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, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-32, Atlanta, Georgia 30333.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Naphthalene
CAS Number: 91-20-3
Date: June 2005
Profile Status: Final Post-Public Comment
Route: [x] Inhalation [ ] Oral
Duration: [ ] Acute [ ] Intermediate [x] Chronic
Graph Key: 6
Species: Rat

Minimal Risk Level: 0.0007 [ ] mg/kg/day [x] ppm

Reference(s): Abdo KM, Grumbein S, Chou BJ, et al. 2001. Toxicity and carcinogenicity study in F344 rats following 2 years of whole-body exposure to naphthalene vapors. Inhal Toxicol 13:931-950.

NTP. 1992a. Toxicology and carcinogenesis studies of naphthalene (CAS No. 91-20-3) in B6C3F1 mice (inhalation studies). Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health. National Toxicology Program. NIH Publication No. 92-3141. Technical report series no. 410.

NTP. 2000. Toxicology and carcinogenesis studies of naphthalene (CAS No. 91-20-3) in F344/N rats (inhalation studies). National Toxicology Program. NTP TR 500, NIH Publ. No. 01-4434.

Experimental design: NTP 1992a: Groups of 75 B6C3F1mice of each sex were exposed by inhalation at concentrations of 0, 10, or 30 ppm. Exposure occurred 5 times/week, 6 hours/day for 104 weeks.

Abdo et al. 2001; NTP 2000: Groups of 49 male and 49 female F344/N rats were exposed to naphthalene at concentrations of 0, 10, 30, or 60 ppm for 6 hours/day, 5 days/week for 105 weeks.

Effects noted in study and corresponding doses: In mice, exposure to 10 or 30 ppm of naphthalene resulted in inflammation of the nose (males: 0/70, 67/69, 133/135; females: 1/69, 65/65, 135/135) and lungs (males: 0/70, 21/69, 56/135; females: 3/69, 13/65, 52/135), metaplasia of the olfactory epithelium (males: 0/70, 66/69, 134/135; females: 0/69, 65/65, 135/135), and hyperplasia of the nasal respiratory epithelium (males: 0/70, 66/69, 134/135; females: 0/69, 65/65, 135/135). Increased incidences of neoplastic lesions were restricted to the lung in females: alveolar/bronchiolar adenomas (5/69, 2/65, 28/135) and alveolar/bronchiolar carcinomas (0/69, 0/65, 1/135).

In rats, increased incidences of nonneoplastic and neoplastic lesions were restricted to the nose as shown in Table A-1.

Dose and end point used for MRL derivation: The lowest exposure level in both studies, 10 ppm, was a LOAEL in both sexes of both species for nonneoplastic lesions in nasal olfactory epithelium and respiratory epithelium. Applying EPA inhalation dosimetry (see below), a human equivalent LOAEL of 0.2 ppm, based on the rat LOAEL, was selected as the point of departure for the chronic inhalation MRL. Benchmark dose analyses were not conducted on the incidence data for nonneoplastic nasal lesions, because the data provided insufficient information on the shape of the dose-response relationship. The lowest exposure level in the principal study induced nasal lesions in essentially all of the rats.

[ ] NOAEL [x] LOAEL

Modifying Factors used in MRL derivation: N/A

Table A-1. Nonneoplastic and Neoplastic Lesions of the Nose in Male and Female F344/N Rats Exposed to Naphthalene 6 Hours/Day, 5 Days/Week for 105 Weeks

	Concentration (ppm)							
	0		10		30		60	
Lesion	M	F	M	F	M	F	M	F
Nonneoplastic lesions								
Olfactory epithelium								
Hyperplasia	0/49	0/49	48/49	48/49	45/48	48/49	46/48	43/49
Atrophy	3/49	0/49	49/49	49/49	48/48	49/49	47/48	47/49
Chronic inflammation	0/49	0/49	49/49	47/49	48/48	47/49	48/48	45/49
Hyaline degeneration	3/49	13/49	46/49	46/49	40/48	49/49	38/48	45/49
Respiratory epithelium								
Hyperplasia	3/49	0/49	21/49	18/49	29/48	22/49	29/48	23/49
Squamous metaplasia	0/49	0/49	15/49	21/49	23/48	17/49	18/48)	15/49
Hyaline degeneration	0/49	8/49	20/49	33/49	19/48	34/49	19/48	28/49
Goblet cell hyperplasia	0/49	0/49	25/49	16/49	29/48	29/49	26/48	20/49
Gland hyperplasia	1/49	0/49	49/49	48/49	48/48	48/49	48/48	42/49
Gland squamous metaplasia	0/49	0/49	3/49	2/49	14/48	20/49	26/48	20/49
Neoplastic lesions								
Respiratory epithelial adenoma	0/49	0/49	6/49	0/49	8/48	4/49	15/48	2/49
Olfactory epithelial neuroblastoma	0/49	0/49	0/49	2/49	4/48	3/49	3/48	12/49

F = female; M = male

Uncertainty Factors used in MRL derivation: Total Uncertainty Factor = 10x3x10=300

[x] 10 for use of a LOAEL
[x] 3 for extrapolation from animals to humans with dosimetric adjustment
[x] 10 for human variability

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

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose:
10 ppm x 6 hours/24 hours x 5 days/7 days=1.8 ppm (duration-adjusted LOAEL for nasal effects in rats or mice)
1.8 ppm x 128.18/24.45=9.4 mg/m^3

Following EPA (1994d) *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry*, equations for a category 1 gas producing nasal effects were used to derive human equivalent concentrations: HEC=Animal Concentration x $RGDR_{ET}$;

$RGDR_{ET}$= regional gas dose ratio in the extrathoracic (ET) region
= $(Dose_{ET})A/(Dose_{ET})H$= $[\text{minute volume/ETsurface area}]_A \div [\text{minute volume/ETsurface area}]_H$;

Reference minute volumes (L/min): 13.8 human, 0.137 rat, 0.0368 mouse;
Reference ET surface area (cm^2): 200 human, 15 rat, 3 mouse;

$RGDR_{ET}$(Rat to Human)=[0.137/15]÷[13.8/200]=0.132;
$LOAEL_{HEC}$=duration-adjusted LOAEL x 0.132=1.8 ppm x 0.132=0.2 ppm
$RGDR_{ET}$(Mouse to Human)=[0.0368/3]÷[13.8/200]=0.178;
$LOAEL_{HEC}$=duration-adjusted LOAEL x 0.132=1.8 ppm x 0.178=0.3 ppm

Using public health protection reasoning, the $LOAEL_{HEC}$ based on the rat data was selected as the point of departure for the chronic inhalation MRL.

