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 a hundredfold 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, 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, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop E-29, Atlanta, Georgia 30333.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Selenium
CAS Number: 7782-49-2 (elemental)
Date: June 5, 2003
Profile Status: Post Public Comments, Draft 3
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Graph Key: 101
Species: Human

Minimal Risk Level: 0.005 [X] mg/kg/day [ ] ppm

Reference: Yang G, Zhou R. 1994. Further observations on the human maximum safe dietary selenium intake in a seleniferous area of China. J Trace Elem Electrolytes Health Dis 8:159-165.

Experimental design: This study was an examination of a group of five individuals who were recovering from selenosis, and who had been drawn from a larger population studied by the same authors (Yang et al. 1989a, 1989b). Yang et al. (1989a, 1989b) examined a population in an area of China where selenosis occurred. Data were collected on selenium levels in the diet, blood, nails, hair, urine, and milk of residents, and the incidence of clinical symptoms of selenosis (morphological changes in fingernails) was compared with dietary intake of selenium and selenium levels in blood. Selenium levels in blood corresponded to the dietary intake of selenium, and symptoms of selenosis occurred at or above a selenium intake level of 910 µg/day (0.016 mg/kg/day) (Yang et al 1989a). In 1992, Yang and Zhou (1994) reexamined five individuals from the high selenium site who had been suffering from symptoms of selenosis (loss of fingernails and hair), but were recovering (nails were regrowing). Since their earlier report, the living conditions of the population had improved; they had been cautioned against consuming high selenium foods and parts of their locally produced corn had been replaced with rice or cereals. Yang and Zhou (1994) found that the mean concentration of selenium in the blood of these selenosis patients had fallen from 1,346 µg/L (measured in 1986) to 968 µg/L (measured in 1992). Using a regression equation derived from the data in their earlier report (Yang et al. 1989b) and average body weights of 55 kg, Yang and Zhou (1994) calculated that the mean dietary intake of selenium associated with selenosis in these individuals was 1,270 µg/day (LOAEL of 0.023 mg/kg/day), while a mean intake of 819 µg selenium/day (NOAEL of 0.015 mg/kg/day) was associated with recovery.

Effects noted in study and corresponding doses: A NOAEL of 0.015 mg/kg/day for nail disease based on recovery from symptoms of selenosis, and a LOAEL of 0.023 mg/kg/day based on nail damage were calculated from selenium concentrations in blood using average body weights of 55 kg and the regression equation: Yblood-Se (mg/L) = 8230 x 10^{-4} Xse-intake (µg) + 0.176 derived in Yang et al. (1989b).

Dose and end point used for MRL derivation: 0.015 mg/kg/day; nail disease (selenosis)

[X] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

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

A factor of 3 was considered appropriate because the individuals in this report were sensitive individuals drawn from the larger population in the Yang et al. (1989a, 1989b) studies and because of the supporting studies described below.

Was a conversion used from ppm in food or water to a mg/body weight dose? No.
If so, explain:

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

Other additional studies or pertinent information which lend support to this MRL:

Yang et al. (1989a, 1989b) examined a population of 349 individuals in an area of China where selenosis occurred. They collected data on selenium levels in the diet, blood, nails, hair, urine, and milk of residents at three sites with low, medium, and high selenium, and compared the incidence of clinical symptoms of selenosis (morphological changes in finger nails) with dietary intake of selenium and selenium levels in blood. They found that selenium levels in blood corresponded to the dietary intake of selenium, and that symptoms of selenosis were found at or above a selenium intake level of 910 µg/day (0.016 mg/kg/day) (Yang et al 1989a). The population included adult men and women, teenagers, children, and infants. High selenium levels were found in individuals of all ages, but symptoms of selenosis were generally confined to adults (97% of cases) and were never observed in children younger than 12 years of age (Yang et al. 1989b). The manifestation of symptoms of selenosis was not solely dependent on selenium intake, but was subject to individual variability, as individuals who exhibited selenosis did not necessarily have the highest blood selenium levels.

