APPENDIX A

ATSDR MINIMAL RISK LEVEL 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.

APPENDIX A

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 agencywide 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, Mailstop E-29, Atlanta, Georgia 30333.

APPENDIX A

MINIMAL RISK LEVEL WORKSHEET

Chemical name: DEHP
CAS number(s): 117-81-7
Date: June 2002
Profile status: Post Public Comment Final
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Key to figure: 131
Species: Mouse

MRL: 0.1 [X] mg/kg/day [ ] ppm [ ] mg/m^3

Reference: Lamb JC, Chapin RE, Teague J, et al. 1987. Reproductive effects of four phthalic acid esters in the mouse. Toxicol Appl Pharmacol 88:255-269.

Experimental design: This is a reproductive toxicity study in which CD-1 Swiss mice were exposed to DEHP in the diet at calculated doses of 0, 14, 140, and 420 mg/kg/day. A continuous breeding protocol was used in which 11-week-old mice were exposed during a 7-day premating period and subsequently as breeding pairs for 98 days. There were 20 breeding pairs in each exposed group and 40 pairs in the control group. The pairs were segregated at the end of the 98-day breeding period so that females could deliver the final litter. The F_0 mice were therefore exposed for a maximum possible duration of 105 days. Clinical signs, food consumption, and body weight were evaluated during the breeding phase. The females were allowed to deliver their pups for determinations of fertility and reproductive performance; indices included number of pairs producing a litter/total number of breeding pairs, number of litters/pair, number of live pups/litter, proportion of pups born alive, and live birth weights. Because an effect on fertility was observed, a crossover mating study was performed in which high dose mice of each sex were mated to unexposed mice of the opposite sex at the end of the breeding period to determine the affected sex. In addition to the fertility/reproductive indices examined in the continuous breeding phase, the high dose F_0 mice in the crossover study were evaluated for body weight, organ weights (liver, testis, epididymis, prostate, seminal vesicles, brain, pituitary, ovaries and oviduct, and/or uterus), and sperm indices (percent motile sperm, sperm concentration, and percent abnormal sperm).

Effects noted in study and corresponding doses: No effects were observed at 14 mg/kg/day. Fertility was reduced at 140 mg/kg/day as indicated by significantly ($p<0.01$) reduced number of litters/pair, number of live pups/litter, and proportion of live pups; mean live pup weight was also significantly reduced. Exposure to 420 mg/kg/day caused significant infertility during the continuous breeding part of the study (0/18 fertile pairs) as well as in both sexes (0/16 fertile females and 4/20 fertile males) during the crossover mating part of the study. Other effects observed at 420 mg/kg/day in the crossover study included significantly reduced testis, epididymis, and prostate weights, percentages of motile sperm and abnormal sperm, and reduced sperm concentration in the males; significantly reduced combined weight of ovaries, oviducts and uterus in the females; and significantly increased liver weights in both sexes. All but one of the high dose males had some degree of bilateral atrophy of the seminiferous tubules, but no exposure-related reproductive histopathology was observed in the females. Considering the reduced fertility and reproductive organ weights in the high dose females, there is evidence that reproductive performance was impaired in both sexes at 420 mg/kg/day. Because the crossover mating study was only

conducted at the high dose, the reduced fertility observed at 140 mg/kg/day is not necessarily due to effects in both sexes.

Dose and end point used for MRL derivation:

[X] NOAEL [ ] LOAEL

The lowest dose, 14 mg/kg/day, is a NOAEL for reproductive toxicity in the male and female mice.

Uncertainty factors used in MRL derivation:

[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?

Yes. The mice were exposed to DEHP dietary concentrations of 0, 0.01, 0.1, and 0.3% (0, 100, 1,000, and 3,000 mg DEHP/kg diet). Using a food factor of 0.14 kg food/kg bw/day based on reported average food consumption (5.1 g/day) and body weight (36 g) values, doses are estimated to be 0, 14, 140, and 420 mg/kg/day.