Other additional studies or pertinent information which lend support to this MRL: Uncertainty in the MRL would likely be decreased with the development and application of hybrid computational fluid dynamics and physiologically based pharmacokinetic models that would estimate regional tissue doses of naphthalene metabolites in rats and humans. The models can incorporate species-specific information on nasal geometry, breathing patterns, and metabolism, as well as chemical-specific information on reactivity, partition coefficients, and diffusivity of the vapor in air and tissue. Such models have been developed for other gases that induce nasal lesions (see Frederick et al. 2001), but have not yet been developed for naphthalene.

Reactive naphthalene metabolites (1,2-naphthalene oxide, 1,2-naphthoquinone, 1,4-naphthoquinone, and 1,2-dihydroxy-3,4-epoxy-1,2,3,4-tetrahydronaphthalene) have been proposed to be involved in naphthalene's toxic modes of action (Buckpitt et al. 2002). CYP isozymes, which might be involved in naphthalene metabolism and bioactivation, have been demonstrated to exist in nasal respiratory epithelial and olfactory epithelial tissue from rodents and humans (Thornton-Manning and Dahl 1997). Studies designed to specifically characterize metabolism of naphthalene in nasal tissue, however, have not been conducted (e.g., which CYP isozymes catalyze naphthalene transformations in nasal tissue?, are there species differences in nasal tissue efficiencies and capabilities for metabolism and/or bioactivation of naphthalene?), with the exception of a single study that examined *in vitro* rates of metabolism of naphthalene to naphthalene oxides in postmitochondrial supernatants from mouse, rat, and hamster olfactory tissue (Buckpitt et al. 1992). In this study, metabolic rates (units of nmol/min/mg protein) showed the following order: mouse (87.1) > rat (43.5) > hamster (3.9). This order did not correspond with species differences in susceptibility to single intraperitoneal injections of naphthalene in a companion study (Plopper et al. 1992a). Rat nasal epithelial tissue (olfactory and respiratory epithelium) was more sensitive than tissue from mice and hamsters, which showed equivalent sensitivities.

Agency Contacts (Chemical Managers): Hisham El-Masri, Ph.D.; Moiz Mumtaz, Ph.D.; and G. Daniel Todd, Ph.D.

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Naphthalene
CAS Number: 91-20-3
Date: June 2005
Profile Status: Final Post-Public Comment
Route: [ ] Inhalation [x] Oral
Duration: [x] Acute [ ] Intermediate [ ] Chronic
Graph Key: 16
Species: Rat

Minimal Risk Level: 0.6 [x] mg/kg/day [ ] ppm

Reference: NTP. 1991a. Developmental toxicity of naphthalene (CAS No. 91-20-3) administered by gavage to Sprague-Dawley (CD) rats on gestational days 6 through 15. Research Triangle Park, NC: National Toxicology Program, National Institute of Environmental Health Sciences, U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health. TER91006.

Experimental design: Groups of 25–26 pregnant female Sprague-Dawley rats received doses of 0, 50, 150, and 450 mg/kg/day by gavage on gestation days 6–15. There were two replicate groups of 12–13 animals.

Effects noted in study and corresponding doses: Rat dams in exposed groups showed one or more of several clinical signs of toxicity (slow respiration, lethargy, or prone body posture) on the first day of dosing (81, 96, and 96% of rats in the 50-, 150-, and 450-mg/kg/day groups). By the third day of dosing, these signs did not occur in any of the 50-mg/kg/day rats. A similar trend was noted in the 150-mg/kg/day group, but apparent tolerance did not develop until the sixth day of dosing. In the 450-mg/kg/day group, the incidence of rats exhibiting these signs of toxicity also declined during the exposure period, but did not fall below 15%. With the development of "tolerance", the slow respiration, lethargy, and prone body posture were replaced with rooting behavior, a common behavior of rodents following gavage administration of chemicals with strong odors or irritant properties. At the end of the exposure period (gestation day 15), incidence of rats showing rooting behavior was 0% for the control and 50-mg/kg/day groups, compared with 24 and 92% of dams in the 150- and 450-mg/kg/day groups, respectively. Weight gain during exposure (gestation days 6–15) was similar between the control and 50-mg/kg/day group, but was decreased by 31 and 53% in the 150- and 450-mg/kg/day groups, compared with controls. From these results, 50 mg/kg/day was judged to be a minimal less serious LOAEL for transient clinical signs of maternal toxicity in pregnant rat dams. At higher doses (150 and 450 mg/kg/day), these effects were more persistent and were accompanied by decreased weight gain.

No statistically significant exposure-related effects were observed on the average number of corpora lutea per dam, implantation sites per litter, live fetuses per litter, or average fetal body weight. The percent of fetuses malformed per litter (4, 4, 7, and 10% for control through 450 mg/kg/day) and the percent of litters with malformed fetuses (23, 27, 33, and 50%) both showed a statistically significant trend test, but pairwise comparisons between individual exposure groups and the control were not statistically significant. The investigators concluded that naphthalene was not fetotoxic or teratogenic in this assay.

Dose and end point used for MRL derivation: A minimal LOAEL of 50 mg/kg/day for transient clinical signs of toxicity in pregnant rat dams.

[] NOAEL [x] minimal LOAEL

Modifying Factors used in MRL derivation: N/A

Uncertainty Factors used in MRL derivation: Total Uncertainty Factor= 3x10x3=90

[x] 3 for use of a minimal LOAEL
[x] 10 for extrapolation from animals to humans
[x] 3 for human variability

An uncertainty factor of 3 was selected for the use of a minimal LOAEL of 50 mg/kg/day. At this dose level, the only adverse effects observed in the pregnant rat dams were signs of maternal toxicity, which were only observed on the first 2 days of exposure.

An uncertainty factor of 10 was used for extrapolating from animals to humans.

