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 100-fold 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 and Environmental Medicine, 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 and Environmental Medicine, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-32, Atlanta, Georgia 30333.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Barium, Soluble Salts
CAS Numbers:
Date: August 2007
Profile Status: Final
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 23
Species: Rat

Minimal Risk Level: 0.2 [X] mg/kg/day [ ] ppm

Reference: NTP. 1994. Toxicology and carcinogenesis studies of barium chloride dihydrate (CAS No. 10326-27-9) in F344/N rats and B6C3F1 mice (drinking water studies). Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Toxicology Program. NTP TR 432.

Experimental design: Groups of 10 male and 10 female F344/N rats were administered 0, 125, 500, 1,000, 2,000, or 4,000 ppm barium chloride dihydrate in drinking water for 90 days. Using measured body weights and water consumption, the investigators estimated the daily barium doses to be 0, 10, 30, 65, 110, and 200 mg barium/kg/day for males and 0, 10, 35, 65, 115, and 180 mg barium/kg/day for females. Neurobehavioral tests (spontaneous motor activity, grip strength, tail flick latency, startle response, hindlimb foot splay) were performed prior to exposure and after 45 and 90 days of exposure. Cardiovascular testing (heart rate, blood pressure, and electrocardiogram) was conducted prior to exposure and after 45 and 91 days of exposure. Organ weights (adrenal gland, brain, heart, liver, kidney, lung, testis, thymus), blood analysis for hematological and clinical chemistry (barium, sodium, potassium, calcium, and phosphorus levels) alterations, and histological examination of major tissues and organs (only in the 200/180 mg/kg/day group) were conducted at termination; kidney, liver, spleen, and thymus of male and female rats in the 110/115 mg/kg/day groups and adrenal gland, heart, and salivary gland of female rats in the 115 mg/kg/day group were also examined microscopically.

Effect noted in study and corresponding doses: Exposure-related deaths were observed during the last week in 30% of the males and 10% of the females exposed to 200/180 mg barium/kg/day. Significant decreases in final body weights were also observed in the 200 mg barium/kg/day males (13% lower than controls) and 180 mg barium/kg/day females (8% lower than controls); significant decreases in water consumption (approximately 30% lower than controls) were also observed at this dose level. Marginal, but statistically significant, decreases in undifferentiated motor activity was observed in all groups of rats exposed to barium for 90 days, except females exposed to 115 mg barium/kg/day; no other alterations in neurobehavioral performance were observed. No significant alterations in heart rate, blood pressure, or EKG readings were observed. Significant increases in serum phosphorus levels were observed in males in the 110 and 200 mg barium/kg/day groups and females in the 35, 65, 115, and 180 mg barium/kg/day groups; however, the investigators noted that these increases were probably an artifact from hemolysis of collected blood samples. Significant increases in absolute and relative kidney weights were observed in females exposed to 115 or 180 mg barium/kg/day and increases in relative kidney weights were also observed in males at 200 mg barium/kg/day. An increase in relative kidney weight was also observed in the females exposed to 65 mg barium/kg/day. The magnitude of the increases in relative kidney weights were 7, 14, and 19% in the females exposed to 65, 115, and 180 mg barium/kg/day and 12% in males exposed to 200 mg barium/kg/day. ;Minimal to mild, focal to multifocal dilatation of the proximal convoluted tubules of the outer medulla and renal cortex was observed in three male and three female rats in the 200/180 mg barium/kg/day group. The small increase in relative kidney weight (7%) observed in

the female rats exposed to 65 mg barium/kg/day was not considered biologically significant because it is not supported by an increase in histological alterations in the kidney at 65 or 115 mg barium/kg/day or in rats exposed to 75 mg barium/kg/day for 2 years (NTP 1994).

Dose and end point used for MRL derivation: The MRL is based on a NOAEL of 65 mg barium/kg/day for increased absolute and relative kidney weight. The increased kidney weight was considered an early indicator of potentially more serious effects in the kidney. A NOAEL/LOAEL approach was used to derive the MRL because none of the available benchmark dose models provided an adequate fit to the absolute or relative kidney weight data.

