APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99–499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that

are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology and Environmental Medicine, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology and Environmental Medicine, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-32, Atlanta, Georgia 30333.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Heptachlor
CAS Numbers: 76-44-8
Date: August 2007
Profile Status: Final
Route: [ ] Inhalation [X] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Graph Key: 19
Species: Rat

Minimal Risk Level: 0.0006 [X] mg/kg/day [ ] ppm

Reference: Amita Rani BE, Krishnakumari MK. 1995. Prenatal toxicity of heptachlor in albino rats. Pharmacol Toxicol 76(2):112-114.

Experimental design: Groups of 30 female CFT-Wistar rats received gavage doses of heptachlor in groundnut oil for 14 days (presumably 7 days/week). The total administered doses were 25 and 50 mg/kg body weight; the daily doses were 1.8 and 3.6 mg/kg/day; a vehicle control group was also used. After 14 days of exposure, the animals were mated with controls.

Effect noted in study and corresponding doses: A significant decrease in the number of pregnant females (56.3 and 44.4%) and increase in the number of resorptions (18.90 and 11.40%) were observed in both groups of heptachlor-exposed rats. Significant decreases in estradiol-17beta and progesterone levels were also observed in the 1.8 mg/kg/day group. No alterations in the number of implantations were observed. The investigators noted that focal necrosis was observed in the liver; however, they did not note at which dose level and no incidence data were provided.

Dose and end point used for MRL derivation: The MRL is based on a serious LOAEL of 1.8 mg/kg/day for reproductive effects.

[ ] NOAEL [X] LOAEL

Uncertainty Factors used in MRL derivation: 1,000

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

Modifying Factor used in MRL derivation: 3

[X] 3 for use of a serious end point

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? No.

Other additional studies or pertinent information that lend support to this MRL: Several targets of toxicity have been identified, in addition to the impaired reproductive performance observed in the Amita Rani and Krishnakumari (1995) study. These include the liver, nervous system, and developing offspring. Gestational exposure to 4.5 or 6.8 mg/kg/day resulted in decreases in pup body weight (Narotsky and Kavlock 1995; Narotsky et al. 1995) and a decrease in pup righting reflex was observed at 4.2 mg/kg/day (Purkerson-Parker et al. 2001b). At twice these dose levels, an increase in pup mortality was observed (Narotsky et al. 1995; Purkerson-Parker et al. 2001b). Liver effects were observed at doses similar to those resulting in developmental effects. Increases in serum alanine aminotransferase and aldolase activity levels, hepatocytomegaly, and minimal monocellular necrosis were observed in rats administered 7 mg/kg/day heptachlor in oil for 14 days (Berman et al. 1995; Krampl 1971). Exposure to 7 mg/kg/day also resulted in excitability and increased arousal in rats administered heptachlor in oil via gavage for 1 or 14 days (Moser et al. 1995).

Agency Contacts (Chemical Managers): Zemoria Rosemond, B.A.; G. Daniel Todd, Ph.D.; Malcolm Williams, D.V.M., Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Heptachlor
CAS Numbers: 76-44-8
Date: June 2007
Profile Status: Final
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 49
Species: Rat

Minimal Risk Level: 0.0001 [X] mg/kg/day [ ] ppm

Reference: Smialowicz RJ, Williams WC, Copeland CB, et al. 2001. The effects of perinatal/juvenile heptachlor exposure on adult immune and reproductive system function in rats. Toxicol Sci 61(1):164-175.

Moser VC, Shafer TJ, Ward TR, et al. 2001. Neurotoxicological outcomes of perinatal heptachlor exposure in the rat. Toxicol Sci 60(2):315-326.

