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, Mailstop E-29, Atlanta, Georgia 30333.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Pentachlorophenol
CAS Number: 87-86-5
Date: June 22, 2001
Profile Status: Final
Route: [ ] Inhalation [X] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Key to Figure: 14
Species: Rats

Minimal Risk Level: 0.005 [X] mg/kg/day [ ] mg/m^3

Reference: Schwetz BA, Keeler PA, Gehring PJ. 1974. The effect of purified and commercial grade pentachlorophenol on rat embryonal and fetal development. Toxicol Appl Pharmacol 28:151-161.

Experimental design (human study details or strain, number of animals per exposure/control groups, sex, dose administration details): Purified (98%+) and commercial-grade (88.4%) pentachlorophenol were administered by gavage in corn oil to groups of 20–40 pregnant Sprague-Dawley rats on days 6–15 of gestation at doses of 0 (corn oil control), 5, 15, 30, and 50 mg/kg/day. At the 5 and 30 mg/kg/day dose levels, the actual amount of pentachlorophenol administered was 5.8 and 34.7 mg/kg/day, which was equivalent to 5 and 30 mg/kg/day pure pentachlorophenol.

Effects noted in study and corresponding concentrations: Maternal body weight gain was significantly decreased at 30 and 50 mg/kg/day with both pure and commercial-grade pentachlorophenol. Otherwise, no signs of maternal toxicity were noted. Significant increases in incidences of resorptions were seen at 15, 30, and 50 mg/kg/day commercial-grade pentachlorophenol and at 30 and 50 mg/kg/day with the pure pentachlorophenol. There was 100% resorption of implantations at the 50 mg/kg/day pure pentachlorophenol dose level. The sex ratio was significantly altered at 30 mg/kg/day pure pentachlorophenol and 50 mg/kg/day of the commercial-grade pentachlorophenol, with the majority of the survivors being male offspring.

Significant decreases in fetal body weight were observed at 30 and 50 mg/kg/day of commercial-grade pentachlorophenol and significant decreases in fetal body weight and crown-rump length were seen with 30 mg/kg/day of pure pentachlorophenol. Fetal malformations and/or variations were observed at 15 mg/kg/day and higher for the commercial-grade pentachlorophenol and 5 mg/kg/day and higher for the pure pentachlorophenol. The observed effects for the commercial-grade groups included subcutaneous edema and lumbar spurs at $15 mg/kg/day, rib, sternebrae, and vertebrae anomalies at $30 mg/kg/day. In the pure pentachlorophenol offspring, the incidence of delayed ossification of the skull was significantly increased at $5 mg/kg/day, and significant increases in the occurrence of subcutaneous edema, lumbar spurs, and skeletal anomalies in the ribs, sternebrae, and vertebrae were observed at $15 mg/kg/day.

Concentration and end point used for MRL derivation: This MRL is based on a LOAEL of 5 mg/kg/day for delayed ossification of the skull in rat pups when the dams were given pure pentachlorophenol by corn oil gavage on gestation days 6 through 15.

[ ] NOAEL [X] LOAEL

Uncertainty Factors used in MRL derivation:

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

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

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

Was a conversion used from intermittent to continuous exposure? NA

Other additional studies or pertinent information that lend support to this MRL: Similar developmental effects have been observed in another developmental toxicity study (Argus 1993b/Bernard et al. 2001b). In this study, significant increases in the occurrence of resorptions, soft tissue and skeletal malformations and variations and decreases in fetal body weight were observed in the offspring of rats were administered by gavage 80 mg/kg/day technical grade (89% pure) pentachlorophenol on gestational days 6–15. This study identified a NOAEL of 30 mg/kg/day. Intermediate-duration oral developmental toxicity studies in rats have also reported increased fetal/neonatal mortality, malformations, and/or variations, and decreased growth (Argus 1997/Bernard et al. 2001c; Courtney et al. 1976; Exon and Koller 1982; Schwetz et al. 1978; Welsh et al. 1987).