An uncertainty factor of 3 was used for human variability because the critical effect is based on effects in a sensitive animal subpopulation. Pregnant rats appear to be more sensitive for the effects observed (clinical signs and decreased body weight gain) than nonpregnant rats. In 13-week gavage studies with nonpregnant rats (NTP 1980b), similar persistent clinical signs were not observed following administration of doses as high as 200 mg/kg/day, but were observed at 400 mg/kg/day. In nonpregnant rats exposed for 13 weeks, significant body weight decreases occurred at 200 mg/kg/day throughout exposure, but not at 100 mg/kg/day (NTP 1980b) or in nonpregnant mice exposed for 13 weeks to 133 mg/kg/day (Shopp et al. 1984) or 200 mg/kg/day (NTP 1980a). Mice in the NTP (1980a) study showed transient signs of toxicity (lethargy, rough hair coats, and decreased food consumption), but these only occurred between weeks 3 and 5 in the 200-mg/kg/day group.

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

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

Other additional studies or pertinent information which lend support to this MRL: Neurologic symptoms have been reported in humans following ingestion of naphthalene at unknown, but presumably high dose levels. These include confusion (Ojwang et al. 1985) and listlessness and lethargy (Bregman 1954; Chusid and Fried 1955; Kurz 1987; Macgregor 1954; Zuelzer and Apt 1949), as well as decreased responses to painful stimuli and coma prior to death (Gupta et al. 1979; Kurz 1987). Persistent neurologic symptoms were not recorded in 13-week studies with rats or mice exposed to doses as high as 200 mg/kg/day (NTP 1980a, 1980b), but the highest exposure level tested in these studies, 400 mg/kg/day, produced lethargy in exposed rats (only rats were exposed to 400 mg/kg/day).

Hemolytic anemia has been identified in many human cases of acute accidental or intentional ingestion of naphthalene (e.g., Gidron and Leurer 1956; MacGregor 1954). Estimations of dose levels involved in these cases, however, are limited to a report (Gidron and Leurer 1956) of hemolytic anemia in a 16-year-old girl who swallowed 6 g of naphthalene (estimated dose=109 mg/kg, assuming body weight of 55 kg). Laboratory animals do not appear to be susceptible to the hemolytic activity of naphthalene. No pronounced changes in red-cell-related hematologic parameters were observed following 13-week oral exposures to doses up to 200 mg/kg/day in mice (NTP 1980a) and 400 mg/kg/day in rats (NTP 1980b), or in mice exposed by inhalation for 14 days to air concentrations as high as 30 ppm (NTP 1992a). Naphthalene-induced hemolytic anemia has been observed in dogs exposed to a single dose of 1,525 mg/kg or 263 mg/kg/day for 7 days (Zuelzer and Apt 1949), but more information on the dose-response relationship for hemolytic anemia in humans or animals acutely exposed to naphthalene is not available.

Another effect associated with acute or repeated oral exposure to naphthalene in animals is cataracts (Kojima 1992; Murano et al. 1993; Van Heyningen and Pirie 1976; Xu et al. 1992b). These effects, however, appear to occur at dose levels (in the range of 500–1,000 mg/kg/day) much higher than the lowest dose level (150 mg/kg/day) producing body weight gain decreases and clinical signs of toxicity in pregnant rats.

Agency Contacts (Chemical Managers): Hisham El-Masri, Ph.D.; Moiz Mumtaz, Ph.D.; and G. Daniel Todd, Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Naphthalene
CAS Number: 91-20-3
Date: June 2005
Profile Status: Final Post-Public Comment
Route: [ ] Inhalation [x] Oral
Duration: [ ] Acute [x] Intermediate [ ] Chronic
Graph Key: 16
Species: Rat

Minimal Risk Level: 0.6 [x] mg/kg/day [ ] ppm

Reference: NTP. 1991a. Developmental toxicity of naphthalene (CAS No. 91-20-3) administered by gavage to Sprague-Dawley (CD) rats on gestational days 6 through 15. Research Triangle Park, NC: National Toxicology Program, National Institute of Environmental Health Sciences, U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health. TER91006.

Experimental design: See the worksheet for the acute-duration oral MRL.

Effects noted in study and corresponding doses: See the worksheet for the acute-duration oral MRL.

Dose and end point used for MRL derivation: A minimal LOAEL of 50 mg/kg/day for transient clinical signs of toxicity in pregnant rat dams.

[ ] NOAEL [x] minimal LOAEL

Modifying Factors used in MRL derivation: N/A

Uncertainty Factors used in MRL derivation: Total Uncertainty Factor =3x10x3=90

[x] 3 for use of a minimal LOAEL
[x] 10 for extrapolation from animals to humans
[x] 3 for human variability

See the worksheet for the acute-duration oral MRL for explanations of the uncertainty factors.

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

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

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

There are three intermediate-duration oral toxicity studies in laboratory animals that were considered for deriving the intermediate oral MRL for naphthalene. A 13-week comprehensive oral toxicity study in Fischer 344 rats found no adverse exposure related effects other than decreased body weight (NTP 1980b). This study identified 100 mg/kg/day as a NOAEL and 200 mg/kg/day as a LOAEL for decreased body weight in male and female rats. Another 13-week comprehensive oral toxicity study in B6C3F1 mice found no adverse effects in mice exposed to doses as high as 200 mg/kg/day (NTP 1980a). Another 90-day gavage study in mice focused on immune system variables and other toxicity variables (e.g., body

weight, organ weight, haematological parameters) and identified 133 mg/kg/day as a LOAEL and 53 mg/kg/day as a NOAEL for weight decreases in several organs (brain, liver, and spleen), but found no biologically significant exposure-related changes in other end points evaluated (Shopp et al. 1984). This study, however, did not include histopathological examination of tissues.

More detailed descriptions of the intermediate-duration oral toxicity studies follow. After the description of the studies, an analysis of their usefulness for MRL derivation is presented.

NTP. 1980b. Subchronic toxicity study: Naphthalene (C52904), Fischer 344 rats. Research Triangle Park, NC: U.S. Department of Health and Human Services, National Toxicology Program.