Experimental design: Groups of 15–20 pregnant Sprague Dawley rats were administered via gavage 0, 0.03, 0.3, or 3 mg/kg/day heptachlor in corn oil on gestational day 12 through postnatal day 7; pups were also exposed from postnatal day 7 to 21 or 42. Neurobehavorial assessment consisted of righting reflex on postnatal days 2–5, functional observational battery test, motor activity, passive avoidance test of learning and memory, and Morris water maze to assess spatial and working memory. The liver, kidneys, adrenals, thymus, spleen, ovaries, uterus/vagina, testes, epididymides, seminal vesicles/coagulating glands, and ventral and dorsolateral prostate were histologically examined in 15–17 offspring from each group on postnatal day 46. The following immunological tests were performed in the 8-week-old offspring: splenic lymphoproliferative (LP) responses to T cell mitogens (e.g., concanavalin A [ConA], phytohemagglutinin [PHA]) and to allogeneic cells in a mixed lymphocyte reaction, primary IgM antibody response to sheep red blood cells, examination of splenic lymphocytes subpopulations, and delayed-type and contact hypersensitivity. Reproductive assessment included evaluation of vaginal opening (index of female puberty) and prepuce separation (index of male puberty) beginning at postnatal days 25 and 35, respectively. The offspring were mated with an untreated mate and the dams were allowed to rear the first litter to postnatal day 10. The results of the neurobehavioral assessment were reported by Moser et al. (2001); the remaining results were reported by Smialowicz et al. (2001).

Effect noted in study and corresponding doses: No significant alterations in maternal body weight, number of dams delivering litters, litter size, or pup survival were observed. Additionally, no alterations in pup growth rates, age at eye opening, anogenital distance, or age at vaginal opening or preputial separation were observed. A significant decrease in pup body weight at postnatal day 1 was observed at 3 mg/kg/day; this effect was not observed at postnatal days 7, 14, or 21. No consistent, statistically significant alterations in offspring body weights were observed at postnatal days 21, 28, 35, or 42. Significant alterations in absolute and relative liver weights were observed in males and females exposed to 3 mg/kg/day; increases in absolute and relative ovary weights were also observed at 3 mg/kg/day. No histological alterations were observed in the examined tissues. No alterations in fertility were observed in the adult males and females mated to untreated partners, and no effects on soft tissue or gross body structure of the offspring (F_2 generation) were observed. No alterations in sperm count or sperm motility were observed.

Righting was significantly delayed in the female offspring of rats exposed to 3 mg/kg/day heptachlor; no significant alterations were observed in the male offspring. The investigators suggested that this was due to a delay in the ontogeny of righting rather than an inability to perform the task. The following significant alterations in the FOB and motor activity tests were found in the offspring dosed until postnatal day 21: increased open field activity in 3 mg/kg/day males, non-dose-related increased activity in figure-eight chambers in females (significant only in 0.03 mg/kg/day group), and faster decline in habituation of activity in 3 mg/kg/day males. Alterations in the offspring dosed until postnatal day 42 included: increased levels of urination in males in the 0.03 and 0.3 mg/kg/day groups, increased landing foot splay in males in the 0.03 mg/kg/day group, and removal reactivity in males and females in the 0.03 mg/kg/day group. No alterations in the passive avoidance test were observed in the offspring exposed until postnatal day 21; in those exposed until postnatal day 42, an increase in the number of nose pokes was observed in all groups of females. No significant alterations in performance on the water maze test were found in the offspring exposed until postnatal day 21. In those exposed until postnatal day 42, increases in latency to find the platform were observed in males and females exposed to 3 mg/kg/day and increases in the time spent in the outer zone were found in males exposed to 0.3 or 3 mg/kg/day. In the water maze memory trial, no differences in performance were found between controls and animals exposed until postnatal day 21. Alterations in significant quadrant bias were observed in 0.03, 0.3, and 3 mg/kg/day males during the first probe test and in 0.3 and 3 mg/kg/day males and 3 mg/kg/day females in the second probe test. The study investigators noted that the heptachlor-exposed rats did not develop an efficient search strategy for locating the platform; they spent more time circling the outer zone of the tank. By the second week of the test, control rats had learned to venture into the zone where the platform was located.