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APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Pentachlorophenol
CAS Number: 87-86-5
Date: June 22, 2001
Profile Status: Final
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Key to Figure: 47
Species: Mink

Minimal Risk Level: 0.001 [X] mg/kg/day [ ] mg/m^3

Reference: Beard AP, McRae AC, Rawlings NC. 1997. Reproductive efficiency in mink (*Mustela vison*) treated with the pesticides lindane, carbofuran, and pentachlorophenol. J Reprod Fertil 111:21-28.

Experimental design (human study details or strain, number of animals per exposure/control groups, sex, dose administration details): Groups of 10 female mink were exposed to 1 mg/kg/day pentachlorophenol in the diet for 3 weeks prior to mating with unexposed males and throughout pregnancy and lactation. The females were mated twice at 7–8 day intervals. The purity of the pentachlorophenol was not reported.

Effects noted in study and corresponding concentrations: A decrease in the proportion of mated females accepting a second mating and the proportion of mink that whelped were observed. No effect on the proportion of mink accepting the first mating or the proportion of mink with visible implantation sites were found. An increase in the severity cystic uterine glands was also observed in the pentachlorophenol-exposed mink.

Concentration and end point used for MRL derivation: This MRL is based on a LOAEL of 1 mg/kg/day for reproductive effects in mink exposed to pentachlorophenol (purity not reported) in the diet.

[ ] NOAEL [X] LOAEL

Uncertainty Factors used in MRL derivation:

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

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Dose was calculated by the study authors.

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

Was a conversion used from intermittent to continuous exposure? NA

Other additional studies or pertinent information that lend support to this MRL: Several other studies have examined the reproductive toxicity of pentachlorophenol. Decreased fertility has been observed in

the first generation of rats exposed to 60 mg/kg/day, but not in the parental or second generations; the NOAEL for this effect is 30 mg/kg/day (Argus 1997/Bernard et al. 2001c). A significant decrease in testicular spermatid count, decreases in absolute testes weight and the ratio of testes weight to brain weight, and focal/multifocal mononuclear cell infiltrate in the epididymis were observed in the F1 rats administered 30 or 60 mg/kg/day. However, no alterations in the average number of motile or nonmotile sperm, epididymal or testicular sperm counts, or sperm morphology were observed in either generation (Argus 1997/Bernard et al. 2001c). No alterations in reproductive tissues were observed in the female rats. Significant increases in the average day of preputial separation and vaginal patency were observed in the F1 generation, suggesting that *in utero* exposure to pentachlorophenol disrupted the normal development of the reproductive system. No adverse reproductive effects were observed in another mink study in which the animals were also fed a diet containing 1 mg/kg/day pentachlorophenol (purity not reported) (Beard and Rawlings 1998). Additionally, no significant alterations in mating response, ovulation rate, follicle and corpus luteum size, gestation length, pregnancy rate, lambing rate, and lamb birth rate were observed in sheep exposed to 1 mg/kg/day pentachlorophenol in the diet for 5 weeks premating and throughout the gestation and lactation periods (Beard et al. 1999b). No effect on fertility was observed in the offspring of these sheep, later mated to unexposed males (Beard and Rawlings 1999).

Several reproductive toxicity and nonreproductive toxicity studies have reported histological alterations in reproductive tissues. The observed effects include focal degeneration of the seminiferous tubules and decreased sperm density in the epididymis body (but not in caput or cauda epididymis) in sheep exposed to 1 mg/kg/day pentachlorophenol (purity not reported) in the diet during gestation, lactation, and for 20 weeks postnatally (Beard et al. 1999a), minimal to marked germinal epithelial degeneration and lack of spermatozoa in the seminiferous tubules of rats exposed to 270 mg/kg/day pure pentachlorophenol in the diet for 28 days (effects may have been secondary to poor condition of animals) (Chhabra et al. 1999; NTP 1999), increased severity of oviductal intraepithelial cysts in sheep administered 2 mg/kg/day pure pentachlorophenol by gavage twice weekly for 43 days (Rawlings et al. 1998), and lymphocyte infiltration into the endometrium in sheep exposed to 1 mg/kg/day pentachlorophenol (purity not reported) in the diet for 5 weeks premating and during the gestation and lactation periods (Beard et al. 1999b). No histological alterations in reproductive tissues were observed in male or female rats chronically exposed to 30 mg/kg/day pure pentachlorophenol in the diet for 2 years (Chhabra et al. 1999; NTP 1999). Additionally, no alterations in reproductive hormones (estradiol, testosterone, progesterone, follicle stimulating hormone, and/or luteinizing hormone levels) have been observed in mink (Beard et al. 1997) or sheep (Beard et al. 1999a).

