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.

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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 (MRL) WORKSHEETS

Chemical name: 1,2-Dichloroethane
CAS number(s): 107-06-2
Date: May 11, 2001
Profile status: Draft 3
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Key to figure: 48
Species: Rat

MRL: 0.6 [ ] mg/kg/day [X] ppm [ ] mg/m^3

Reference: Cheever KL, Cholakis JM, el-Hawari AM, et al. 1990. Ethylene dichloride: The influence of disulfiram or ethanol on oncogenicity, metabolism, and DNA covalent binding in rats. Fundam Appl Toxicol 14: 243-261.

Experimental design: Groups of 50 male and 50 female Sprague-Dawley rats were exposed to 50 ppm 1,2-dichloroethane for 7 hours/day, 5 days/week for 2 years. Additional rats were similarly exposed to 50 ppm with either 0.05% disulfiram in the diet or 5% ethanol in the drinking water. Signs of toxicity, body weight and food consumption were evaluated during the study, and comprehensive gross and histological examinations were performed at the end of the exposure period.

Effects noted in study and corresponding doses: The only effect associated with exposure to 1,2-dichloroethane alone was a slight increase in the incidence of unspecified basophilic focal cellular changes in the pancreas in female rats. The significance of the pancreatic changes is unclear because the incidence was not reported, dose-response cannot be assessed because only one exposure level was tested, the effect was induced in only one sex, and the study was designed to evaluate carcinogenicity.

Effects due to combined exposure to 1,2-dichloroethane and disulfuram included increased kidney lesions (chronic nephropathy, calculi of the renal pelvis, and hyperplasia of the pelvic epithelium) in males, increased liver lesions (mostly bile duct cysts) in both sexes, and increased tumor incidences in both sexes (intrahepatic bile duct cholangiomas in males and females, mammary neoplasms in females, testicular interstitial cell tumors in males). No significant increases in tumor incidences were found after exposure to either 1,2-dichloroethane alone or in combination with ethanol. Congestion of the mesenteric lymph node was reported in both disulfuram-only and disulfuram/1,2-dichloroethane combined treatment groups to a similar extent and appears to be related to disulfuram exposure. Disulfuram, a known inhibitor of the microsomal aldehyde dehyderogenase system, apparently produced an overall decrease in the rate of biotransformation, leading to increased blood levels of 1,2-dichloroethane which may have contributed to the carcinogenic effect of combined exposure.

Dose and end point used for MRL derivation:

The 50 ppm exposure concentration is a NOAEL for histopathology in the liver and other tissues.

[X] NOAEL [ ] LOAEL

Uncertainty factors used in MRL derivation:

[X] 3 for interspecies extrapolation since a dosimetric adjustment was applied to the exposure concentration
[X] 10 for human variability
[X] 3 used as a modifying factor to account for database deficiencies

Was a conversion factor used from ppm in food or water to a mg/body weight dose?

Not applicable.

Was a conversion used from intermittent to continuous exposure?

No conversion from intermittent to continuous exposure was used since blood levels of 1,2-dichloroethane reach equilibrium within 2 to 3 hours of the onset of inhalation exposure (see Section 2.3.1.1).

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

The human equivalent concentration ($NOAEL_{[HEC]}$) was determined following U.S. EPA (1994; *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry*), Section 4.3.6.2 (Remote (Extrarespiratory) Effects) for exposure to Category 3 gases. The equation used for obtaining the $NOAEL_{[HEC]}$ from the NOAEL (50 ppm) is as follows:

$$NOAEL_{[HEC]} = NOAEL_{[ADJ]} \times [(H_{b/g})_A/(H_{b/g})_H)]$$

where,

$NOAEL_{[HEC]}$	= human equivalent NOAEL (ppm)
$NOAEL_{[ADJ]}$	= exposure-adjusted NOAEL (ppm) [no adjustment was used]
$(H_{b/g})_A$ and $(H_{b/g})_H$	= blood/gas partition coefficient for animals (A) and humans (H) (unitless)

The following default value was used:

$(H_{b/g})_A / (H_{b/g})_H = 1$ (unitless).

