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. 99-4991, 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 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.

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name(s): Cadmium
CAS number(s): 7440-43-9
Date: March 16, 1999
Profile status: Draft 2 post-public comment
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Key to figure: 137
Species: Human

Minimal Risk Level: 0.0002 [X] mg/kg/day [ ] ppm [ ] mg/m^3

Reference: Nogawa K, Honda R, Kido T. et al. 1989. A dose-response analysis of cadmium in the general environment with special reference to total cadmium intake limit. Environmental Research 48:7-16.

Experimental design: Nogawa et al. (1989) investigated the dose-response for renal effects of cadmium exposure, using the average cadmium concentration in locally produced rice as the measure of cadmium intake and urinary β_2-microglobulinuria as the index of renal damage. Subjects were 1,850 (878 male and 972 female) cadmium-exposed and 294 (133 male and 161 female) nonexposed inhabitants of the Kakchashi River basin in the Ishikawa Prefecture. Mean residence time in the polluted area ranged from 1 to more than 70 years. The cadmium content of "household" (homegrown) rice was evaluated for 22 locations in the region in 1974, and cadmium intake was adjusted for proportion of commercial rice in the diet, determined by questionnaire.

Effects noted in study and corresponding doses: Abnormal urinary β_2-microglobulin concentration was defined as $\geq$1,000 µg/L or 1,000 µg/g creatinine in morning urine. The prevalence of β_2-microglobulinuria was 5.3% in control males and 3.1% in control females. A regression equation relating total cadmium intake to prevalence of β_2-microglobulinuria was derived for exposed males and females, each divided into 12 dose groups. Both regressions were highly significant (for males, r=0.88, P<0.001, for females, r=0.81, p<0.01). For both sexes, the regression equation gave a prevalence of β_2-microglobulinuria equal to controls at a total lifetime cadmium intake of 2,000 mg. This was calculated by the authors to be 110 µg/day. Using an adult body weight of 53 kg for Japanese, this corresponds to 0.0021 mg/kg/day. This can be considered the threshold for cadmium-induced β_2-microglobulinuria.

Dose endpoint used for MRL derivation: 0.0021 mg/kg/day, renal damage (proteinuria)

[X] NOAEL [ ] LOAEL

Uncertainty factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[ ] 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 for intermittent to continuous exposure?
No.

If an oral study in animals, list conversion factors used in determining human equivalent dose:
Not an oral study in animals. No conversion factor needed.

Additional studies or pertinent information that lend support to this MRL: There is a huge database supporting the kidney as the most sensitive target organ for chronic cadmium exposure. An integrated, comprehensive kinetic model has been developed to predict the concentration of cadmium in the human renal cortex as a function of cadmium intake by the inhalation and/or oral routes (Kjellstrom and Nordberg 1978). This model is based on extensive animal and human data on the toxicokinetics and toxicity of cadmium. Kjellstrom (1986a) extended the model by considering that individuals would vary in the concentration of cadmium in the renal cortex at a given intake, and that individuals would also vary in the level of cadmium causing renal damage (the "critical concentration"). Assuming a log-normal distribution of both parameters, and a critical concentrations of 180 μg/g wet weight for 10% of the population, this model predicts the percentage of a nonsmoking population with kidney cadmium level above the critical concentration to be 2.7% at 0.0014 mg/kg/day (100 μg/day with a body weight of 70 kg) and 11% at 0.0029 mg/kg/day. Comparison with the threshold derived by the Nogawa et al. (1989) study indicates that 0.0021 mg/kg/day would be about a 7% response. Thus, the Nogawa et al. (1989) study is generally consistent with the model. An uncertainty factor of 10 is used to account for human variability.

A relevant consideration is whether the proteinuria caused by cadmium exposure should be considered an adverse effect. The increased excretion of low-molecular-weight proteins *per se* probably has no adverse effect on health. On the other hand, several studies have indicated that increased excretion of calcium also occurs at approximately the same level as proteinuria, and this is definitely an adverse effect if it leads to increased calcium wasting and osteoporosis, particularly in post-menopausal women.