[X] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation: 100

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

Modifying Factor used in MRL derivation: 3

[X] 3 for database deficiences

A modifying factor of 3 was included to account for deficiencies in the oral toxicity database, particularly the need for an additional developmental toxicity study. Decreases in pup birth weight and a nonstatistically significant decrease in live litter size were observed in the offspring of rats exposed to 180/200 mg Ba/kg/day as barium chloride in drinking water prior to mating (Dietz et al. 1992). Maternal body weight gain and water consumption were not reported, thus it is not known if the decreases in pup body weight were secondary to maternal toxicity or direct effect on the fetus. No developmental effects were observed in mice at the highest dose tested (200 mg Ba/kg/day) (Dietz et al. 1992). One other study examined the potential for developmental toxicity in orally exposed animals (Tarasenko et al. 1977). However, because the study was poorly reported and no incidence data or statistical analysis were presented in the published paper, the reported findings of increased mortality and systemic toxicity in the offspring of an unspecified species orally exposed to barium during conception and pregnancy can not be adequately evaluated. The Dietz et al. (1992) study was designed to be a mating trial and did not expose the animals during gestation; thus, database is lacking an adequate study to evaluate the potential for barium to induce developmental effects.

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No. Doses were calculated by the investigators using measured drinking water consumption and body weight data.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? Not applicable.

Other additional studies or pertinent information that lend support to this MRL: There are limited data on the toxicity of barium in humans following repeated doses. Wones et al. (1990) found no significant alterations in blood pressure or ECG readings, relative to initial baseline measurements in men experimentally exposed to up to 0.2 mg barium/kg/day as barium chloride in drinking water for 4 week (Wones et al. 1990). These findings are supported by several animal studies that did not find significant

alterations in blood pressure or ECG readings in rats exposed to 150–180 mg barium/kg/day in drinking water for 13 or 16 weeks, respectively (McCauley et al. 1985; NTP 1994). A study by Perry et al. (1983, 1985, 1989) found significant increases in blood pressure in rats administered 8.6 or 11 mg barium/kg/day as barium chloride in drinking water for 1 or 4 months, respectively. The reason for the differences between the results from the Perry et al. (1983, 1985, 1989) study and the NTP (1994) and McCauley et al. (1985) studies is not known. It is possible that the diet used in the Perry et al. (1983, 1985, 1989) study influenced the results. In this study, the rats were fed a low-mineral diet; the calcium content of the rye-based diet was 3.8 mg/kg, which is lower than the concentration recommended for maintenance, growth, and reproduction of laboratory rats (NRC 1995b).

The results of studies by McCauley et al. (1985) and NTP (1994) suggest that the kidney is the most sensitive target of toxicity in rats and mice. In the McCauley et al. (1985) study, glomerular alterations consisting of fused podocytes and thickening of the capillary basement membrane were found in rats exposed to 150 mg barium/kg/day in drinking water for 16 weeks. This lesion was found in uninephrectomized Sprague Dawley rats, Dahl salt-sensitive rats, and Dahl salt-resistant rats. In the NTP (1994) rat study, significant increases in absolute and relative kidney weights were observed in female rats exposed to 115 or 180 mg barium/kg/day and in males exposed to 200 mg barium/kg/day. A statistically significant increase in relative kidney weight was also observed in the females exposed to 65 mg barium/kg/day; however, the increase was small (7%) and was not considered biologically significant. At 200 and 180 mg barium/kg/day, minimal to mild dilatation of the proximal renal cortex was observed in the males and females, respectively; an increase in mortality (30%) was also observed in the males exposed to 200 mg barium/kg/day. In mice, mild to moderate nephropathy (characterized as tubule dilatation, regeneration, and atrophy) was observed in 100% of the males exposed to 450 mg barium/kg/day and 90% of the females exposed to 495 mg barium/kg/day; no renal lesions were observed at the next lowest dose level (205 and 200 mg barium/kg/day in males and females, respectively). Other effects observed at the 450/495 mg barium/kg/day dose level included weight loss, spleen and thymus atrophy, and increased mortality (60% of the males and 70% of females died after 5 weeks of exposure).