Liver and developmental effects also appear to be sensitive end points of pentachlorophenol following intermediate-duration oral exposure; the lowest adverse effect levels for these effects are 10-fold higher than the reproductive effects reported in mink. Significant increases in relative liver weight and the occurrence of centrilobular hepatocellular hypertrophy have been reported in rats and mice exposed to <10 mg/kg/day pure or technical-grade pentachlorophenol (Blakley et al. 1998; Kerkvliet et al. 1982; Kimbrough and Linder 1978; Knudsen et al. 1974). At higher doses, hepatocyte degeneration and necrosis have been observed (Kerkvliet et al. 1982; NTP 1989, 1999). Developmental effects (decreased pup body weight) have also been observed in rat offspring at 10–15 mg/kg/day (Argus 1997/Bernard et al. 2001c; Welsh et al. 1987).

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MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Pentachlorophenol
CAS Number: 87-86-5
Date: June 22, 2001
Profile Status: Final
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Key to Figure: 54
Species: Mink

Minimal Risk Level: 0.001 [X] mg/kg/day [ ] mg/m^3

Reference: Beard AP, Rawlings NC. 1998. Reproductive effects in mink (*mustela vison*) exposed to the pesticides lindane, carbofuran and pentachlorophenol in a multigeneration study. J Reprod Fertil 113:95-104.

Experimental design (human study details or strain, number of animals per exposure/control groups, sex, dose administration details): Pentachlorophenol (Sigma, St. Louis, Missouri; purity not indicated) was administered at a dose of 1 mg/kg/day in the diet to parental-generation female mink from 3 weeks prior to mating (with untreated males) until weaning of first-generation offspring. Male and female offspring in the first and second generations were continued on the pentachlorophenol diet effectively from conception until sexual maturity. As with the parental generation, females of the first generation were mated with untreated males. The number of control and treated females in the parental generation was not indicated. Ten control and 8 pentachlorophenol-treated females of the first generation, continued on the pentachlorophenol diet throughout growth, mating, pregnancy, lactation, and for 3 months after the end of lactation, were mated to produce the second generation. Ten control and 6 pentachlorophenol males of the first generation were killed when their testis development was maximal at about 42 weeks of age. The study group in the second generation consisted of 8 males and 10 females given control diet and 8 males and 10 females continued on the pentachlorophenol diet. At necropsy of the first-generation males, weights of the testes, epididymides, and penis were recorded, and these organs and samples of the pancreas, liver, and pituitary gland were fixed for microscopic examination; dimensions of the testes and penis were also recorded. At necropsy of the first-generation females, weights of the ovaries, oviduct, uterus, pituitary, thyroid, parathyroid, and adrenals were recorded, and samples of these and the pancreas were fixed for microscopic examination. Weights of the heart, brain, liver, and kidney were also recorded. In the second-generation animals, the same tissues were weighed and measured, but no tissues were examined histologically in the females and only endocrine and reproductive tissues were examined histologically in the males. Serum from blood samples collected at necropsy of first and second generation males and females was analyzed for estradiol and thyroxine. Serum cortisol was also measured in first-generation females and serum testosterone was measured in first- and second-generation males.

Effects noted in study and corresponding concentrations: No overt signs of toxicity were seen and no reproductive effect end points were altered in the pentachlorophenol-treated groups compared with controls. The only effects noted in the pentachlorophenol-treated groups were significantly-decreased serum thyroxine concentrations in males of the first generation and in males and females of the second generation, and significantly-decreased relative thyroid weight in females of the second generation.