Buchet et al. (1990) conducted a large scale epidemiology study (called the Cadmibel study) to establish whether environmental exposure to cadmium induces renal dysfunction and to determine the critical level of the general population. A cross-sectional study was conducted from 1985 to 1989. A stratified random sample of 2,327 people was obtained from two areas with low exposure and two with high exposure. For each exposure level, one district was rural and one was urban. Subjects filled out a detailed questionnaire and provided blood and urine (spot and 24 hour) samples for analysis. Excluded from the analysis were subjects occupationally exposed to heavy metals, those under 20 or over 80 years of age, those who could provide no reliable information on smoking habits or occupational exposure to heavy metals, and those whose 24-hour urine were not considered reliable (criteria were previously published). Determinants significantly affecting the renal measurements were traced with stepwise regression. To avoid co-linearities, independent variables considered in the model were centered. A logistic model was used to study the relation between the frequency of abnormal values of the renal measurement and the internal dose of cadmium assessed by its urinary excretion. For the multiple regression and the logistic analyses, the urinary excretion of cadmium was expressed as either the total amount excreted in 24 hours or as the concentration in the 24 hour urine. Body burden of cadmium increased with age in males and females, and with increased level of smoking. In nonsmokers of all ages, women had significantly higher blood and urine cadmium levels (possibly due to higher gastrointestinal uptake). Cadmium in urine was correlated with changes in measures of proximal tubular function. Five measures of renal effects were significantly associated with 24 hour urinary cadmium excretion: urinary excretion of retinol-binding protein (RBP), Nacetyl-β-glucosaminidase (NAG), β_2-microglobulin (B2M), aminoacids (AA), and calcium (CA). It was estimated that more than 10% of the renal measurements would be abnormal when the cadmium excretion rate exceeded 2.87 μg/24 hours for RBP, 2.74 μg/24 hours for NAG, 3.05 μg/24 hours for B2M, 4.29 μg/24 hours for AA, and 1.92 μg/24 hours for CA. Of the population tested, 184 or 10.8% had 24 hour urinary cadmium levels of more than 2 μg. The authors suggest that, for the general population, a urinary cadmium excretion of <2 μg/24 hours would result in a low risk of renal effects. This level may be lower for diabetics since cadmium body burden and diabetes had a synergistic effect on the urinary excretion of NAG and B2M. The 2 μg/24 hours urinary level for the general population is considerably below previous studies by the authors on adult workers that showed no detectable renal effects at urinary cadmium excretion of about 10 μg/24 hours. The 10 μg/24 hours level corresponded with a renal cortex concentration of 200 ppm. This finding supports the "healthy worker" effect (i.e., that risk levels based upon worker populations underestimate the risk to the general population).

On the basis of current toxicokinetic models (i.e., oral absorption rate of 5%, daily excretion rate of 0.005% of body burden, and a third of the body burden residing in the kidneys), the authors estimate that a urinary cadmium excretion of 2 μg/24 hours corresponds to a mean renal cortex concentration of about 50 ppm (wet weight). In nonsmokers, this level is reached after 50 years of an oral daily intake of about 1 μg/kg body weight. This study indicates that the critical concentration of 180 μg/g in the kinetic model (Kjellstrom 1986a) may underpredict renal damage in the general population. A LOAEL for cadmium of 1.1 μg/kg/day was derived by an independent group based on urinary calcium as the effect measure (TERA, internet communication). The agreement of the Nogawa et al. (1989) study with the Kjellstrom model could possibly be attributed to the use of a more sensitive cutoff for β_2-microglobulinuria in the Buchet et al. (1989) study (283 μg/day vs. 1,000 μg/L) and/or to the use of too high a value for absorption of cadmium from food in the Kjellstrom and Nordberg (1978) model. Since cadmium intakes were not measured in the Buchet et al. (1990) study, and urinary or renal cadmium levels were not measured in the Nogawa et al. (1989) study, it is not possible to resolve this discrepancy at this time. However, the use of the uncertainty factor of 10 is likely to account for possible increased sensitivity demonstrated by the Buchet et al. (1990) study.