Longnecker et al. (1991) examined two groups of adults (142 individuals) in areas of Wyoming and South Dakota with elevated selenium intake. The average daily intake of selenium in this population was 239 µg/day (0.003 mg/kg/day) and some individuals consumed as much as 724 µg/day (0.01 mg/kg/day). The highest blood concentration of selenium noted in this population was 0.67 mg/kg, a concentration lower than the 1.05 mg/L concentration associated with effects in China. No symptoms of selenosis or any other significant health effects associated with selenium exposure were reported for individuals in this study. This study suggests that the estimates of dietary intake of selenium produced by the regression equation in Yang et al. (1989b) may be conservative. Longnecker et al. (1991) reported doses of 68–724 µg/day associated with blood concentrations of 0.18–0.67 mg/kg. If the doses from the Longnecker et al. (1991) study are placed in the regression equation from Yang et al. (1989b), blood concentrations of 0.14 and 0.88 mg/L are calculated. If it is assumed that a liter of blood weighs approximately 1 kg, then this regression equation overpredicts blood levels of selenium at the higher doses in the population from North Dakota. This provides support for additional exposure (e.g., inhalation exposure) in the Chinese population that was not accounted for in the regression equation.

Selenium is a component of all three members of the deiodinase enzyme family, the enzymes responsible for deiodination of the thyroid hormones (St. Germain and Galton 1997). Two human studies were located that describe significant decreases in triiodothyronine levels in response to elevated selenium; however, the hormone levels observed in these studies were subclinical within the normal human range and the biological significance of the effect is not clear. In the first study, Brätter and Negretti De Brätter (1996) examined a Venezuelan population with high selenium intake. Serum, erythrocyte, toenail, and breast milk selenium concentrations were determined for 65 women living in three seleniferous regions of Venezuela. Selenium dietary intakes were determined from the selenium concentration of breast milk by regression (Bratter et al. 1991), and free thyroxine (T_4), free triiodothyronine (T_3), and human thyroid stimulating hormone (TSH) levels were measured. Selenium intake ranged from 170 to 980 µg/day. There was a significant inverse correlation between free T_3 and selenium levels in serum (Spearman R

test), but free T_3, free T_4, and TSH levels were found to be within normal ranges. No symptoms of selenosis were found in the women included in this study.

In the second human study, serum hormone, semen, immunological, and hematological status was evaluated in a 120-day double blind study of healthy men (20–45 years old) who consumed a controlled diet of foods naturally low or high in selenium (Hawkes and Turek 2001; Hawkes et al. 2001). Eleven subjects were fed a diet that provided 47 μg Se/day (0.0006 mg/kg/day) for the first 21 days of the study. For the following 99 days, six of the subjects were fed a diet providing 13 μg Se/day (0.0002 mg/kg/day), and five of the remaining subjects were fed a diet providing 297 μg/day (0.004 mg/kg/day). Comprehensive evaluations were performed at weeks 3 (baseline), 17 (ending value), and several interim time points on end points that included selenium levels (in blood plasma, erythrocytes, seminal plasma, and sperm); thyroid hormone levels (serum T_3 and TSH); reproductive hormone levels (serum testosterone, follicle-stimulating hormone, luteinizing hormone, prolactin, estradiol, and progesterone); semen quality (sperm concentration, semen volume, sperm total number, fraction motile sperm, percent progressive sperm, mean forward velocity, and various sperm morphology parameters); immunological indices (complete blood counts, lymphocyte phenotypes, serum immunoglobulins (IgA, IgG, IgM); complement fractions; peripheral blood mononuclear cell (PBMNC) *in vitro* proliferative responses to mitogenic stimulation with phytohemagglutinin (PHA), concanavalin A (ConA), and pokeweed; natural-killer cell (NKC) activity; delayed-type hypersensitivity (DHS) skin responses to recall antigens (tuberculin purified-protein derivative, mumps, tetanus toxoid, candida, trichophyton, streptokinase strepase, and coccidioidin); antibody responses to diptheria-tetanus and influenza vaccines); and hematological indices (complete blood counts, white blood cells, lymphocytes, granulocytes, platelets, erythrocytes, hematocrit, and hemoglobin concentration). For measurements repeated more than twice, the baseline value was subtracted from the value at each time point to calcuate within-subject changes, and two-way repeated measures analysis of variance was used to test for significant effects of dietary selenium and time. When the selenium main effect or the selenium x time interaction was significant, the Student-Newman-Keuls comparison test was used to identify significant differences between the low-selenium and high-selenium groups at individual time points. For measurements obtained only twice (during baseline and at end of study), within-subject changes were compared between groups with a two-tailed ttest. Measurements obtained only at the end of the study were compared between groups with a two-tailed t-test without any correction. A probability of ≤ 0.05 was considered significant in all tests.