Empirical blood/gas partition coefficients were available for rats and humans (Gargas et al. 1989). However, the default value of 1 was used for both rat and human blood/gas partition coefficients, since $(H_{b/g})_A > (H_{b/g})_H$ (U.S. EPA 1994).

The $NOAEL_{[HEC]}$ was calculated as follows:

$NOAEL_{[HEC]} = 50$ ppm x (1) = 50 ppm

Application of an uncertainty factor of 90 (3 for interspecies extrapolation, 10 for human variability, and 3 for database deficiencies) results in a chronic duration inhalation MRL of 0.6 ppm.

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

The MRL is based on a free-standing NOAEL for liver histopathology. Although other concentrations of 1,2-dichloroethane were not tested, there is confidence in the NOAEL due to the number of animals (50/sex) and scope of histological examinations. Additionally, the liver is a documented target of 1,2-dichloroethane toxicity in several acute and intermediate-duration inhalation studies (Heppel et al. 1946; Spencer et al. 1951), as well as in a number of studies of orally-exposed animals. Limitations in the acute and intermediate inhalation studies preclude considering them as the basis for derivation of an MRL for intermediate-duration inhalation exposure, but the weight-of-evidence indicates that NOAELs for hepatotoxicity in the intermediate-duration studies are higher than the chronic liver NOAEL. Consequently, the chronic-duration inhalation MRL of 0.6 ppm is also expected to be protective of toxic effects after intermediate duration inhalation exposures to 1,2-dichloroethane.

Agency Contact (Chemical Manager): Malcolm Williams

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MINIMAL RISK LEVEL (MRL) WORKSHEETS

Chemical name: 1,2-Dichloroethane
CAS number(s): 107-06-2
Date: May 11, 2001
Profile status: Draft 3
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Key to figure: 25
Species: Rat

MRL: 0.2 [X] mg/kg/day [ ] ppm [ ] mg/m^3

Reference: NTP. 1991a. Toxicity studies of 1,2-dichloroethane (ethylene dichloride) (CAS No. 107-06-2) in F344/N rats, Sprague Dawley rats, Osborne-Mendel rats and B6C3F1 mice (drinking water and gavage studies). Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service, National Institute of Health, National Toxicology Program. NIH Publication No. 91-3123.

Experimental design: Groups of F344/N rats, Sprague-Dawley rats, Osborne-Mendel rats, and B6C3F1 mice (10 animals/sex/strain) were exposed to drinking water containing 0, 500, 1,000, 2,000, 4,000, or 8,000 ppm of 1,2-dichloroethane for 13 weeks. The high concentration was close to the solubility limit for 1,2-dichloroethane in water. Reported estimates of intake from the water were 0, 49-60, 86-99, 146-165, 259-276, and 492-518 mg/kg/day in the male rats and 0, 58-82, 102-126, 172-213, 311-428, and 531-727 mg/kg/day in the female rats. Intake estimates in the mice were 0, 249, 448, 781, 2,710, and 4,207 mg/kg/day in males and 0, 244, 647, 1,182, 2,478, and 4,926 mg/kg/day in females. Additional groups of F344/N rats (10/sex) were administered 1,2-dichloroethane by gavage on 5 days/week for 13 weeks to compare toxicity resulting from bolus administration with that of the continuous exposure in drinking water. Gavage doses were 0, 30, 60, 120, 240, and 480 mg/kg in the male rats and 0, 18, 37, 75, 150, and 300 mg/kg in the female rats. Signs of toxicity, body weight, food and water consumption, hematology, and serum chemistry were evaluated throughout the study, and comprehensive gross and histological examinations were performed at the end of the exposure period.