Was a conversion used from intermittent to continuous exposure? NA

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

Other additional studies or pertinent information that lend support to this MRL: Other studies have established that testicular toxicity is a critical effect of DEHP. It is well documented that oral exposure to DEHP in adult rats and mice causes decreased weights of the testes, prostate, seminal vesicles, and epididymis, atrophy and degeneration of the seminiferous tubules, and/or altered sperm measures and reduced fertility (David et al. 2000a; Dostal et al. 1988; Ganning et al. 1991; Gray and Butterworth 1980; Gray and Gangolli 1986; Kluwe et al. 1982a; Lamb et al. 1987; Oishi 1986, 1994; Parmar et al. 1987, 1995; Price et al. 1987; Sjoberg et al. 1986a, 1986b). The lowest reproductive effect levels in these studies are a NOAEL and LOAEL for testicular histopathology of 3.7 and 38 mg/kg/day, respectively, in rats exposed for 90 days (Poon et al. 1997), and 5.8 and 29 mg/kg/day, respectively, in rats exposed for 104 weeks (David et al. 2000a). Because the 14 mg/kg/day NOAEL in the critical study (Lamb et al. 1987) is higher than the NOAELs of 3.7 and 5.9 mg/kg/day (David et al. 2000a; Poon et al. 1997), and is based on an assessment of fertility rather than histological examination without evaluation of reproductive function, the 14 mg/kg/day NOAEL is the most appropriate basis for derivation of the intermediate duration MRL.

Other studies have shown that gestational and lactational exposure to DEHP adversely affected the morphological development of the reproductive system, as well as caused reduced fetal and neonatal testosterone levels and adult sexual behavioral changes, in male rat offspring (Arcadi et al. 1998; Gray et al. 1999, 2000; Moore et al. 2001; Parks et al. 2000). One of these studies (Arcadi et al. 1998) was used as the basis of a provisional intermediate-duration oral MRL in the previous draft of the DEHP toxicological profile (i.e., the Draft for Public Comment). In the Arcadi et al. (1998) study, severe testicular histopathological changes were observed at 21–56 days of age in male offspring of rats that were exposed to DEHP in the drinking water at reported estimated doses of 3.3 or 33 mg/kg/day throughout pregnancy and continuing during postnatal days 1–21. The 3.3 mg/kg/day dose was classified as a serious LOAEL and was used to derive an MRL of 0.01 mg/kg/day by using an uncertainty factor of

300 (10 for the use of a LOAEL, 10 for interspecies extrapolation, and 3 for human variability). A component factor of 3 was used for human variability because DEHP was administered during the most sensitive period during development. The MRL was provisional because it was derived from a serious LOAEL, which is not conventional ATSDR methodology. The Arcadi study is now judged to be inadequate for MRL derivation because the NTP-CERHR Expert Panel on DEHP (NTP 2000b) concluded that the effect levels are unreliable and are unsuitable for identifying a LOAEL. In particular, NTP (2000b) found that (1) the methods used to verify and characterize the administered doses were not clearly described or completely reported, and could not be resolved, and (2) the study authors did not reconcile their blood DEHP concentration data with other studies.

In the 1993 toxicological profile for DEHP, an MRL of 0.4 mg/kg/day was derived for intermediate oral exposure to DEHP based on a NOAEL of 44 mg/kg/day for fetal malformations from a developmental toxicity study in mice (Tyl et al. 1988). An uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability) was used in this derivation. The 44 mg/kg/day NOAEL for developmental toxicity is no longer a suitable basis for MRL derivation because the more recent Poon et al. (1997) study found testicular toxicity at a lower dose (38 mg/kg/day) in rats exposed to DEHP for 90 days (Poon et al. 1997).

Agency Contact (Chemical Manager): Stephanie Miles-Richardson, D.V.M., Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name: DEHP
CAS number(s): 117-81-7
Date: June 2002
Profile status: Post Public Comment Final
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Key to figure: 161
Species: Rat

MRL: 0.06 [X] mg/kg/day [ ] ppm [ ] mg/m^3

Reference: David RM, Moore MR, Finney DC, et al. 2000a. Chronic toxicity of di(2-ethylhexyl)phthalate in rats. Toxicol Sci 55:433-443.

Experimental design: Groups of F344 rats were fed a diet containing DEHP in concentrations of 0 ppm (80/sex), 100 ppm (50/sex), 500 ppm (55/sex), 2,500 ppm (65/sex) or 12,500 ppm (80/sex) for up to 104 weeks. Reported average daily doses based on food consumption were 0, 5.8, 29, 147, or 789 mg/kg/day in males and 0, 7.3, 36, 182, or 939 mg/kg/day in females. The animals were observed for clinical signs, moribundity, and mortality twice daily throughout the study. Body weights and food consumption were measured weekly for weeks 1–17 and every 4 weeks thereafter. Final body weight and organ weights (brain, lungs, spleen, kidneys, testes, and uterus) were measured at the end of the study. Comprehensive hematology, clinical chemistry, and urine analyses were performed on 10 rats/sex/dose during weeks 26, 52, 78, and 104. Ten rats/sex from the control and two highest dose groups were sacrificed at week 78 for a complete necropsy and histological examination of tissues from major tissues. Animals that died during the study were also examined microscopically. Surviving animals were sacrificed during week 105 and the control and high-dose groups were subjected to comprehensive histological examination of tissues listed in EPA test guidelines for combined chronic toxicity/oncogenicity studies. Target tissues and gross lesions from the other dose groups were additionally examined at the end of the study. Effects on carcinogenicity, hepatomegaly, and peroxisome proliferation were reported by David et al. (1999).