Naphthalene (>99% pure) in corn oil was administered by gavage to groups of 10 male and 10 female Fischer 344 rats at dose levels of 0, 25, 50, 100, 200, or 400 mg/kg/day, 5 days/week for 13 weeks (NTP 1980b). End points included weekly measurement of food consumption and body weight, twice daily observation for clinical signs of toxicity, measurement of hematological parameters for blood collected at termination (hemoglobin, hematocrit, total and differential white blood cell count, red blood cell count, mean cell volume, mean cell hemoglobin concentration), necropsy of all rats in the study, and complete histopathological examination of 27 organs and tissues (including the eyes, lungs, stomach, liver, reproductive organs, thymus, and kidneys) from all control and 400-mg/kg rats. Male kidneys and female thymuses from the 200-mg/kg group were also examined histopathologically (according to the histopathology tables; however, the report text states that the 100 mg/kg group was examined). Organ weight data were not reported.

At the highest dose level, two male rats died during the last week of treatment, and rats of both sexes displayed diarrhea, lethargy, hunched posture, and rough coats at intermittent intervals throughout the study. Food consumption was not affected by exposure. Mean terminal body weights were decreased by more than 10% relative to the controls in several groups (28 and 12% decrease in the 400- and 200-mg/kg males, respectively and 23% decrease in 400-mg/kg females). The terminal body weights at 13 weeks' exposure were 250.6, 306.7, 333.4, 351.2, 353.4, and 348.9 g for males and 156.7, 190.5, 197.2, 203.5, 197.8, and 203.4 g for females for the 400, 200, 100, 50, 25, and 0 dose groups, respectively. Differences between mean values of hematological parameters in exposed groups and those in control groups were <10% of control values, except for a 94% increase in numbers of mature neutrophils and a 25.1% decrease in numbers of lymphocytes in male 400 mg/kg rats and a 37.2% increase in mature neutrophils in 400 mg/kg females. Due to a lack of a consistent pattern of change in the hematologic parameters, the observed changes are not considered adverse. Histological examinations revealed low incidences of lesions in exposed male kidneys and exposed female thymuses; no lesions were observed in respective control kidneys or thymuses. Focal cortical lymphocytic infiltration or focal tubular regeneration were observed in kidneys in 2/10 male rats exposed to 200 mg/kg naphthalene, and diffuse renal tubular degeneration occurred in 1/10 male rats exposed to 400 mg/kg naphthalene. Lymphoid depletion of the thymus occurred in 2/10 females exposed to 400 mg/kg naphthalene, but not in any other females or in males. No other tissue lesions were detected. In this study, 100 mg/kg/day was a NOAEL, 200 mg/kg/day was a LOAEL, and 400 mg/kg/day was a serious LOAEL for decreased body weight in rats orally exposed to naphthalene for 13 weeks.

NTP. 1980a. Subchronic toxicity study: Naphthalene (C52904), B6C3F1 mice. Research Triangle Park, NC: U.S. Department of Health and Human Services, National Toxicology Program.

Ten male and 10 female B6C3F1 mice were administered gavage doses of naphthalene in corn oil at levels of 0, 12.5, 25, 50, 100, or 200 mg/kg, 5 days/week for 13 weeks (NTP 1980a). Seven mice (three males and two females of the 200 mg/kg group, one female of the 25 mg/kg group, and one control male) died during the second, third, and fourth weeks from gavage trauma or accident. Transient signs of

toxicity (lethargy, rough hair coats, and decreased food consumption) occurred between weeks 3 and 5 in the 200-mg/kg groups. Due to their transient nature, these effects are not considered to be adverse. All exposed male mice gained more weight during the study than did control males (weight gains expressed as a percentage of control weight gain were 154.3, 116.0, 125.9, 122.2, and 107.4 for the 12.5–200 mg/kg groups, respectively). In contrast, exposed female mice displayed decreased weight gain compared with controls (weight gains expressed as a percentage of control weight gain were 97.5, 81.5, 81.5, 77.8, and 76.5% for the 12.5–200 mg/kg groups, respectively). The average change in body weight between day 0 and the 13th week was 6.2 g/mouse for the 200-mg/kg female mice compared with 8.1 g/mouse for the control females. The investigators believed that a difference in weight gain of 1.9 g over a 13-week period "was not large enough to conclusively indicate a toxic effect." Respective mean terminal body weights (g) for control through the 200-mg/kg group were: 33.2, 37.7, 34.7, 34.7, 36.0, and 34.7 for males, and 26.7, 26.8, 25.4, 26.0, 26.1, and 25.6 for females. Mean terminal body weight values in exposed females were ≥95% of control values.

All mice were necropsied, and 27 organs (including the eyes, thymus, reproductive organs, and lungs) from the mice in the control and high-dose groups were examined histologically. No exposure-related lesions were observed in any organs. The highest incidence of lesions observed was for minimal to mild, focal or multifocal, subacute pneumonia in both controls (4/10 males and 2/10 females) and high-dose mice (4/10 males and 5/10 females). Organ weight data were not reported. Hematological analyses were performed on all groups. Exposed groups displayed mean values that were within 10% of the control means for the following parameters: hemoglobin, hematocrit, total white blood cells, and total red blood cells. An increase in lymphocytes (18% increase) and a decrease in segmented neutrophils (38.8% decrease) in high-dose males were not considered biologically significant by the authors. The highest dose in this study, 200 mg/kg/day, is judged to be a NOAEL for nonneoplastic lesions, hematologic changes, and adverse neurologic symptoms.

Shopp GM, White KL JR, Holsapple MP, et al. 1984. Naphthalene toxicity in CD-1 mice: General toxicology and immunotoxicology. Fundam Appl Toxicol 4:406-419.