A dose-related, statistically significant suppression of primary IgM antibody response to sRBC was found in males, but not females. The primary IgM response to sRBCs was reduced in 21-week-old males exposed to 0.3 mg/kg/day. A second immunization with sRBCs administered 4 weeks later resulted in a significant reduction in IgG antibody response in males administered 0.03, 0.3, or 3 mg/kg/day heptachlor; no response was seen in females. A decrease in the $OX12^{+}OX19^{-}$ (i.e., B/plasma cells) population was also found in the spleen of males exposed to 3 mg/kg/day. No alterations in the following immunological parameters assessed at 8 weeks of age were found: lymphoid organ weights, splenic NK cell activity, splenic cellularity or cell viability, and lymphoproliferative responses of splenic lymphocytes to T-cell mitogens ConA and PHA or to allogenic cells in the mixed lymphocyte reaction. The results of this portion of the study suggest that exposure to heptachlor adversely affects the development of the immune system.

Dose and end point used for MRL derivation: The MRL is based on a minimal LOAEL of 0.03 mg/kg/day for developmental immunological and neurological effects. The observed alterations were considered to be minimally adverse and suggestive of immunotoxicity and neurotoxicity.

[ ] NOAEL [X] LOAEL

Uncertainty Factors used in MRL derivation:

- [X] 3 for use of a minimal 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? 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? No.

Other additional studies or pertinent information that lend support to this MRL: The results of the Smialowicz et al. (2001) study suggest that exposure to heptachlor adversely affects the development of the immune system. A framework for testing a chemical's potential to induce developmental immunotoxicological effects has not been established. Based on the results of studies in mature animals (Luster et al. 1992), two panels of government, industry, and academia immunotoxicology experts (Holsapple et al. 2005; Luster et al. 2003) reached a consensus that assays measuring the response to a T-cell dependent antigen (e.g., sheep red blood cells) should be included in included in a developmental immunotoxicology protocol. In mature animals, the sheep red blood cells antibody plague-forming cell test was the most reliable single test predictor of immunotoxicity (Luster et al. 1992).

Intermediate-duration oral exposure studies have identified a number of targets of heptachlor toxicity including the liver, nervous system, reproductive system, and the developing offspring. Other less documented effects have also been observed. The developing organism appears to be the most sensitive target. In the absence of maternal toxicity, heptachlor is not associated with alterations in pup mortality or body weight gain (Lawson and Luderer 2004; Purkerson-Parker et al. 2001b; Smialowicz et al. 2001) or alterations in the development of the reproductive system (Lawson and Luderer 2004; Smialowicz et al. 2001). In contrast, heptachlor appears to adversely affect the development of the nervous and immune systems. The observed effects include impaired spatial memory at 0.03 mg/kg/day and higher (Moser et al. 2001), impaired spatial learning at 0.3 mg/kg/day and higher (Moser et al. 2001), and decreased in righting reflex (Moser et al. 2001; Purkerson-Parker et al. 2001b) and increased open field activity (Moser et al. 2001) at 3 mg/kg/day. These effects were observed in rats exposed *in utero*, during lactation, and postnatally until day 42; spatial memory and learning were not adversely affected when the exposure was terminated at postnatal day 21 (Moser et al. 2001). The conflicting results may have resulted in the higher heptachlor epoxide body burden in rats exposed to postnatal day 42, testing at different ages, or exposure may have occurred during a critical window of vulnerability. The effects observed in rats are consistent with those observed in humans. Impaired performance on several neurobehavioral tests, including abstract concept formation, visual perception, and motor planning, was observed in high school students presumably prenatally exposed to heptachlor from contaminated milk products (Baker et al. 2004b). Alterations in immune function were also observed in the rats exposed until postnatal day 42. At 0.03 mg/kg/day and higher, suppression of the immune response to sheep red blood cells was observed (Smialowicz et al. 2001). A reduction in the percentage of B lymphocytes was also observed in the spleen of rats exposed to 3 mg/kg/day. Other tests of immune function were not significantly altered.