Effects noted in study and corresponding doses: Rat drinking water studies: Dose-related decreased water consumption occurred in all strains and both sexes. There was >10% reduction in body weight gain at $259 mg/kg in male F344/N rats, 518 mg/kg in male Sprague-Dawley rats, and 492 mg/kg in male Osborne-Mendel rats. There were no significant reductions in body weight gain in female rats of any strain. Liver weight and/or liver:body weight ratio significantly increased at $147 mg/kg in F344/N males and 102, 320, and 601 mg/kg in females; at $60 mg/kg in Sprague-Dawley males and 531 mg/kg in females; and at $88 mg/kg in Osborne-Mendel males. Kidney weight and/or kidney:body weight ratio significantly increased at $58 and $86 mg/kg in F344/N females and males, respectively; at $60 and $76 mg/kg in Sprague-Dawley males and females, respectively; and at $82 and $88 mg/kg in Osborne-Mendel females and males, respectively. There was a dose-related increase in the incidence of renal tubular regeneration (minimal to mild) in F344/N females at $58 mg/kg/day; incidences progressively increased from 1/10 at 102 mg/kg/day to 9/10 at 601 mg/kg/day.

Mouse drinking water study: No mortality except in 90% of high-dose females. Body weight gain significantly reduced in high-dose males. Increased liver weight/liver:body weight ratio, significant at $249 mg/kg/day in males and $647 mg/kg/day in females. Increased kidney weight and kidney:body weight ratio, significant at $448 mg/kg/day in males and $244 mg/kg/day in females. Increased tubular

regeneration (minimal to moderate) in males, increasing in incidence from 1/10 at 249 mg/kg/day to 9/10 at $4,207 mg/kg/day. Karyomegaly, dilatation, protein casts, and mineralization in kidneys also occurred in males at 4,207 mg/kg/day.

Rat gavage study: Deaths occurred in all males at $240 mg/kg and 90% of females at 300 mg/kg; clinical signs preceding death included tremors, salivation, and emaciation. Pathology in moribund/dead animals included necrosis in the thymus and cerebellum. Small but significant changes in various hematological parameters occurred in higher dose groups and were considered to be indicative of dehydration and attributed to significantly reduced in water consumption (60% compared to controls). No effects on growth at sublethal doses. Other effects included minimal to mild hyperplasia and inflammation of the forestomach epithelium (sometimes with foci of necrosis and mineralization) in 5/10 males at 240 mg/kg, 3/10 males at 480 mg/kg, and 3/10 females at 300 mg/kg. Liver weight and liver:body weight ratio significantly increased in males at 120 mg/kg (no data from higher doses due to mortality) and females at all doses (appears dose-related). Kidney weight and/or kidney:body weight ratio significantly increased in males at $30 mg/kg and $75 mg/kg in females. Kidney weight changes appeared to be dose-related, but no renal histopathological changes were observed.

Dose and end point used for MRL derivation:

The lowest dose in female rats, 58 mg/kg/day, is a LOAEL for kidney effects. The increased kidney weight is considered to be an early-stage adverse effect because dose-related renal histopathology (tubular regeneration, indicative of previous tubular injury with subsequent repair) developed at higher doses in the same strain of rats.

[X] NOAEL [ ] LOAEL

Uncertainty factors used in MRL derivation:

[X] 3 for use of a minimal LOAEL
[X] 10 for interspecies extrapolation
[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose?

Estimated daily doses were reported by the investigators.

Was a conversion used from intermittent to continuous exposure?

Not applicable.

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

Not applicable.

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

1,2-Dichloroethane is acutely nephrotoxic in humans following both inhalation and ingestion; renal effects observed in people who died following acute high-level exposure included diffuse necrosis, tubular necrosis, and kidney failure (Hueper and Smith 1935; Lochhead and Close 1951; Nouchi et al. 1984; Yodaiken and Babcock 1973). Renal effects (e.g., increased kidney weight and tubular epithelial degeneration) were also found in animals following high-level acute- and intermediate-duration inhalation exposure (Heppel et al. 1946; NTP 1991a; Spencer et al. 1951). Reports of increased relative kidney weight in rats that were treated with $75 or 90 mg/kg/day by gavage for 90 days (Daniel et al. 1994; van Esch et al. 1977) are supportive of the 58 mg/kg/day LOAEL used to derive the MRL.

