

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

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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.

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MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Aluminum
CAS Numbers: 7429-90-5
Date: June 2008
Profile Status: Final
Route: Inhalation Oral
Duration: Acute Intermediate Chronic
Graph Key: 46
Species: Mouse

Minimal Risk Level: 1 mg/kg/day ppm

Reference: Golub MS, Germann SL. 2001. Long-term consequences of developmental exposure to aluminum in a suboptimal diet for growth and behavior in Swiss Webster mice. *Neurotoxicol Teratol* 23:365-372.

Experimental design: Groups of pregnant Swiss Webster mice were exposed to 0, 100, 500, or 1,000 mg Al/kg diet on gestational days 0–21 and during lactation until day 21. On PND 21, one male and one female pup from each litter were placed on the same diet as the dam. The offspring were exposed until PND 35. The composition of the diet was modified from the National Research Council's recommendations; the investigators noted that the nutrients were reduced to correspond to the usual intake of these nutrients by young women. The average daily intakes of phosphorus, calcium, magnesium, iron, and zinc in women aged 18–24 years are 83, 56, 71, 69, and 67% of the RDA; these percents were used to modify the recommended dietary intake for the mice used in this study. Doses of 26, 130, and 260 mg Al/kg/day are calculated by averaging reported estimated doses of 10, 50, and 100 mg Al/kg/day for adults (i.e., at beginning of pregnancy) and 42, 210, and 420 mg Al/kg/day maximal intake during lactation. The doses at lactation were calculated using doses estimated in previous studies with similar exposure protocols performed by the same group of investigators (Golub et al. 1995). At 3 months of age, the females were tested for neurotoxicity using the Morris water maze. At 5 months of age, males were tested for motor activity and function using rotarod, grip strength, wire suspension, mesh pole descent, and beam traversal tests.

Effect noted in study and corresponding doses: No alterations in pregnancy weight gain or pup birth weights were observed. At PND 21, significant decreases in pup body weights were observed at 130 and 260 mg/kg/day. No information on maternal weight gain during lactation was reported; however, the investigators noted that the decrease in pup weight was not associated with reduced maternal food intake. At PND 35, the decrease in body weight was only significant at 260 mg/kg/day. On PND 90, female mice in the 260 mg/kg/day group weighed 15% less than controls. Decreases in heart and kidney weights were observed at 260 mg/kg/day in the females. Also, decreases in absolute brain weight were observed in females at 260 mg/kg/day and relative brain weights were observed at 26 or 260 mg/kg/day. In the males, significant decreases in body weight were observed at 130 (10%) and 260 (18%) mg/kg/day at 5 months; an increase in food intake was also observed these doses. In the Morris maze (tested at 3 months in females), fewer animals in the 260 mg/kg/day group had escape latencies of <60 seconds during sessions 1–3 (learning phase) and a relocation of the visible cues resulted in increased latencies at 130 and 260 mg/kg/day. Body weight did not correlate with latency to find the platform or with the distribution of quadrant times. The investigators concluded that controls used salient and/or nonsalient cues, 26 and 130 mg/kg/day animals used both cues, but had difficulty using only one cue, and 260 mg/kg/day animals only used the salient cues. In the males tested at 5 months, a significant decrease in hindlimb grip strength was observed at 260 mg/kg/day, an increase in the number of rotations on the rotarod as observed at 260 mg/kg/day, and a shorter latency to fall in the wire suspension test as was

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observed at 130 and 260 mg/kg/day. The investigators noted that there were significant correlations between body weight and grip strength and number of rotations. When hindlimb grip strength was statistically adjusted for body weight, the aluminum-exposed mice were no longer significantly different from controls.

Reference: Colomina MT, Roig JL, Torrente M, et al. 2005. Concurrent exposure to aluminum and stress during pregnancy in rats: effects on postnatal development and behavior of the offspring. *Neurotoxicol Teratol* 27:565-574.

Experimental design: Groups of female Sprague-Dawley rats were exposed to 0, 50, or 100 mg Al/kg/day aluminum nitrate nonahydrate in drinking water; citric acid (710, 355, and 710 mg/kg/day in the control, 50, and 100 ppm groups, respectively) was added to the drinking water to increase aluminum absorption. The adult rats were exposed to aluminum for 15 days prior to mating and the during gestation and lactation periods; after weaning, the pups were exposed to the same aluminum concentration as the mothers from postnatal day 21 through 68. The basal diet (Panlab rodent chow) contained 41.85 µg Al/g diet. Aluminum doses were calculated by adding the basal dietary aluminum doses (calculated using reference values for mature Sprague-Dawley rats) to reported aluminum doses from water; the total aluminum doses were 3, 53, and 103 mg Al/kg/day. In addition to aluminum exposure, some animals in each group underwent restraint stress for 2 hours/day on gestation days 6–20; the restraint consisted of placing the rats in cylindrical holders. The following neurobehavioral tests were performed on the offspring: righting reflex (PNDs 4, 5, 6), negative geotaxis (PNDs 7, 8, 9), forelimb grip strength (PNDs 10–13), open field activity (PND 30), passive avoidance (PND 35), and water maze (only tested at 53 mg/kg/day on PND 60). On PND 68, rats were killed and aluminum levels were measured in the cortex, hippocampus, striatum, cerebellum, and brainstem.