Other end points that have been examined in rats and mice include neurotoxicity, reproductive toxicity, and developmental toxicity. In male and female rats, slight decreases in undifferentiated motor activity were observed at 10 mg barium/kg/day and higher. However, with the exception of female rats exposed to 200 mg barium/kg/day, the difference between motor activity in the barium-exposed rats and the controls was less than 20%; this was not considered to be biologically significant. At 200 mg barium/kg/day, the difference was 30%, which was considered to be adverse. No significant alterations were found in performance on the remaining neurobehavioral tests (grip strength, tail flick latency, startle response, and hindlimb foot splay). In mice, a significant decrease in forelimb grip strength was observed in females exposed to 495 mg barium/kg/day; this may have been due to debilitation. No other alterations in neurobehavioral performance were found. No effects on reproductive tissues or reproductive performance were observed in rats or mice exposed to approximately 200 mg barium/kg/day (Dietz et al. 1992; NTP 1994). Pre-mating exposure to 180/200 mg barium/kg/day resulted in decreased litter size and body weight in rat offspring; the NOAEL for these effects was 110/115 mg barium/kg/day (Dietz et al. 1992). No developmental effects were observed in mice exposed to 200 mg barium/kg/day (Dietz et al. 1992).

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APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Barium, Soluble Salts
CAS Numbers:
Date: August 2007
Profile Status: Final
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Graph Key: 49
Species: Mouse

Minimal Risk Level: 0.2 [X] mg barium/kg/day [ ] ppm

Reference: NTP. 1994. Toxicology and carcinogenesis studies of barium chloride dihydrate (CAS No. 10326-27-9) in F344/N rats and B6C3F1 mice (drinking water studies). U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Toxicology Program, Research Triangle Park, NC. NTP TR 432.

Experimental design: Groups of 60 male and 60 female B6C3F1 mice were administered 0, 500, 1,250, or 2,500 ppm barium chloride dehydrate in drinking water for 2 years. Using measured body weights and water consumption, the investigators estimated the daily barium doses to be 0, 30, 75, and 160 mg barium/kg/day for males and 0, 40, 90, and 200 mg barium/kg/day for females. Organ weights, blood analysis for hematological and clinical chemistry (barium, sodium, potassium, calcium, and phosphorus levels, and alanine aminotransferase, creatine kinase, lactate dehydrogenase, and gamma-glutamyltransferase activities) alterations (measured after 15 months), and histological examination of major tissues and organs were conducted at termination.

Effect noted in study and corresponding doses: Increased mortality attributed to renal lesions was observed in the 160/200 mg/kg/day group. Decreased body weights (<7%) were observed in the barium-exposed mice. The investigators noted that a moderate to marked weight loss was observed in animals dying early. No significant alterations in hematology or clinical chemistry parameters were observed. A significant increase in the incidence of nephropathy was observed in male and female mice exposed to 160/200 mg/kg/day. The nephropathy was characterized by extensive regeneration of cortical and medullary tubule epithelium, tubule dilatation, hyaline cast formation, multifocal interstitial fibrosis, and glomerulosclerosis in some kidneys. The incidence of nephropathy was 1/50, 0/50, 2/48, and 19/50 in the males and 0/50, 2/53, 1/50, and 37/50 in the females, respectively. The average severity of the nephropathy was 3.6 (moderate to marked) for both the males and females in the 160/200 mg/kg/day group. An increased incidence of lymphoid depletion in the spleen and decreased relative and absolute spleen were also observed in the 160/200 mg/kg/day group; however, this was attributed to debilitation associated with nephropathy rather than a direct effect on the spleen. No significant increases in the incidences of neoplasms were observed.

Dose and end point used for MRL derivation: Benchmark dose analysis of the dose-response data (Table A-1) for nephropathy in male and female mice exposed to barium chloride in drinking water for 2 years (NTP 1994) was conducted. EPA's Benchmark Dose Software (version 1.3.2) was used to fit nine mathematical models to the incidence data. Model fit was judged by the p-values associated with the chi-square goodness-of-fit statistic generated by the models and visual inspection of the plot of observed and predicted values. As assessed by the chi-square goodness-of-fit test, several models in the software provided adequate fits to the data for the incidence of nephropathy in male and female mice (x^2 p-value $\geq$0.1). As assessed by lowest Akaike Information Criterion (AIC), the logistic model for the male mouse

data and the gamma model for the female mouse data provide the greatest fit. The results of the benchmark dose analysis are presented in Table A-2.