Concentration and end point used for MRL derivation: This MRL is based on a LOAEL of 1 mg/kg/day (only dose tested) for significantly-decreased serum thyroxine concentrations in males of the first generation and males and females of the second generation and decreased relative thyroid weight in females of the second generation when mink were administered pentachlorophenol of unspecified purity continuously in the diet in a multigeneration reproduction study.

[ ] NOAEL [X] LOAEL

Uncertainty Factors used in MRL derivation:

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

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No. The dose of 1 mg/kg/day was estimated by the study authors. Details of the method of dose estimation were not provided.

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

Was a conversion used from intermittent to continuous exposure? NA

Other additional studies or pertinent information that lend support to this MRL: Single intraperitoneal injections of pentachlorophenol of unspecified purity at doses up to 28 mg/kg caused marked, statistically significant, dose-related decreases in the serum total thyroxine level in male rats (van Raaij et al. 1991a). The decreases were maximal at 6–24 hours after administration, and thyroxine levels slowly returned to control values within 96 hours after administration. Further in vitro studies by these investigators revealed that the likely mechanism of action for this anti-thyroid effect was competition for serum protein thyroxine binding sites (van Raaij et al. 1991b). A decrease in maternal serum thyroxine (T4) concentration throughout pregnancy and lactation and a significant increase in maternal thyroid gland follicle size were found in female sheep administered 1 mg/kg/day pentachlorophenol (purity not indicated) in the diet 5 weeks prior to mating and throughout pregnancy and lactation until 2 weeks after weaning of the lambs (Beard et al. 1999b). Additionally, increased thyroxine levels were observed in their ewe and ram lambs that also received postnatal exposure to pentachlorophenol (Beard and Rawling 1999; Beard et al. 1999a). Oral gavage administration of pure pentachlorophenol to young adult female rats over a 28-day period at doses of 3 or 30 mg/kg produced decreases in circulating and free concentrations of the thyroid hormones triiodothyronine (T3) and T4 in serum, a decrease in serum thyroid stimulating hormone, decreases in intrathyroidal levels of T3 and T4, a decrease in the T4:T3 ratio in serum, and a reduction in thyroidal hormone stores. Technical-grade pentachlorophenol, tested only at a dose of 3 mg/kg, produced the same effects except the reduction in free T3 in serum (data for free serum T4 were not reported) (Jekat et al. 1994). Single intraperitoneal injections of pentachlorophenol of unspecified purity into adult male rats at doses of 7, 14, or 28 mg/kg also caused marked, statistically significant, dose-related decreases in the uptake of radiolabeled T4 into cerebrospinal fluid compared with control (van Raaij et al. 1994).

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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, 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