Groups of male and female albino CD-1 mice (approximately 6 weeks old at the start) were administered gavage doses of 0, 5.3, 53, or 133 mg/kg naphthalene (99.3% pure) in corn oil for 90 consecutive days (Shopp et al. 1984). A naive control group and the 5.3 and 53 mg/kg dose groups each contained 76 male mice and 40 female mice. The vehicle control group contained 112 male mice and 76 female mice. The high-dose group contained 96 male mice and 60 female mice. Statistical analysis consisted of a one-way analysis of variance of means and Dunnett's t-test to compare control and treatment means using a significance level of $p<0.05$. Statistically significant chemical-related decreases in terminal body weights or survival were not observed in either sex. Respective mean terminal body weight values were (naïve, vehicle, 5.3, 53, and 133 mg/kg/day groups): 39.3, 37.3, 37.2, 36.2, and 36.8 g for male mice and 29.2, 29.0, 27.9, 27.0, and 27.1 g for female mice. No significant alterations in absolute or relative organ weights occurred in exposed male mice. Significant decreases in absolute weights of brain (9%), liver (18%), and spleen (28%) and relative weight of spleen (24%) occurred in high-dose females compared with controls. Histopathological examination of organs was not conducted, but the authors noted that cataracts were not formed in exposed mice (methods used to assess the presence of cataracts were not specified).

Examination of hematological parameters (including numbers of leucocytes, erythrocytes, and platelets and determination of hematocrit and hemoglobin) at termination revealed only slight, but statistically significant, increases in hemoglobin in high-dose females only; however, the hematological data were not shown in the available report. Chemical analysis of serum showed statistically significant decreased blood urea nitrogen in all exposed female groups. Compared with vehicle controls, the percent decreases in BUN were 16, 20, and 34% for the 5.3, 53, and 133 mg/kg/day groups, respectively. Increased serum

globulin (about 55%) and protein (about 40%) occurred in the two highest female dose groups compared with vehicle control values. Hepatic microsomal activities of aniline hydroxylase and aminopyrine N-demethylases were not statistically significantly changed in exposed versus control mice, but benzo[a]pyrene hydroxylase activities were statistically significantly decreased in exposed groups compared with control values (0.8, 0.62*, 0.55* and 0.41* nmol/min/mg protein for males in the control through high-dose group, and 1.40, 1.24, 1.13*, and 0.89* nmol/min/mg protein for females; statistically significant differences from control noted with *). The toxicological significance of the statistically significant changes in hematological parameters, hepatic enzyme activities, and serum chemical parameters is not clear, and these changes are not considered to be adverse.

No exposure-related responses were found in a battery of immunological assays (humoral immune response, lymphocyte responsiveness, delayed-type hypersensitivity response, popliteal lymph node response, and bone marrow function); immunotoxic responses were observed in positive controls given intraperitoneal injections of 50 mg/kg cyclophosphamide on days 87, 88, 89, and 90. The study identified a LOAEL of 133 mg/kg/day and a NOAEL of 53 mg/kg/day for statistically significant decreases in absolute weight of brain, liver, and spleen and relative weight of spleen in female mice, but not male mice. The biological significance of these changes, however, is uncertain because the effects were only observed in female mice, and histological changes in these organs were not observed in Fischer 344 rats (NTP 1980b) or B6C3F1 mice (NTP 1980a) exposed to naphthalene for 13 weeks.

Intermediate-Duration Oral MRL Derivation Considerations

The findings from the three intermediate-duration oral toxicity studies (one in rats and two in mice) do not collectively identify a clear, biologically significant, toxicity target other than body weight changes in rats. Consideration was given to basing the MRL on the NOAEL of 53 mg/kg/day and LOAEL of 133 mg/kg/day for decreases in absolute weight of brain, liver, and spleen, and in relative weight of spleen, in female mice (Shopp et al. 1984). However, the biological significance of these effects is uncertain because (1) small changes in organ weights are difficult to consistently measure in mice; (2) the effects were only observed in females; and (3) histological effects in the affected organs were not observed in the other 13-week oral studies with rats and mice. The biological significance of these effects in female, but not male, mice was less clearly biologically significant than the naphthalene-induced body weight changes observed in male and female rats.

In deriving a potential intermediate-duration MRL, the NOAEL of 100 mg/kg/day for decreased body weight in male and female rats should be adjusted to a continuous duration dose (100x5 days/7 days=71 mg/kg/day). The use of this adjusted dose and a total uncertainty factor of 100 (10 for extrapolating from rats to humans and 10 for human variability) arrives at a potential intermediate-duration oral MRL of 0.7 mg/kg/day, which is slightly larger than the acute-duration oral MRL for naphthalene, 0.6 mg/kg/day. Thus, the acute-duration oral MRL of 0.6 mg/kg/day is expected to be protective for intermediate-duration exposure scenarios and was adopted as the intermediate-duration oral MRL.

Agency Contacts (Chemical Managers): Hisham El-Masri, Ph.D.; Moiz Mumtaz, Ph.D.; and G. Daniel Todd, Ph.D.

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: 1-Methylnaphthalene
CAS Number: 90-12-0
Date: June 2005
Profile Status: Final Post-Public Comment
Route: [ ] Inhalation [x] Oral
Duration: [ ] Acute [ ] Intermediate [x] Chronic
Graph Key: 46
Species: Mouse

Minimal Risk Level: 0.07 [x] mg/kg/day [ ] ppm

Reference: Murata Y, Denda A, Maruyama H, et al. 1993. Chronic toxicity and carcinogenicity studies of 1-methylnaphthalene in B6C3F1 mice. Fundam Appl Toxicol 21:44-51.

Experimental design: Groups of 50 B6C3F1 mice ingested the following doses (in mg/kg/day) over an 81-week period: 0 (M/F), 71.6 (M), 75.1 (F), 140.2 (M), and 143.7 (F). Tissues were examined histologically: brain, salivary glands, heart, thymus, lung, liver, pancreas, spleen, kidneys, testis, adrenals, trachea, stomach, small intestine, seminal vesicle, ovary, uterus, vagina, mammary gland, skeletal muscle, eye, Harderian glands, spinal cord, bone, and skin.

Effects noted in study and corresponding doses: Exposure-related lesions were restricted to the lung. Incidences for pulmonary alveolar proteinosis were (control through high-dose groups): 5/50, 23/50, and 17/49 for females and 4/49, 23/50, and 19/50 for males.

The only other exposure-related lesions found were lung tumors. Incidences for mice with adenomas were 4/50, 2/50, and 4/49 in females, and 2/49, 13/50, and 12/50 for males. Combined incidences for mice with lung adenomas or adenocarcinomas were: 5/50, 2/50, and 5/50 for females, and 2/49, 13/50, and 15/50 for males.