Table A-1. Incidence of Nephropathy in Male and Female Mice Exposed to Barium Chloride in Drinking Water for 2 Years (NTP 1994)

Water concentration (ppm)	Dose (mg barium/kg/day)	Incidence
Males		
0	0	1/50
500	30	0/50
1,250	75	2/48
2,500	160	19/50
Females		
0	0	0/50
500	40	2/53
1,250	90	1/50
2,500	200	37/50

Table A-2. Predictions from Models for Doses Associated with 10 and 5% Extra Risk for the Incidence of Nephropathy in Male and Female Mice Exposed to Barium in Drinking Water for 2 Years (NTP 1994)

Model	BMD_{10} mg/kg/day	$BMDL_{10}$ mg/kg/day	BMD_5 mg/kg/day	$BMDL_5$ mg/kg/day	x^2 p-value	AIC
Male mice						
Logistic	**103.96**	**87.26**	**80.06**	**61.13**	**0.28**	**99.34**
Probit	96.13	80.07	71.96	54.66	0.13	100.11
Log-probit[a]	99.73	77.90	83.39	59.54	0.31	100.25
Gamma[b]	102.31	80.06	84.94	59.65	0.31	100.28
Log-logistic[a]	104.44	80.50	86.43	59.69	0.31	100.32
Weibull[b]	106.59	81.79	87.63	59.54	0.31	100.35
Quantal quadratic	82.83	69.51	57.80	48.5	0.14	101.89
Multi-stage[c]	82.83	69.14	57.80	44.97	0.14	101.89
Quantal linear	NA	NA	NA	NA	0.0032	111.94
Female mice						
Gamma[b]	125.59	101.49	113.96	87.66	0.34	90.89
Log-probit[a]	134.85	100.63	125.10	88.39	0.17	92.84
Log-logistic[a]	147.43	101.75	137.35	87.01	0.17	92.84
Weibull[b]	153.60	102.66	142.51	84.95	0.17	92.84
Logistic	NA	NA	NA	NA	0.08	92.35

Table A-2. Predictions from Models for Doses Associated with 10 and 5% Extra Risk for the Incidence of Nephropathy in Male and Female Mice Exposed to Barium in Drinking Water for 2 Years (NTP 1994)

Model	BMD_{10} mg/kg/day	$BMDL_{10}$ mg/kg/day	BMD_5 mg/kg/day	$BMDL_5$ mg/kg/day	x^2 p-value	AIC
Probit	NA	NA	NA	NA	0.03	94.03
Quantal quadratic	NA	NA	NA	NA	0.01	102.21
Multi-stage[c]	NA	NA	NA	NA	0.01	102.21
Quantal linear	NA	NA	NA	NA	0.00	126.61

[a]slope restricted to >1
[b]restrict power ≥1
[c]restrict betas ≥0

degree of polynomial = 2; NA = not applicable

The $BMDL_{05}$ for male mice was selected as the point of departure for deriving the chronic-duration oral MRL. Data from the male mice were used because they identify a lower BMDL than the female data. The predicted 5% incidence approach was selected over the other two approaches as a precaution due to the severity of the observed effects (moderate to marked severity nephropathy), which resulted in marked weight loss and increased mortality.

[ ] NOAEL [ ] LOAEL [X] BMDL

Uncertainty Factors used in MRL derivation: 300

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

Modifying Factor used in MRL derivation: 3

[X] 3 for database deficiences

A modifying factor of 3 was included to account for deficiencies in the oral toxicity database, particularly the need for an additional developmental toxicity study. Decreases in pup birth weight and a nonstatistically significant decrease in live litter size were observed in the offspring of rats exposed to 180/200 mg Ba/kg/day as barium chloride in drinking water prior to mating (Dietz et al. 1992). Maternal body weight gain and water consumption were not reported, thus it is not known if the decreases in pup body weight were secondary to maternal toxicity or direct effect on the fetus. No developmental effects were observed in mice at the highest dose tested (200 mg Ba/kg/day) (Dietz et al. 1992). One other study examined the potential for developmental toxicity in orally exposed animals (Tarasenko et al. 1977). However, because the study was poorly reported and no incidence data or statistical analysis were presented in the published paper, the reported findings of increased mortality and systemic toxicity in the offspring of an unspecified species orally exposed to barium during conception and pregnancy can not be adequately evaluated. The Dietz et al. (1992) study was designed to be a mating trial and did not expose

the animals during gestation; thus, database is lacking an adequate study to evaluate the potential for barium to induce developmental effects.

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No. Doses were calculated by the investigators using measured drinking water consumption and body weight data.