Selenium levels in blood plasma began to change within 3 days of starting the low- and high-selenium diets and progressively continued throughout the study (Hawkes and Turek 2001). By week 17, mean plasma selenium concentrations had increased by 109% in the high-selenium group and decreased by 38.5% in the low-selenium group. Group mean serum T_3 concentrations (averages of within-subject changes from baseline) were significantly different in the low-selenium subjects and high-selenium subjects at all time points, but the magnitudes of the changes are insufficient to be considered biologically significant in either group. In the low-selenium group, serum T_3 levels increased an average of 14 and 8% from baseline during weeks 8 and 17, respectively. In the high-selenium group, serum T_3 levels decreased an average of 23 and 11% from baseline during weeks 8 and 17, respectively. Analysis of variance (ANOVA) indicated a significant effect of dietary selenium on serum T_3 concentrations and that the magnitude of the effect was modified by the duration of exposure (i.e., the group changes in T_3 levels decreased over time). Although the decreases in serum T_3 in the high selenium group and increases in serum T_3 in the low selenium group lessened in magnitude during the study, all group mean values appear to have remained within the normal range (only week 17 values were actually reported). The respective baseline and week 17 serum T_3 values (mean±SD) were 1.82±0.36 and 1.57±0.07 nmol/L in the high-selenium group and 1.57±0.25 and 1.64±0.16 nmol/L in the low-selenium group, compared to a normal human range of 1.1–2.7 nM/L for total T_3, indicating that the changes were subclinical and not biologically significant. Serum TSH concentrations increased significantly by 32% over its baseline concentration in the high-selenium group but did not change significantly in the low-selenium group.

Baseline and ending TSH values in the high-selenium group were 2.25±0.81 and 2.96±1.05 mU/L, respectively, both of which are in the normal range of 0.3–4.0 mU/L (Stockigt 2000). There were no significant changes in the serum levels, nor any significant differences between groups in free or total testosterone, follicle-stimulating hormone, luteinizing hormone, prolactin, estradiol, or progesterone.

The pattern of changes in seminal plasma selenium levels was similar to that observed for blood selenium, although selenium levels in sperm did not change significantly in either group (Hawkes and Turek 2001). Mean sperm motility (average of within-subject changes from baseline in fraction of motile sperm) was significantly different in the low-selenium subjects and high-selenium subjects at week 13, but not at weeks 8 or 17. The fraction of motile sperm increased an average of 10% in the low-selenium group at week 13, and was essentially the same as baseline at week 17. Sperm motility decreased an average of 32% in the high-selenium group at week 13, and ended 17% lower than the baseline value at week 17. The ANOVA indicated a significant effect of dietary selenium on sperm motility and that the effect of selenium was modified by duration of exposure (the groups diverged over time). Baseline and ending motile sperm fractions in the high-selenium group were 0.588±0.161 and 0.488±0.193, respectively; >50% motility is considered normal (FDA 1993). The decrease in sperm motility in the high-selenium group cannot be clearly attributed to exposure because the effect was not related to duration of treatment, and is unlikely to be adverse because the effect is at the low end of the normal range and not accompanied by any significant significant effects of high- or low-selenium treatment on sperm progression, concentration, total number, or morphology. Additionally, there were no effects of selenium on serum levels of the reproductive hormones, and changes in the thyroid hormones, which could also affect sperm function, were not outside normal ranges.