Dose and end point used for MRL derivation: Because the lowest exposure level was a LOAEL for increased incidence of alveolar proteinosis in male and female mice, benchmark dose analyses of the incidence data were conducted to determine a point of departure (POD) for the chronic-duration oral MRL. Available models in the EPA Benchmark Dose Software were fit to the incidence data for males and females, separately. None of the models provided adequate fit of the incidence data for females or for males, as assessed by chi-square goodness of fit statistics (p-values were <0.1). These results indicate that the data provide insufficient information to model the shape of the dose-response relationship. The lack of fit of the models to the data appears to be due to the apparent plateau of the response between the low- and high-dose levels. Thus, the LOAEL of 71.6 mg/kg/day for increased incidence of alveolar proteinosis in male mice was selected as the POD for the MRL.

[ ] NOAEL [x] LOAEL

Modifying Factors used in MRL derivation: N/A

Uncertainty Factors used in MRL derivation: Total Uncertainty Factor=10x10x10=1,000

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

Was a conversion used from ppm in food or water to a mg/body weight dose? If so, explain: Groups of 50 male and 50 female B6C3F1 mice were fed 0, 0.075, or 0.15% 1-methylnaphthalene (1-MN) in their diet for 81 weeks (567 days). Cumulative dose equivalents were provided by the investigators included: males: 0.075%=40,600 mg 1-MN/kg/body weight/567 days=71.6 mg/kg/day; 0.15%=79,500 mg 1-MN/kg/body weight/567 days=140.2 mg/kg/day; females: 0.075%=42,600 mg 1-MN/kg body weight/567 days=75.1 mg/kg/day; 0.15%=81,500 mg 1-MN/kg body weight/567 days=143.7 mg/kg/day.

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

Other additional studies or pertinent information which lend support to this MRL: Increased incidence of pulmonary alveolar proteinosis has also been reported in B6C3F1 mice exposed to 2-methylnaphthalene in the diet for 81 weeks at dose levels of 50–54 and 108–114 mg/kg/day (Murata et al. 1997), and in mice dermally exposed to 30 or 119 mg/kg of methylnaphthalene for 30–61 weeks (a mixture of 1- and 2-methylnaphthalene) (Emi and Konishi 1985; Murata et al. 1992).

Goodness-of-fit statistics [p-values for chi-square goodness of fit and the Akaike Information Criteria (AIC)] from the benchmark dose analyses of the incidence data for pulmonary alveolar proteinosis are summarized in the table below.

Table A-2. Goodness-of-fit Statistics From Benchmark Dose Analyses of Incidence Data for Male and Female Mice Exposed to 1-Methyl-naphthalene in the Diet for 81 Weeks (Murata et al. 1993).

	Male mouse data		Female mouse data	
Model	chi-square p-value	AIC	chi-square p-value	AIC
Log-logistic[b]	0.024	172.13	0.014	174.71
Gamma[a]	0.01	173.57	0.007	175.88
Multi-stage[c]	0.01	173.57	0.007	175.88
Quantal linear	0.01	173.57	0.007	175.88
Weibull[a]	0.01	173.57	0.007	175.88
Log-probit[b]	0.002	176.68	0.001	179.07
Probit	0.002	177.06	0.002	178.42
Logistic	0.001	177.45	0.002	178.71
Quantal quadratic	0.0002	181.03	0.0002	182.00

[a] = Restrict power >=1; [b] = Slope restricted to >1; [c] = Restrict betas >=0, Degree of polynomial = 1

Agency Contacts (Chemical Managers): Hisham El-Masri, Ph.D.; Moiz Mumtaz, Ph.D.; and G. Daniel Todd, Ph.D.

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: 2-Methylnaphthalene
CAS Number: 91-57-6
Date: June 2005
Profile Status: Final Post-Public Comment
Route: [ ] Inhalation [x] Oral
Duration: [ ] Acute [ ] Intermediate [x] Chronic
Graph Key: 47
Species: Mouse

Minimal Risk Level: 0.04 [x] mg/kg/day [ ] ppm

Reference: Murata Y, Denda A, Maruyama H, et al. 1997. Chronic toxicity and carcinogenicity studies of 2-methylnaphthalene in B6C3F1 mice. Fundam Appl Toxicol 36(1):90-93.

Experimental design: Groups of 50 male and 50 female B6C3F1 mice were exposed to dietary levels of 0, 0.075, or 0.15% 2-MN for 81 weeks. Average intakes were reported as 0, 54.3, or 113.8 mg/kg/day for males and 0, 50.3, or 107.6 mg/kg/day for females.

Effects noted in study and corresponding doses: Survival and food consumption were not affected by exposure. Mean final body weights were decreased by 7.5 and 4.5% in high-dose males and females, respectively; these changes are not considered to be biologically significant. Histopathology only found exposure-related changes in the lung. Tissues examined were brain, heart, kidney, liver, lung, pancreas, salivary glands, spleen, testis, adrenals, bone, eye, Harderian glands, mammary gland, ovary, seminal vesicle, skeletal muscle, skin, small and large intestine, spinal cord, stomach, trachea, uterus, and vagina. No evidence of bronchiolar Clara cell necrosis or sloughing was found. Females showed statistically significantly decreased differential counts of stab and segmented form neutrophils and increased lymphocytes compared to controls, but biological significance of these changes is not clear due to a lack of reporting of the data (i.e., the report did not specify the response magnitudes or the dose levels at which they occurred).

Incidences for mice with pulmonary alveolar proteinosis were (control through high-dose groups): 5/50, 27/49, and 22/48 for females, and 4/49, 21/49, and 23/49 for males.

Incidences for mice with lung adenomas were: 4/50, 4/49, and 5/48 in females, and 2/49, 9/49, and 5/49 in males. Only the incidence in the male 54.3-mg/kg/day groups was significantly different from the control incidence. Combined incidences for lung adenomas or adenocarcinomas were: 5/50, 4/49, and 6/48 for females, and 2/49, 10/49, and 6/49 for males.

