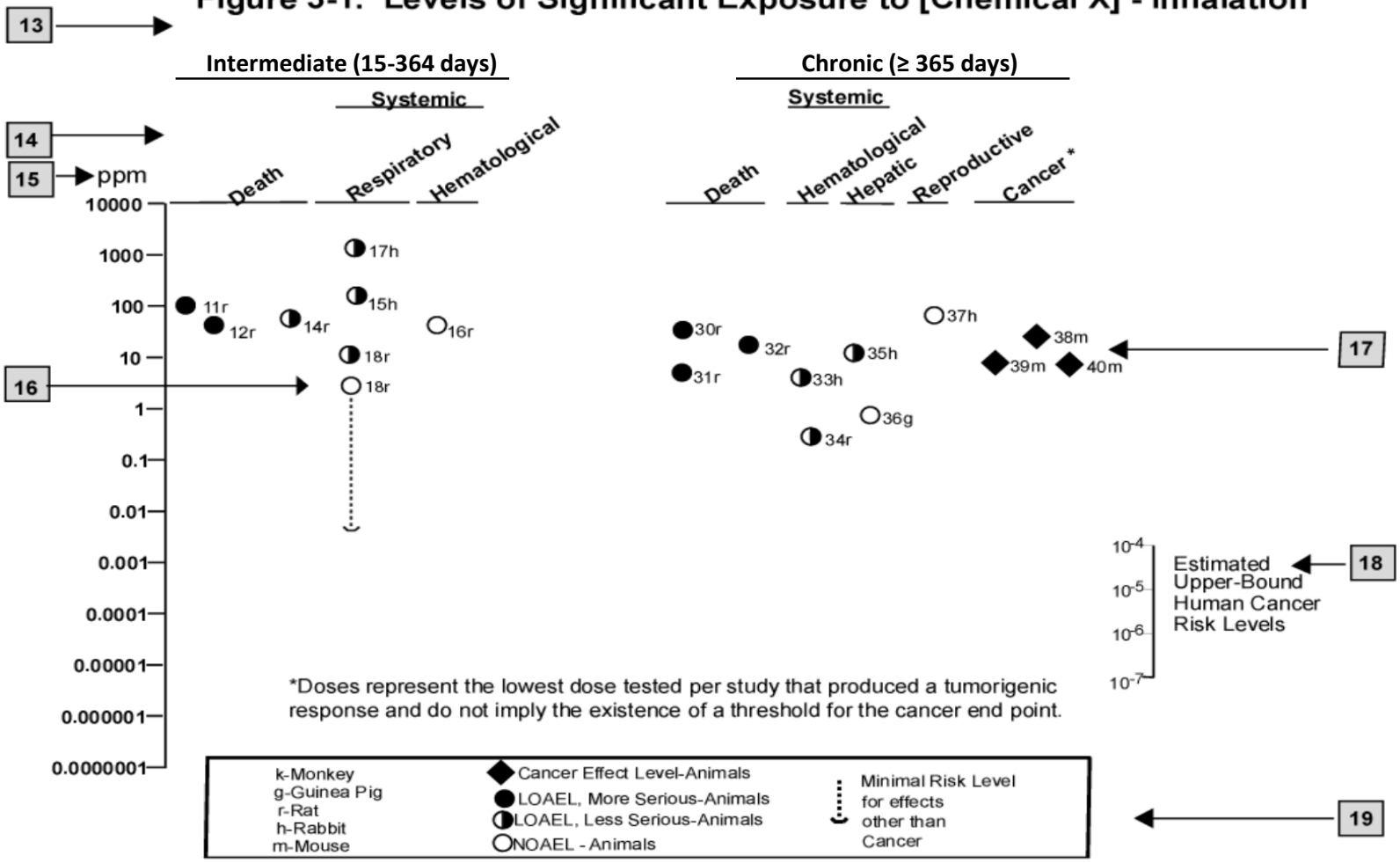
1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

	Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
2 →	INTERMEDIATE EXPOSURE							
		5	6	7	8	9		10
3 →	Systemic	↓	↓	↓	↓	↓		↓
4 →	18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
	CHRONIC EXPOSURE							
	Cancer					11		
						↓		
	38	Rat	18 mo 5 d/wk 7 hr/d			20	(CEL, multiple organs)	Wong et al. 1982
	39	Rat	89–104 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, nasal tumors)	NTP 1982
	40	Mouse	79–103 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, hemangiosarcomas)	NTP 1982

12 → [a] The number corresponds to entries in Figure 3-1.
[b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of $5x10^{-3}$ ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

SAMPLE

Figure 3-1. Levels of Significant Exposure to [Chemical X] - Inhalation



This page is intentionally blank.

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