The immunological assessment showed that the high-selenium diet was not immunotoxic and had some mild and transient immune-enhancing properties (Hawkes et al. 2001). There is an indication that selenium supplementation increased the secondary immune response to diphtheria vaccine when rechallenged at the end of the study. The mean within-subject ratio of diphtheria antibody titers 14 days after reinoculation (day 116) to titers 14 days after the initial challenge at baseline (day 19) was significantly greater in the high-selenium group than in the low-selenium group (2.7±1.8-fold vs. 0.9±0.6-fold, p=0.03). Lymphocyte counts were significantly increased in the high-selenium group on day 45, but not at the end of the study, and there were no clear effects of selenium on numbers of activated or cytotoxic T-cells. The proliferative response of peripheral lymphocytes to stimulation with pokeweed mitogen (a B-cell mitogen) was significantly higher in the high-selenium group than in the low-selenium group on days 45 and 72, although not at the end of the study. There was no selenium-induced lymphocyte proliferation in response to the T-cell mitogens (phytohemagglutinin or concanavalin A) or changes in any of the other immunological end points. The hematological assessment (Hawkes et al. 2001) found minor mean within-subject changes from baseline in white blood cell counts that were significantly different in the low- and high-selenium groups at the last two time points (days 70 and 99); WBCs were decreased by 5% in the high-selenium group and increased by 10% in the low-selenium group at the end of the study. The changes in WBC counts were due mainly to changes in granulocytes. Lymphocyte counts were significantly increased in the high-selenium group on day 45, but not at the end of the study.

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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 they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, 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. If data are located in the scientific literature, a table of genotoxicity information is included.

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, we have derived minimal risk levels (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.

They 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 the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses for lifetime exposure (RfDs).

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 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 LSE Tables.

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables (3-1, 3-2, and 3-3) and figures (3-1 and 3-2) 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, minimal risk levels (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 No-Observed-Adverse-Effect Levels (NOAELs), Lowest-Observed-Adverse-Effect Levels (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 LSE Table 3-1

(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. When sufficient data exists, 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 Table 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 2 "18r" data points in 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 regimen 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 1,1,2,2-tetrachloroethane via inhalation for 6 hours per day, 5 days per week, for 3 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, 1 systemic effect (respiratory) was investigated.

(8) NOAEL A No-Observed-Adverse-Effect Level (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 Lowest-Observed-Adverse-Effect Level (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 Cancer Effect Level (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 the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Figure 3-1

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 intermediate and chronic 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 38r is 1 of 3 studies for which Cancer Effect Levels were derived. The diamond symbol refers to a Cancer Effect Level 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
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