The liver effects observed in rats or mice exposed to heptachlor in the diet include increased liver weights (Izushi and Ogata 1990; Pelikan 1971), increased serum alanine aminotransferase levels (Izushi and Ogata 1990), steatosis (Pelikan 1971), and hepatitis and necrosis (Akay and Alp 1981). The lowest LOAEL values for these effects range from 5 to 8.4 mg/kg/day. Neurological signs such as hyperexcitability, seizures, and difficulty standing, walking, and righting were observed at similar dose levels; LOAELs ranged from 1.7 to 17 mg/kg/day (Akay and Alp 1981; Aulerich et al. 1990; Crum et al. 1993). The reproductive system appeared to be more sensitive to heptachlor toxicity. Decreases in epididymal sperm count were observed in rats administered 0.65 mg/kg/day heptachlor in groundnut oil for 70 days (Amita Rani and Krishnakumari 1995). This dose also resulted in increased resorptions when the exposed males were mated with unexposed females. Infertility was observed in all mice exposed to 8.4 mg/kg/day heptachlor for 10 weeks (Akay and Alp 1981).

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APPENDIX B. USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public, especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Relevance to Public Health

This chapter provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions:

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The chapter covers end points in the same order that they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, and dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this chapter.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal Risk Levels (MRLs) for noncancer end points (if derived) and the end points from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Chapter 3 Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, ATSDR has derived MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

MRLs should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2, "Relevance to Public Health," contains basic information known about the substance. Other sections such as Chapter 3 Section 3.9, "Interactions with Other Substances," and Section 3.10, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables.

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, MRLs to humans for noncancer end points, and EPA's estimated range associated with an upper- bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 3-1 and Figure 3-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See Sample LSE Table 3-1 (page B-6)

(1) Route of Exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Tables 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures.

(2) Exposure Period. Three exposure periods—acute (less than 15 days), intermediate (15–364 days), and chronic (365 days or more)—are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Health Effect. The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) Key to Figure. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the two "18r" data points in sample Figure 3-1).

(5) Species. The test species, whether animal or human, are identified in this column. Chapter 2, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 3.4, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequency/Duration. The duration of the study and the weekly and daily exposure regimens are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to “Chemical x” via inhalation for 6 hours/day, 5 days/week, for 13 weeks. For a more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Nitschke et al. 1981).

(7) System. This column further defines the systemic effects. These systems include respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, one systemic effect (respiratory) was investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system, which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less Serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

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

(11) CEL. A CEL is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

(12) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates that the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Sample Figure 3-1 (page B-7)

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure Period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the acute and intermediate exposure periods are illustrated.

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

(15) Levels of Exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16) NOAEL. In this example, the open circle designated 18r identifies a NOAEL critical end point in the rat upon which an intermediate inhalation exposure MRL is based. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17) CEL. Key number 38m is one of three studies for which CELs were derived. The diamond symbol refers to a CEL for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18) Estimated Upper-Bound Human Cancer Risk Levels. This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

(19) Key to LSE Figure. The Key explains the abbreviations and symbols used in the figure.