Dose and end point used for MRL derivation: Because the lowest exposure level was a LOAEL for increased incidence of alveolar proteinosis in male and female mice, benchmark dose (BMD) analyses of the incidence data were conducted to determine a point of departure (POD) for the chronic-duration oral MRL. Available models in the EPA Benchmark Dose Software were fit to the incidence data for males and females, separately. None of the models provided adequate fit of the incidence data for females, as assessed by chi-square goodness of fit statistics (p-values were <0.1). These results indicate that the female data provide insufficient information to model the shape of the dose-response relationship. The apparent plateau of the response between the low- and high-dose levels appears to contribute to the lack of fit of the models to the data. In contrast, the log-logistic and multi-stage models provided marginally adequate fits (p-values >0.1) to the male data, showing p-values of 0.23 and 0.11, respectively, for the chi-square goodness-of-fit statistic (Table A-3). The fitting algorithms for the gamma, quantal-linear, and

Weibull models provided identical model parameters and fit statistics as the multi-stage model. The Akaike Information Criteria (AIC) for the log-logistic model was lower than that for the multi-stage model indicating a better fit; thus the log-logistic model of the male data was selected to calculate the BMD POD for the MRL.

A benchmark response of 5% extra risk was selected over a default value of 10% extra risk in order to provide protection for children who may develop pulmonary alveolar proteinosis. This selection is supported by reports that children with pulmonary alveolar proteinosis (albeit of unknown etiology) experience more severe symptoms of respiratory dysfunction than do adults (EPA 2003r; Mazzone et al. 2001).

To derive the MRL of 0.04 mg/kg/day, the $BMDL_{05}$ of 4.3 mg/kg/day was divided by an uncertainty factor of 100 (10 for extrapolation from mice to humans and 10 for human variability).

An alternative NOAEL/LOAEL approach arrives at a similar value for the MRL. In the alternative approach, the LOAEL of 50.3 mg/kg/day for pulmonary alveolar proteinosis in female mice would be divided by an uncertainty factor of 1000 (10 for extrapolation from mice to humans, 10 for human variability, and 10 for extrapolation from a LOAEL to a NOAEL), arriving at a value of 0.05 mg/kg/day.

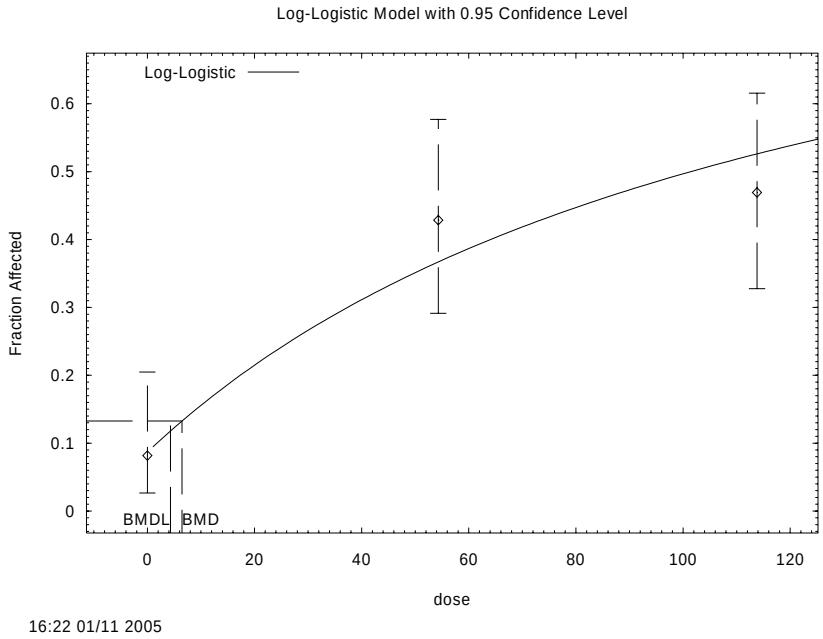
Table A-3. Benchmark Doses and Goodness-of-Fit Statistics from Modeling of Incidence Data for Pulmonary Alveolar Proteinosis in Male Mice Exposed to 2-Methylnaphthalene in the Diet for 81 Weeks (Murata et al. 1997)

	Benchmark doses (mg/kg/day)		Goodness-of-fit statistics	
Model	BMD (ED05)	BMDL (LED05)	chi-square p-value	AIC
Log-logistic[b]	6.47	4.30	0.23	167.81
Gamma[a]	8.76	6.4	0.11	168.93
Multi-stage[c]	8.76	6.4	0.11	168.93
Quantal linear	8.76	6.4	0.11	168.93
Weibull[a]	8.76	6.4	0.11	168.93
Log-probit[b]	20.92	15.95	0.03	170.99
Probit	17.23	13.8	0.01	172.4
Logistic	18.43	14.62	0.01	172.84
Quantal quadratic	32.73	26.51	0.001	175.87

[a] = Restrict power >=1; [b] = Slope restricted to >1; [c] = Restrict betas >=0, Degree of polynomial = 1

BMD(ED05) = predicted benchmark dose associated with 5% extra risk; BMDL (LED05) = 95% lower confidence limit on benchmark dose associated with 5% extra risk

Figure A-1. Observed and Predicted Incidence of Pulmonary Alveolar Proteinosis in Male Mice Exposed to 2-Methylnaphthalene in the Diet for 81 Weeks (Murata et al. 1997): Log-Logistic Model BMD=ED_{05}; BMDL=LED_{05}



Observed and predicted incidences of olfactory epithelial neuroblastomas in male rats exposed to naphthalene: Weibull model. BMD=EC_{10}; BMDL=LEC_{10}; dose unit= ppm.

[ ] NOAEL [ ] LOAEL [x] BMDL =

Modifying Factors used in MRL derivation: N/A

Uncertainty Factors used in MRL derivation: Total Uncertainty Factor=10x10=100

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

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

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

Other additional studies or pertinent information which lend support to this MRL: Increased incidence of pulmonary alveolar proteinosis has also been reported in B6C3F1 mice exposed to 1-methylnaphthalene in the diet for 81 weeks at dose levels as low as 71.6 mg/kg/day (Murata et al. 1993), and in mice dermally exposed to 30 or 119 mg/kg of methylnaphthalene for 30–61 weeks (a mixture of 1- and 2-methylnaphthalene) (Emi and Konishi 1985; Murata et al. 1992).