Effects noted in study and corresponding doses: No exposure-related effects were observed at 5.8 mg/kg/day in the males or 7.3 mg/kg/day in the females. Bilateral aspermatogenesis was significantly ($p \leq 0.05$) increased at $\geq$29 mg/kg/day. The incidences of bilateral aspermatogenesis were 37/64 (58%), 34/50 (64%), 43/55 (78%), 48/65 (74%), and 62/64 (97%) in the control to high-dose males. The increase in aspermatogenesis was dose-related and is consistent with a significant reduction in relative testes weight that occurred at 789 mg/kg/day (59% less than controls). The examinations at week 78 showed aspermatogenesis at 789, but not 147 mg/kg/day (no interim exams were performed in the lower dose groups), suggesting the possibility that the lesion was age- rather than treatment-related at 29 and 147 mg/kg/day. Also observed in the high dose in males was a significantly increased incidence of castration cells in the pituitary gland, which are promoted by reduced testosterone secretions from the testes. Castration cells are vacuolated basophilic cells in the anterior pituitary gland usually observed after castration. Hepatic effects included significantly increased absolute and relative liver weights accompanied by increased peroxisome proliferation in males at $\geq$147 mg/kg/day and females at $\geq$182 mg/kg/day, spongiosis hepatis in males at $\geq$147 mg/kg/day, and hepatocellular neoplasms in males at

≥147 mg/kg/day and females at 939 mg/kg/day. Renal effects included significantly increased absolute and relative kidney weights in males at ≥147 mg/kg/day and females at ≥182 mg/kg/day, a dose-related increased incidence and severity of mineralization of the renal papilla in males at ≥5.8 mg/kg/day, increased severity of normally occurring chronic progressive nephropathy in males at 789 mg/kg/day, and increased severity of normally occurring renal tubule pigmentation in males at 789 mg/kg/day and females at 939 mg/kg/day. The renal lesions were unlikely to be toxicologically significant because (1) they are age- and/or species-related, (2) the increased mineralization in the kidneys was probably related to male rat-specific alpha2μ-globulin and hyaline droplet formation, and (3) the increased kidney weights may reflect peroxisome proliferation. Mean body weight gain was significantly lower than controls throughout the study in the males at 789 mg/kg/day and females at 939 mg/kg/day (15.0 and 15.5% lower, respectively, at the end of the study).

Dose and end point used for MRL derivation:

[X] NOAEL [ ] LOAEL

The lowest dose, 5.8 mg/kg/day, is a NOAEL for testicular toxicity in the male rats.

Uncertainty factors used in MRL derivation:

[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.

Was a conversion used from intermittent to continuous exposure? NA.

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

Other additional studies or pertinent information that lend support to this MRL: Other studies have established that testicular toxicity is a critical effect of DEHP. It is well documented that oral exposure to DEHP in adult rats and mice caused decreased weights of the testes, prostate, seminal vesicles, and epididymis, atrophy and degeneration of the seminiferous tubules, and/or altered sperm measures and reduced fertility (Dostal et al. 1988; Ganning et al. 1991; Gray and Butterworth 1980; Gray and Gangolli 1986; Kluwe et al. 1982a; Lamb et al. 1987; Oishi 1986, 1994; Parmar et al. 1987, 1995; Price et al. 1987; Sjoberg et al. 1986a, 1986b). Additionally, gestational and lactational exposure to DEHP adversely affected the morphological development of the reproductive system, as well as caused reduced fetal and neonatal testosterone levels and adult sexual behavioral changes, in male rat offspring (Arcadi et al. 1998; Gray et al. 1999, 2000; Moore et al. 2001; Parks et al. 2000). The 5.8 mg/kg/day NOAEL and 29 mg/kg/day LOAEL for testicular histopathology in the chronic MRL study (David et al. 2000a) are similar to the testicular NOAEL and LOAEL values of 3.7 and 38 mg/kg/day, respectively, in rats exposed for 90 days (Poon et al. 1997), but are somewhat lower than the NOAEL and LOAEL of 14 and 130 mg/kg/day, respectively, for reduced fertility in mice exposed for up to 105 days in the intermediate-duration MRL study (Lamb et al. 1987).