Was a conversion used from intermittent to continuous exposure? Not applicable.

Other additional studies or pertinent information that lend support to this MRL: Several studies have examined the toxicity of barium following chronic-duration exposure. Significant increases in blood pressure were observed in rats exposed to 0.8 mg barium/kg/day as barium chloride in drinking water for 16 months (Perry et al. 1983, 1985, 1989); the NOAEL for this effect was 0.17 mg barium/kg/day. At higher doses (7.2 mg barium/kg/day), depressed rates of cardiac contraction, reduced cardiac electrical conductivity, and decreased cardiac ATP levels were observed. As noted in the discussion of the intermediate-duration oral MRL, interpretation of the results of this study is limited due to the low mineral diet which may have supplied inadequate levels of calcium.

No adverse effects were observed in rats exposed to 60 mg barium/kg/day as barium chloride in drinking water for 2 years (NTP 1994), 15 mg barium/kg/day to an unspecified barium compound in drinking water for 68 weeks (McCauley et al. 1985), or 0.7 mg barium/kg/day as barium acetate in drinking water for a lifetime (Schroeder and Mitchener 1975a). In mice exposed to barium chloride in drinking water for 2 years, marked renal nephropathy was observed at 160 mg barium/kg/day; the increased incidence of nephropathy in the next lowest dose group (75 mg barium/kg/day) was not statistically significant. Other adverse effects observed at 160 mg barium/kg/day included weight loss and increased mortality.

The animal data provide suggestive evidence that the kidney is the most sensitive target of toxicity. A serious LOAEL of 160 mg barium/kg/day was identified for nephropathy in mice (NTP 1994); the NOAEL identified in this study is 75 mg/kg/day. Although no kidney lesions were observed in rats exposed to doses as high as 60 mg barium/kg/day (NTP 1994), the doses utilized in the study may not have been high enough to cause kidney damage. Biologically significant kidney alterations were observed at 115 mg barium/kg/day and higher in rats exposed for an intermediate duration (NTP 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 that they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, and 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.

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, ATSDR has derived 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.

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

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 no-observed-adverse-effect level (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 levels of significant exposure (LSE) tables.

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures 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, 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 NOAELs, 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 Sample LSE Table 3-1 (page B-6)

(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. Typically when sufficient data exist, 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 Tables 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 two "18r" data points in sample 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 regimens 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 “Chemical x” via inhalation for 6 hours/day, 5 days/week, for 13 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, one systemic effect (respiratory) was investigated.

(8) NOAEL. A 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 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 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 that the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Sample Figure 3-1 (page B-7)

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 acute and intermediate exposure periods are illustrated.

(14) Health Effect. These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

(15) Levels of Exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16) NOAEL. In this example, the open circle designated 18r identifies a NOAEL critical end point in the rat upon which an intermediate inhalation exposure MRL is based. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17) CEL. Key number 38m is one of three studies for which CELs were derived. The diamond symbol refers to a CEL for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18) Estimated Upper-Bound Human Cancer Risk Levels. This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

(19) Key to LSE Figure. The Key explains the abbreviations and symbols used in the figure.