Alternative methods of deriving a Minimum Risk Level based on the benchmark dose approach and pharmacokinetic modeling (Clewell et al. 1997, Crump 1995) have been investigated by the K.S. Crump Group for cadmium and the results presented in a special report prepared for ATSDR (Crump 1998). Crump (1998) used the Nogawa et al. (1989) endpoint of kidney dysfunction based upon abnormal urinary β_2-microglobulin and creatinine levels, and the percent response data was converted to quantal response rates. The quantal endpoints were then modeled using Weibull or polynomial models. Benchmark dose levels ($BMDL_{10}$s) were derived for the 95% lower bound on the estimated bench mark dose (BMD_{10}) that corresponded to a 10% extra risk. Separate BMDs were estimated for males and females using the two models (Weibull and polynomial). Cumulative exposure levels in mg/kg were converted to mg/kg/day by dividing by 70 years of environmental exposure and 365 days/year resulting in $BMDL_{10}$s of 0.00075-0.0013 mg/kg/day. Dividing by an uncertainty factor of 10 for human variability, the resulting MRLs would be 0.000075-0.00013 mg/kg/day, a factor of 1.5 to 3 times lower than the current MRL of 0.0002 mg/kg/day (Crump 1998).

A BMD could not be derived from the data of Buchet et al. (1990) because only very broadly grouped data were reported (Crump 1998). However, a modification of a pharmacokinetic model developed by Oberdorster (1990) was used to calculate the lifetime daily oral intake of cadmium that would result in a urinary excretion of 2.7 μg Cd/day. Based upon this pharmacokinetic modeling approach, and assuming a half-life of 20 years for cadmium excretion from the body, a urinary cadmium level of 2.7 μg Cd/day corresponding to a daily oral intake of 0.84 μg/kg body weight/day was derived. This estimate assumes that all cadmium intake is via the oral route. The 0.84 µg/kg/day estimate, based upon the Buchet et al. (1990) data, represents a LOAEL (i.e., the Buchet et al. analysis is a best estimate of the critical cadmium concentration in the kidney). An uncertainty factor for interindividual variability was not considered necessary because of the large size of the population in the Buchet et al. (1990) study. Using an uncertainty factor of 3 for a minimal LOAEL an MRL of 0.0003 mg/kg/day was derived, which is a factor of 1.5 times greater than the current MRL based on the Nogawa et al. (1989) study.

Agency Contact (Chemical Manager): Jessilyn B. Taylor

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

Tables and Figures for Levels of Significant Exposure (LSE)

Tables (2-1, 2-2, and 2-3) and figures (2-1 and 2-2) 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 2-1 and Figure 2-1 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 2-1

(1) <u>Route of Exposure</u> 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 2-1, 2-2, and 2-3, respectively). LSE figures are limited to the inhalation (LSE Figure 2-1) and oral (LSE Figure 2-2) 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 2-1).

(5) Species The test species, whether animal or human, are identified in this column. Section 2.5, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 2.3, "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 endpoint 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 8 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 2-1

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 endpoint 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 →