Agency Contact (Chemical Manager): Malcolm Williams

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

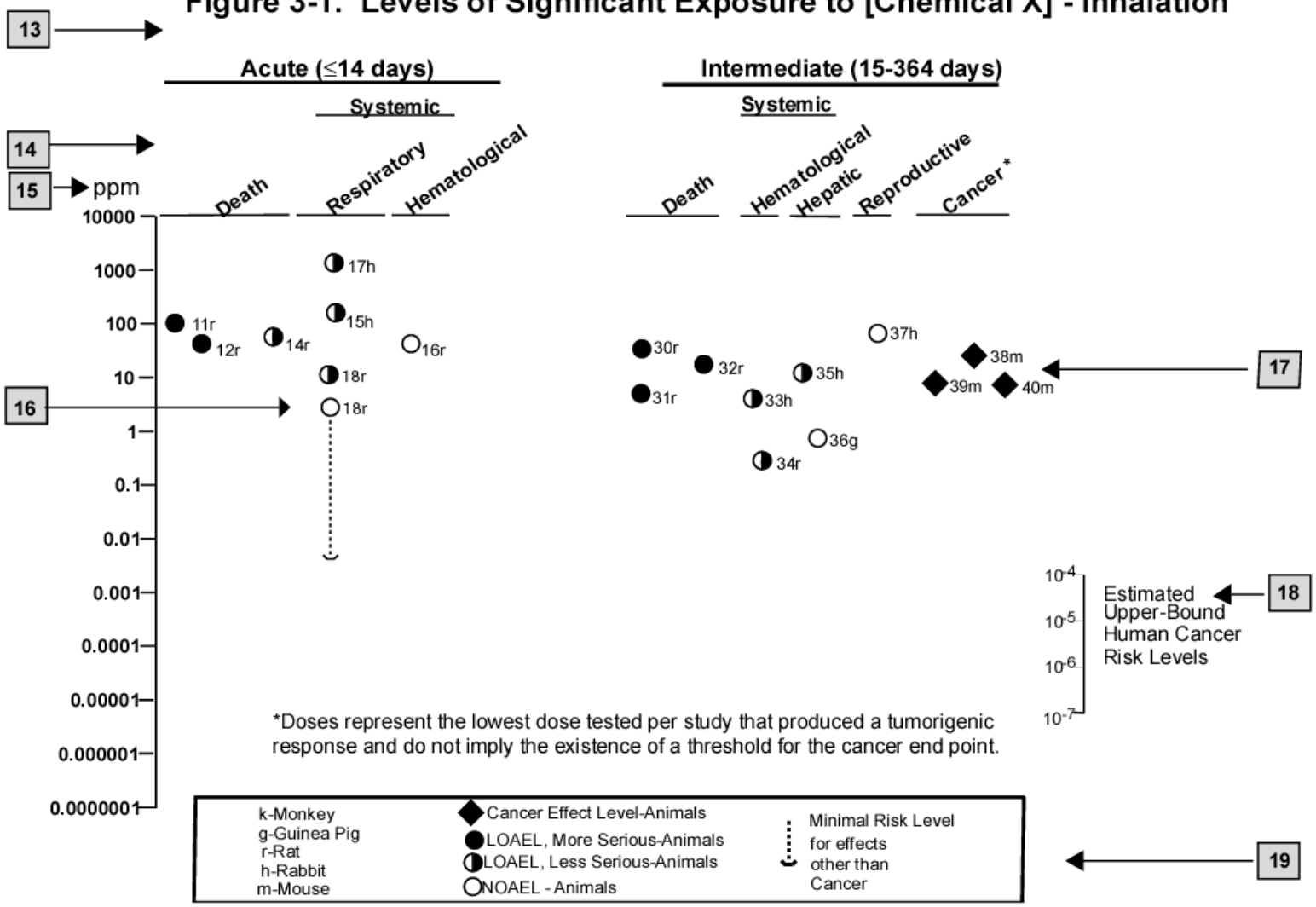
Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
INTERMEDIATE EXPOSURE							
5	6	7	8	9			10
3 Systemic	9	9	9	9	9		9
4 18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
CHRONIC EXPOSURE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

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APPENDIX D

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