In a range-finding study, groups of B6C3F1 mice (10/sex/group) were fed diets containing 2-methylnaphthalene for 13 weeks delivering approximate average daily doses of 0, 31, 92, 276, 827, or 2,500 mg/kg/day (Murata et al. 1997). No histopathologic lesions were found in tissues and organs of male or female mice exposed to 827 or 2,500 mg/kg-day; tissues from mice in lower dose groups were not examined histologically. Decreased body weights, compared with control values, were seen at the three highest dose levels in both males and females, and were attributed to food refusal (Murata et al. 1997). The absence of pulmonary alveolar proteinosis in the prechronically exposed mice, which were exposed to much higher doses than those experienced by mice with this lesion in the chronic study, suggests that the development of pulmonary alveolar proteinosis from oral exposure to 2-methylnaphthalene requires chronic-duration exposure. The limited reporting of experimental details and results from this intermediate-duration study, however, precludes its use as the basis of an intermediate oral MRL for 2-methylnaphthalene.

The EPA (2003r) Toxicological Review of 2-Methylnaphthalene calculated an oral exposure RfD of 0.004 mg/kg-day for 2-methylnaphthalene based on a value of 3.5 mg/kg-day for a 95% lower confidence limit on a benchmark dose associated with 5% extra risk ($BMDL_{05}$) for pulmonary alveolar proteinosis in mice exposed to 2-methylnaphthalene in the diet for 81 weeks (Murata et al. 1992). The combined incidence data for this lesion in male and female mice in the control and low-dose groups were modeled with the quantal-linear model algorithm in the BMDS software (the high-dose data were excluded from the analysis, because when they were included adequate fit of models to the data were not obtained). A total uncertainty factor of 1,000 was used to derive the RfD: 10 for interspecies variability, 10 for interindividual variability, and 10 for database deficiencies.

Agency Contacts (Chemical Managers): Hisham El-Masri, Ph.D.; Moiz Mumtaz, Ph.D.; and G. Daniel Todd, Ph.D.

APPENDIX B. USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public, especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Relevance to Public Health

This chapter provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions:

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The chapter covers end points in the same order 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 judgment, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgment 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

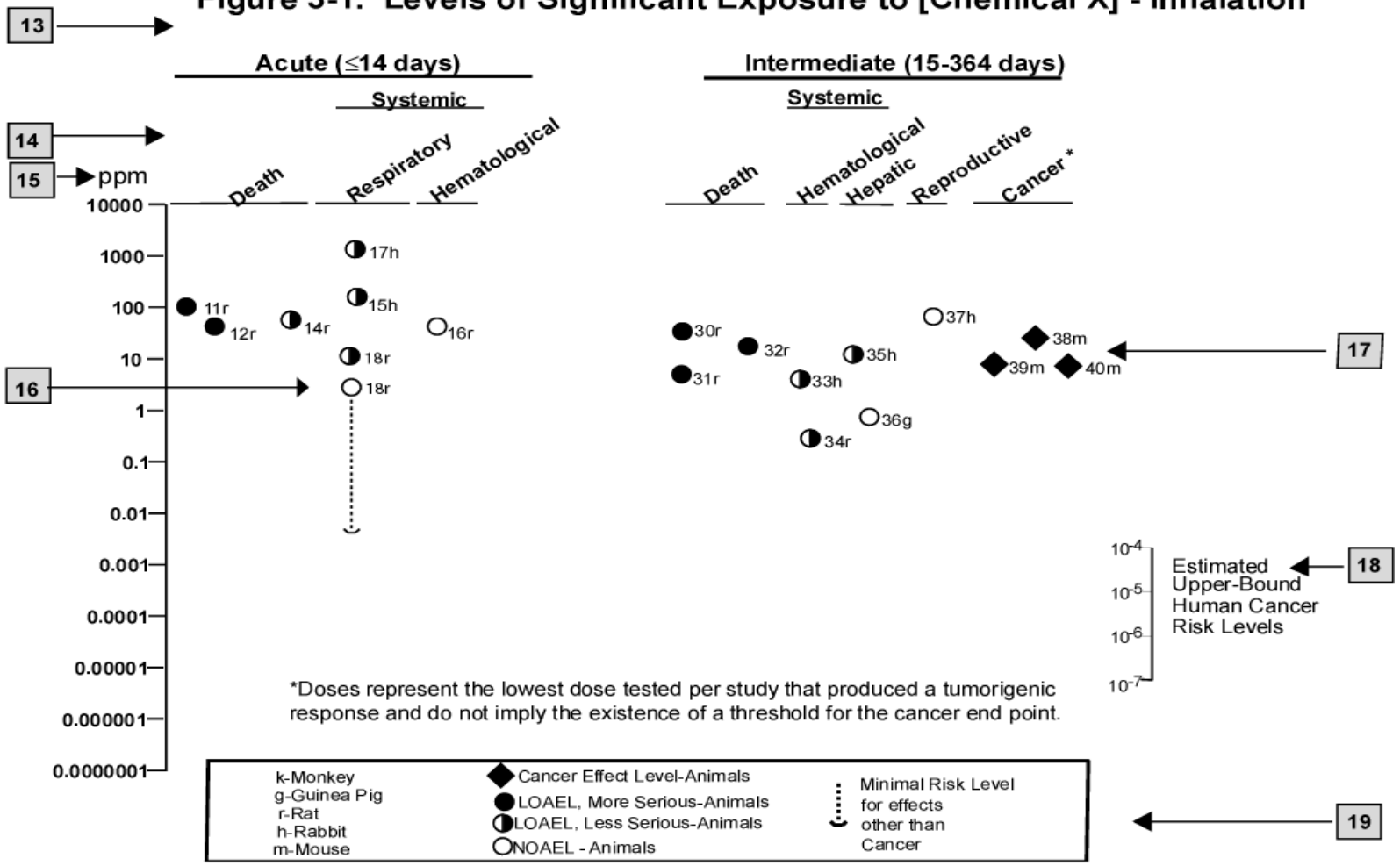
1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

	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



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/International Maritime Dangerous Goods Code
DWEL	drinking water exposure level
ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F_1	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
FR	Federal Register
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
ILO	International Labor Organization
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
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

APPENDIX D. INDEX