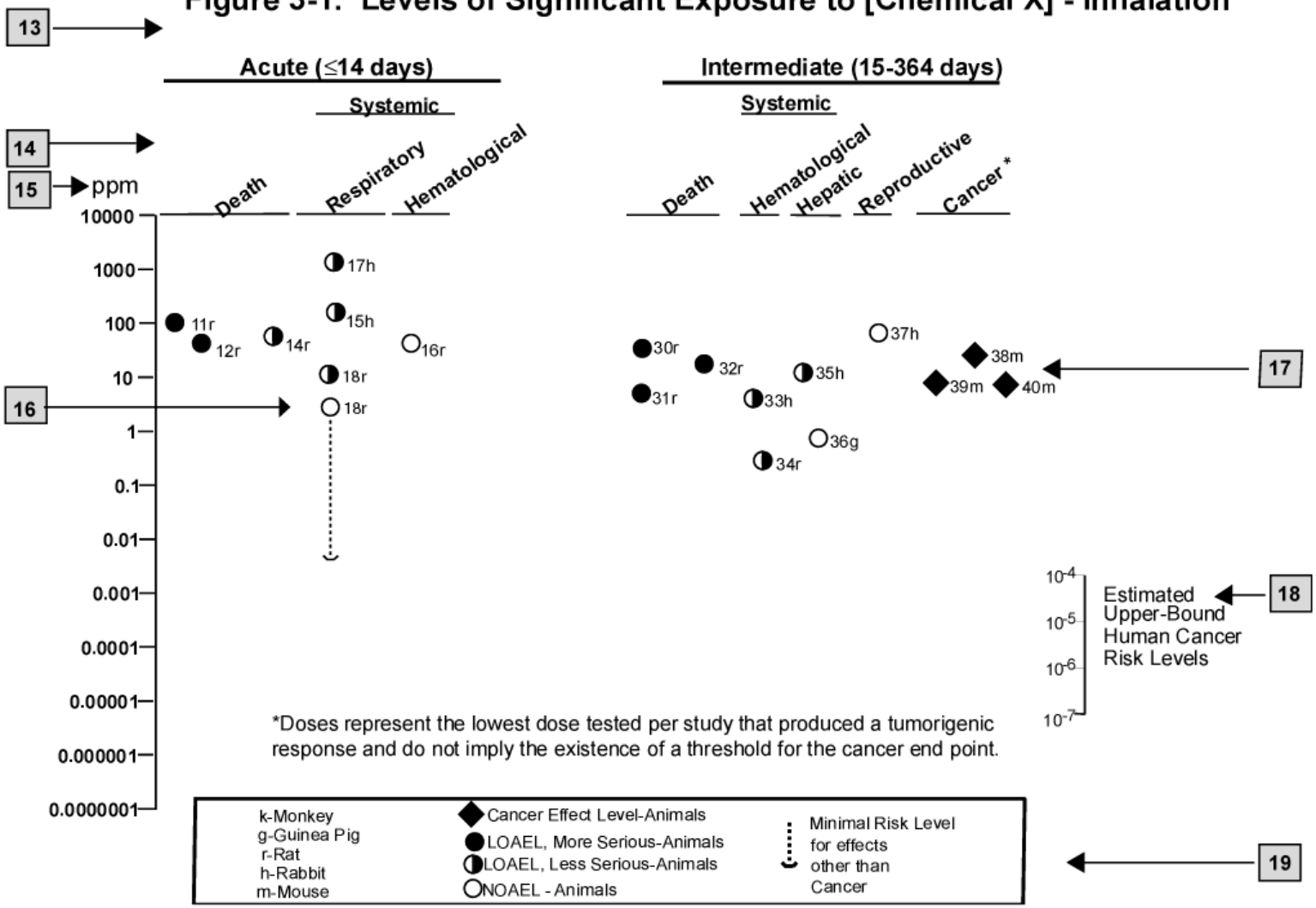
12 →

[a] The number corresponds to entries in Figure 3-1.

[b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5×10^{-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).

SAMPLE

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



APPENDIX B

APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACOEM	American College of Occupational and Environmental Medicine
ACGIH	American Conference of Governmental Industrial Hygienists
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
AOEC	Association of Occupational and Environmental Clinics
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANOVA	analysis of variance
AOAC	Association of Official Analytical Chemists
AP	alkaline phosphatase
APHA	American Public Health Association
AST	aspartate aminotranferase
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
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/International 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
GPX	glutathione peroxidase
GSH	glutathione
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
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{Lo}	lethal concentration, low
LC_{50}	lethal concentration, 50% kill
LD_{Lo}	lethal dose, low
LD_{50}	lethal dose, 50% kill
LDH	lactic dehydrogenase
LH	luteinizing hormone
LT_{50}	lethal time, 50% kill
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
MA	*trans,trans*-muconic acid
MAL	maximum allowable level
mCi	millicurie

MCL	maximum contaminant level
MCLG	maximum contaminant level goal
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
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
NHANES	National Health and Nutrition Examination Survey
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
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OR	odds ratio
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
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	pictogram
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
RDA	Recommended Daily Allowance
REL	recommended exposure level/limit
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
RR	relative risk
RTECS	Registry of Toxic Effects of Chemical Substances
RQ	reportable quantity
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
T_3	triiodothyronine
T_4	thyroxine
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
TSH	thyroid stimulating hormone
TWA	time-weighted average
UF	uncertainty factor
UL	Tolerable Upper Intake Level
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