Agency Contact (Chemical Manager): Stephanie Miles-Richardson, D.V.M., Ph.D

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, epigenetic, 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, 18r NOAEL is the critical end point for which an intermediate inhalation exposure MRL is based. As you can see from the LSE figure key, the open-circle symbol indicates to a NOAEL for the test species-rat. 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 6

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

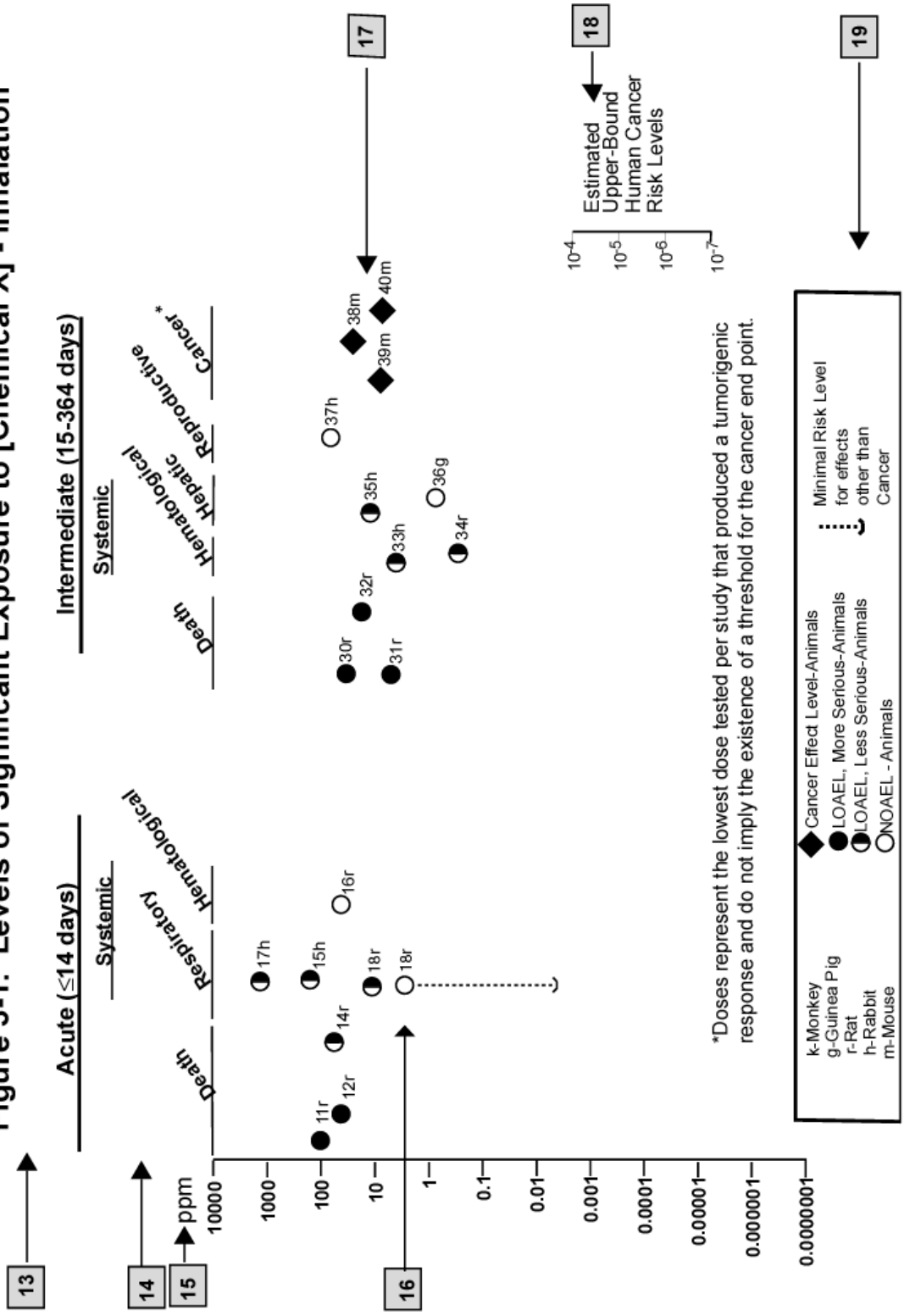
Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
2 6 INTERMEDIATE EXPOSURE							
	5	6	7	8	9		10
3 6 Systemic	9	9	9	9	9		9
4 6 18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
CHRONIC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

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

12 6 [b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5 x 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 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
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
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
PID	photo ionization detector
pg	picogram
pmol	picomole
PHS	Public Health Service
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
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
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

APPENDIX D

INDEX

APPENDIX D