TABLE 2-1. Levels of Significant Exposure to [Chemical x] – Inhalation

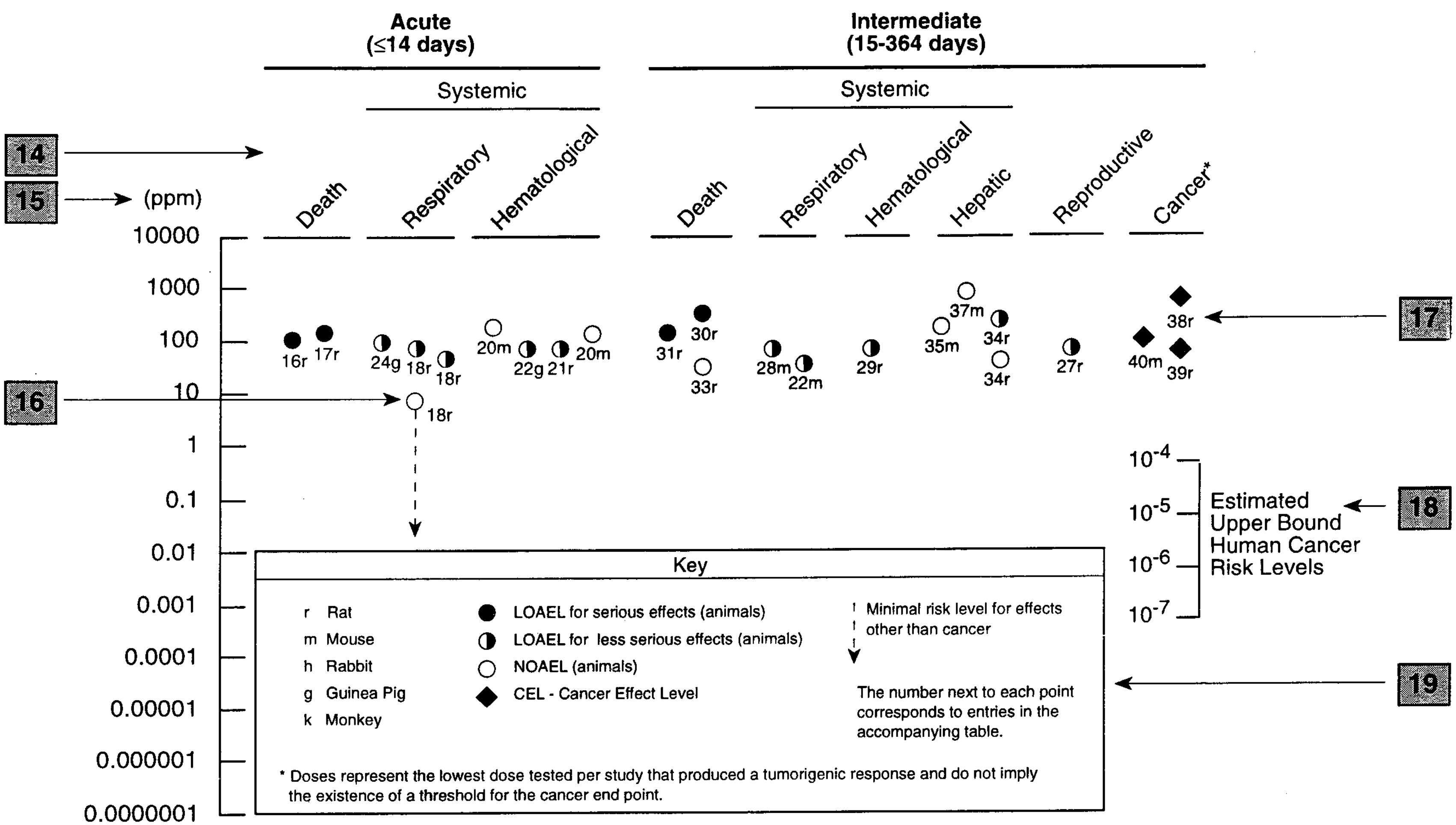
Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect): Less serious (ppm)	LOAEL (effect): Serious (ppm)	Reference
2 → INTERMEDIATE EXPOSURE							
	5	6	7	8	9		10
3 → Systemic	↓	↓	↓	↓	↓		↓
4 → 18	Rat	13 wk 5d/wk 6hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
CHRONIC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

[a] The number corresponds to entries in Figure 2-1.

12 → [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

13 → **Figure 2-1. Levels of Significant Exposure to [Chemical X] – Inhalation**



Chapter 2 (Section 2.5)

Relevance to Public Health

The Relevance to Public Health section 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 section 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 section. 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 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 2.5, "Relevance to Public Health," contains basic information known about the substance. Other sections such as 2.8, "Interactions with Other Substances," and 2.9, "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 endpoint 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 endpoint 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.

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

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