SAMPLE

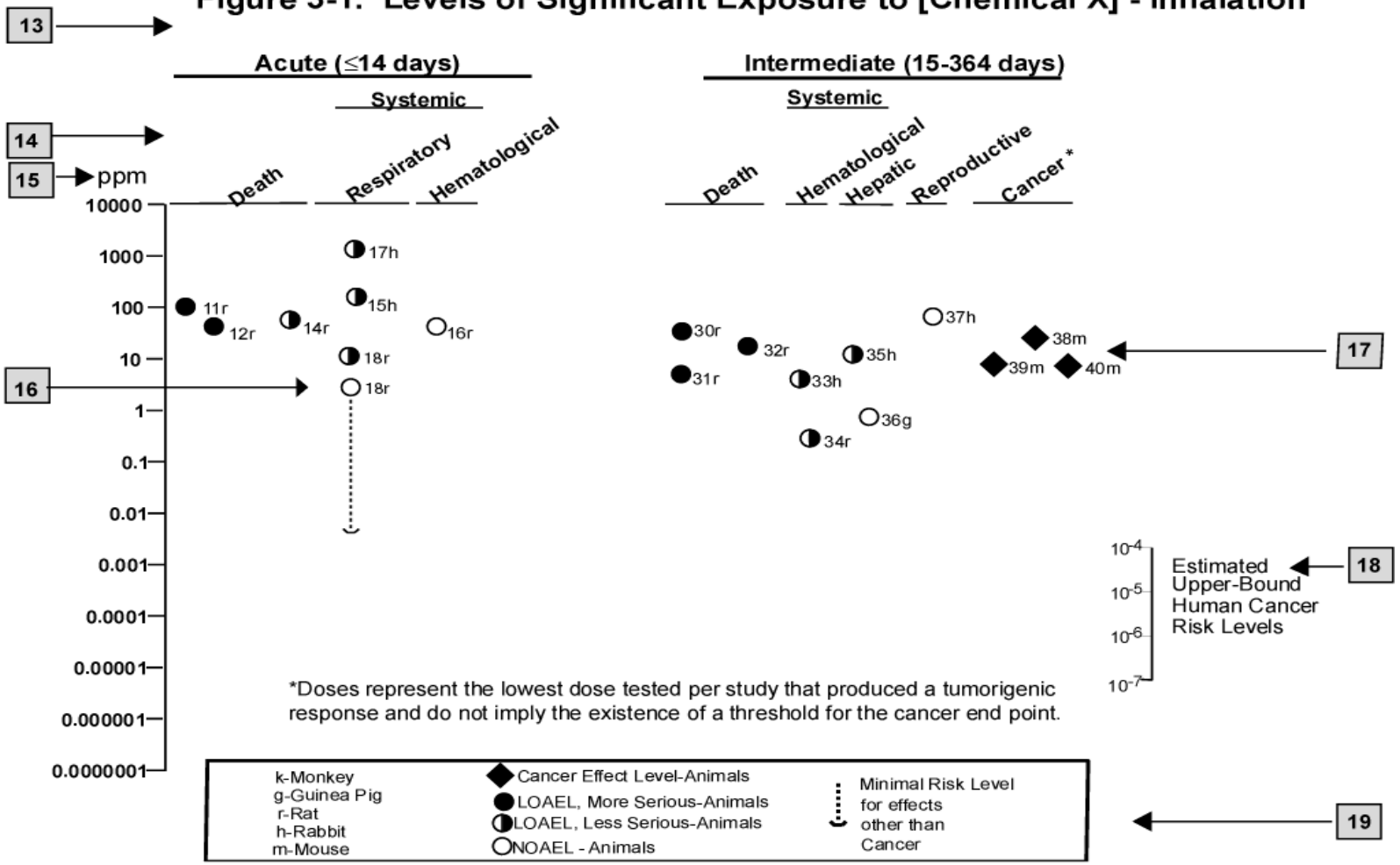
1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

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

12 → [a] The number corresponds to entries in Figure 3-1.
[b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of $5x10^{-3}$ 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



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APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
APHA	American Public Health Association
AST	aspartate aminotransferase
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
BMD	benchmark dose
BMR	benchmark response
BSC	Board of Scientific Counselors
C	centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor
DOT	Department of Transportation
DOT/UN/ NA/IMCO	Department of Transportation/United Nations/ North America/Intergovernmental Maritime Dangerous Goods Code

DWEL	drinking water exposure level
ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F_1	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
FR	Federal Register
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
ILO	International Labor Organization
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
MA	*trans,trans*-muconic acid
MAL	maximum allowable level
mCi	millicurie
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor

MFO	mixed function oxidase
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCEH	National Center for Environmental Health
NCI	National Cancer Institute
ND	not detected
NFPA	National Fire Protection Association
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NLM	National Library of Medicine
nm	nanometer
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
OPPT	Office of Pollution Prevention and Toxics, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OR	odds ratio
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
pg	picogram
PHS	Public Health Service
PID	photo ionization detector
pmol	picomole
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	pretreatment standards for new sources
RBC	red blood cell
REL	recommended exposure level/limit
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
RQ	reportable quantity
RTECS	Registry of Toxic Effects of Chemical Substances
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SIC	standard industrial classification
SIM	selected ion monitoring
SMCL	secondary maximum contaminant level
SMR	standardized mortality ratio
SNARL	suggested no adverse response level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short term exposure limit
STORET	Storage and Retrieval
TD_{50}	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	total organic carbon
TPQ	threshold planning quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result

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APPENDIX D. INDEX