SAMPLE

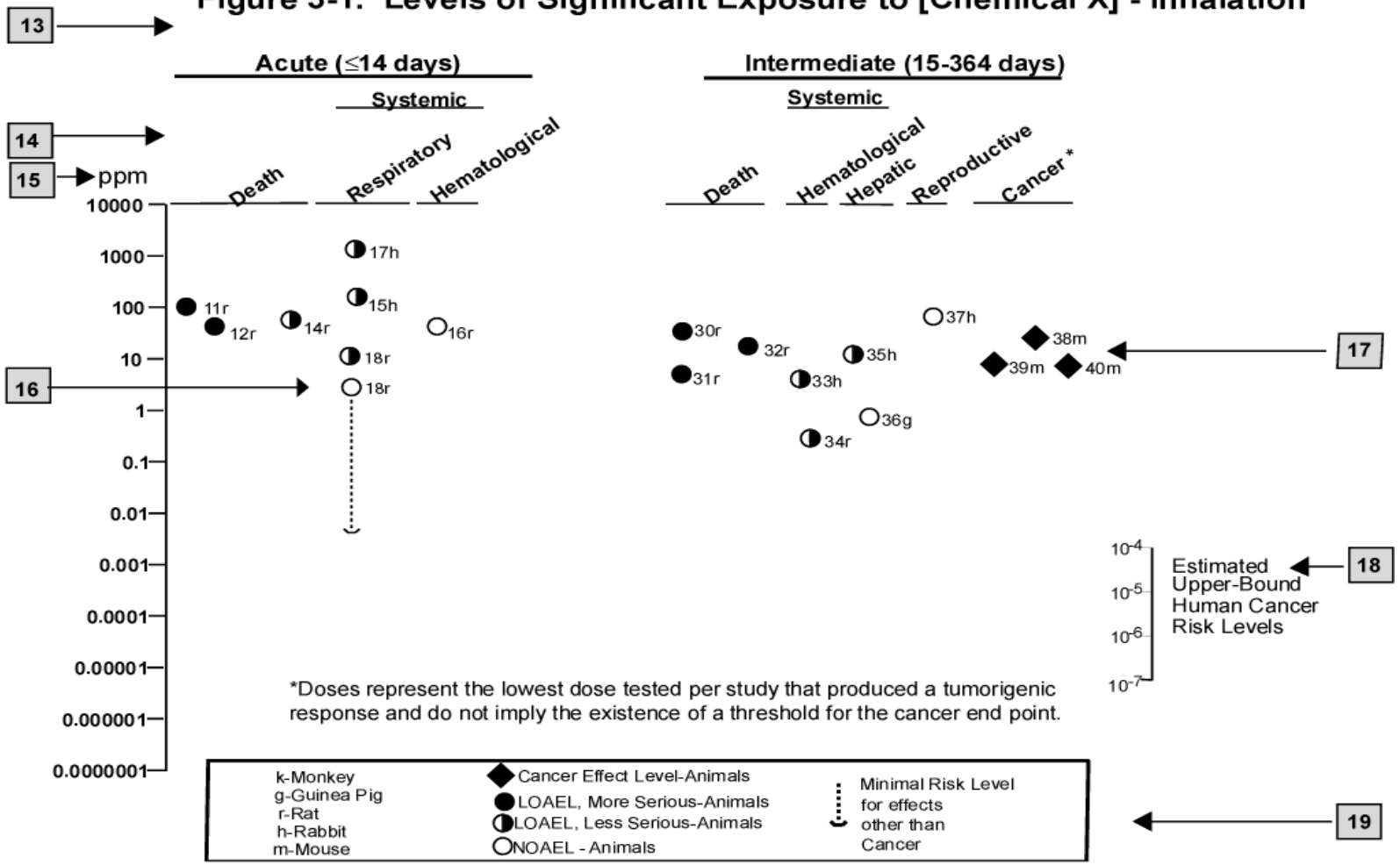
1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
2 → INTERMEDIATE EXPOSURE							
	5	6	7	8	9		10
3 → Systemic	↓	↓	↓	↓	↓		↓
18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
4 → 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



APPENDIX B

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APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
APHA	American Public Health Association
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	best available technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BMD	benchmark dose
BMR	benchmark response
BSC	Board of Scientific Counselors
C	centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor
DOT	Department of Transportation
DOT/UN/ NA/IMCO	Department of Transportation/United Nations/ North America/Intergovernmental Maritime Dangerous Goods Code

DWEL	drinking water exposure level
ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F_1	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
FR	Federal Register
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
ILO	International Labor Organization
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
MA	*trans,trans*-muconic acid
MAL	maximum allowable level
mCi	millicurie
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor

MFO	mixed function oxidase
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCEH	National Center for Environmental Health
NCI	National Cancer Institute
ND	not detected
NFPA	National Fire Protection Association
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OR	odds ratio
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OTS	Office of Toxic Substances
OW	Office of Water
OWRS	Office of Water Regulations and Standards, EPA
PAH	polycyclic aromatic hydrocarbon

PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
pg	picogram
PHS	Public Health Service
PID	photo ionization detector
pmol	picomole
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	pretreatment standards for new sources
RBC	red blood cell
REL	recommended exposure level/limit
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
RQ	reportable quantity
RTECS	Registry of Toxic Effects of Chemical Substances
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SIC	standard industrial classification
SIM	selected ion monitoring
SMCL	secondary maximum contaminant level
SMR	standardized mortality ratio
SNARL	suggested no adverse response level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short term exposure limit
STORET	Storage and Retrieval
TD_{50}	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	total organic carbon
TPQ	threshold planning quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result

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APPENDIX D. INDEX