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

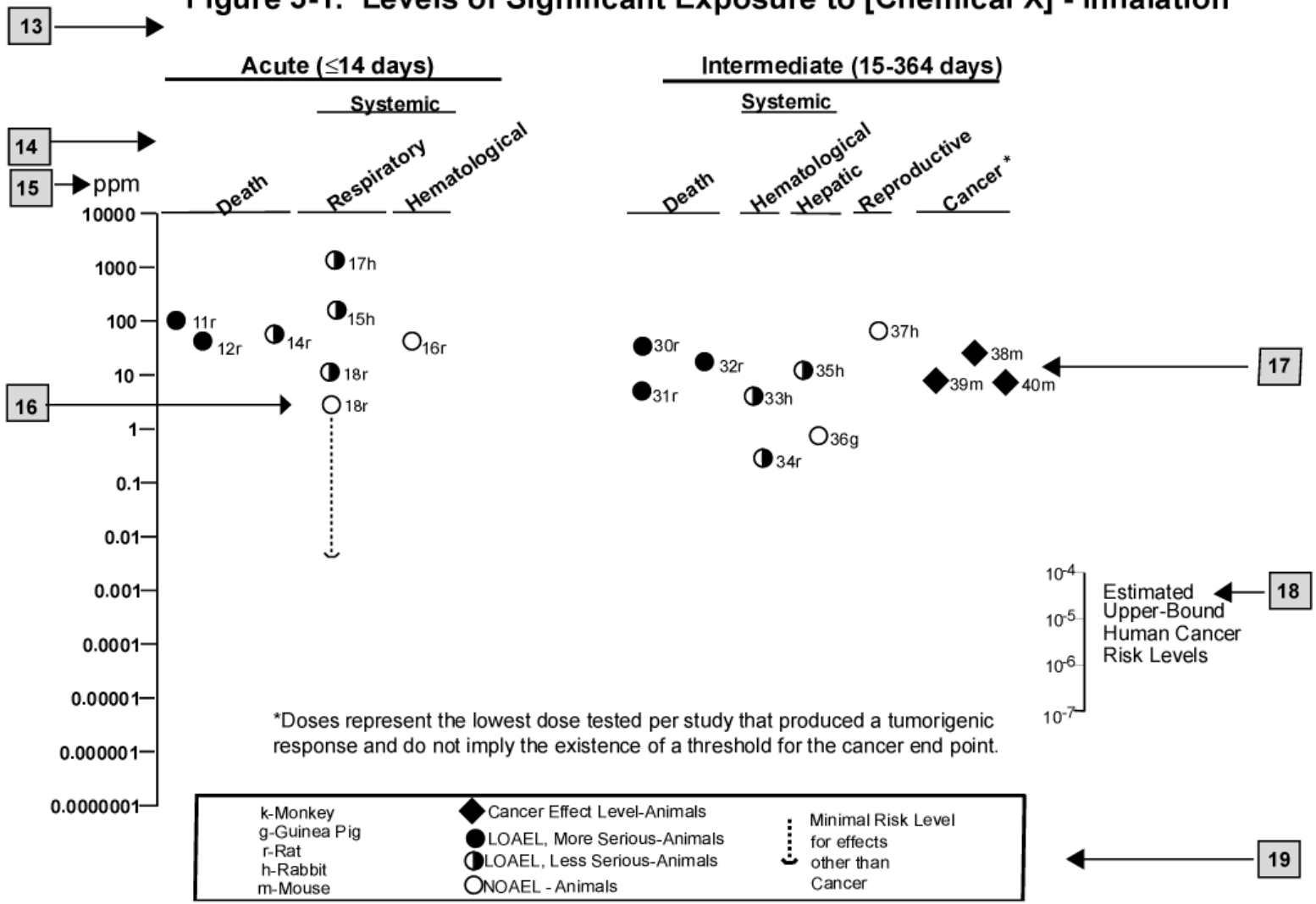
Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
INTERMEDIATE EXPOSURE							
	5	6	7	8	9		10
3	Systemic	9	9	9	9	9	9
4	18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3[b]	10 (hyperplasia)	Nitschke et al. 1981
CHRONIC EXPOSURE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

[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

ACGIH	American Conference of Governmental Industrial Hygienists
ADI	Acceptable Daily Intake
ADME	Absorption, Distribution, Metabolism, and Excretion
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
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
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CNS	central nervous system
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
d	day
Derm	dermal
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
ft	foot
FR	*Federal Register*
g	gram
GC	gas chromatography
Gd	gestational day
gen	generation
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
hr	hour
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IDLH	Immediately Dangerous to Life and Health
IARC	International Agency for Research on Cancer
ILO	International Labor Organization
in	inch
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_{Lo}	lethal concentration, low
LC_{50}	lethal concentration, 50% kill
LD_{Lo}	lethal dose, low
LD_{50}	lethal dose, 50% kill
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
mg	milligram
min	minute
mL	milliliter

mm	millimeter
mm Hg	millimeters of mercury
mmol	millimole
mo	month
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
NCI	National Cancer Institute
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NFPA	National Fire Protection Association
ng	nanogram
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
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
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
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
sec	second
SIC	Standard Industrial Classification
SIM	selected ion monitoring
SMCL	Secondary Maximum Contaminant Level
SMR	standard 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 Compound
TPQ	Threshold Planning Quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TRI	Toxics Release Inventory
TWA	time-weighted average
U.S.	United States
UF	uncertainty factor
VOC	Volatile Organic Compound
yr	year
WHO	World Health Organization
wk	week

>	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

APPENDIX D