Effect noted in study and corresponding doses: No significant alterations in body weight, food consumption, or water consumption were observed during gestation in the dams exposed to aluminum. The investigators noted that decreases in water and food consumption were observed during the lactation period in the rats exposed to 103 mg Al/kg/day, but the data were not shown, and maternal body weight during lactation was not mentioned. No significant alterations in the number of litters, number of fetuses per litter, viability index, or lactation index were observed. Additionally, no differences in days at pinna detachment or eye opening were observed. Age at incisor eruption was significantly higher in males exposed to 53 mg/kg/day, but not in males exposed to 103 mg/kg/day or in females. A significant delay in age at testes descent was observed at 103 mg/kg/day and vagina opening was delayed at 53 and 103 mg/kg/day. A decrease in forelimb grip strength was observed at 103 mg/kg/day; no alterations in other neuromotor tests were observed. Additionally, no alterations in open field behavior or passive avoidance test were observed. In the water maze test, latency to find the hidden platform was decreased in the 53 mg/kg/day group on test day 2, but not on days 1 or 3; no significant alteration in time in the target quadrant was found.

Dose and end point used for MRL derivation: The Golub and Germann (2001) and Colomina et al. (2005) studies identify four end points that could be used as the point of departure for derivation of the intermediate-duration oral MRL:

- (1) latency to fall off wire in wire suspension test; adverse effect level of 130 mg Al/kg/day, no effect level of 26 mg Al/kg/day (Golub and Germann 2001);
- (2) latency to locate the platform following cue relocation in the water maze test; adverse effect level of 130 mg Al/kg/day, no effect level of 26 mg Al/kg/day (Golub and Germann 2001);
- (3) decreased forelimb grip strength; adverse effect level of 103 mg Al/kg/day, no effect level of 53 mg Al/kg/day (Colomina et al. 2005); and

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- (4) delay in vagina opening; adverse effect level of 53 mg Al/kg/day, no effect level not identified (Colomina et al. 2005).

Benchmark dose modeling was considered for each of these end points. Continuous variable models in the EPA Benchmark Dose Software (BMDS version 1.3.2) were fit to the data. A change of 1 standard deviation from control was selected as the BMR. Benchmark dose modeling was not conducted for latency to fall from the wire and forelimb grip strength because it is unclear whether the data reported in Table 5 (Golub and Germann 2001) and Figure 2 (Colomina et al. 2005), respectively, was for the mean \pm SEM or the mean \pm standard deviation. For delay in maturation, none of the available models provided an adequate fit (as assessed by the p-values for variance); therefore, the data set is unsuitable for BMD modeling. For the change in the latency to find the platform, the constant variance linear model provided an adequate fit. However, the BMD (419 mg Al/kg/day) and BMDL (186 mg Al/kg/day) were higher than the dose at which the change in latency was statistically significant (130 mg Al/kg/day), suggesting that using the change of 1 standard deviation from controls may not be an appropriate BMR for these data.

Using a NOAEL/LOAEL approach, the NOAEL of 26 mg Al/kg/day identified in the Golub and Germann (2001) study was selected as the point of departure for the MRL.

NOAEL LOAEL

Uncertainty Factors used in MRL derivation:

- 10 for use of a LOAEL
 10 for extrapolation from animals to humans
 10 for human variability

Modifying Factors used in MRL derivation:

- 0.3 to account for possible differences in the bioavailability of the aluminum lactate used in the Golub and Germann (2001) study and the bioavailability of aluminum from drinking water and a typical U.S. diet.

No studies were identified that estimated the bioavailability of aluminum lactate following long-term dietary exposure; however, a bioavailability of 0.63% was estimated in rabbits receiving a single dose of aluminum lactate (Yokel and McNamara 1988). Yokel and McNamara (2001) and Powell and Thompson (1993) suggested that the bioavailability of aluminum from the typical U.S. diet was 0.1%; the bioavailability of aluminum from drinking water ranges from 0.07 to 0.39% (Hohl et al. 1994; Priest et al. 1998; Stauber et al. 1999; Steinhausen et al. 2004). These data suggest that aluminum lactate has a higher bioavailability than aluminum compounds typically found in drinking water or the diet.

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Golub and Germann (2001): Doses of 26, 130, and 260 mg Al/kg/day are calculated by averaging reported estimated doses of 10, 50 and 100 mg Al/kg/day for adults (i.e., at beginning of pregnancy), and 42, 210, and 420 mg Al/kg/day maximal intake during lactation. The doses at lactation were calculated using doses were estimated in previous studies with similar exposure protocols performed by the same group of investigators (e.g., Golub et al. 1995).

Colomina et al. (2005): Doses of 3, 53, and 103 mg Al/kg/day were calculated by adding the basal dietary aluminum doses (calculated using reference values for mature Sprague-Dawley rats) to reported aluminum doses from water.

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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: The neurotoxicity and neurodevelopmental toxicity of aluminum are well-documented effects of aluminum in orally-exposed in mice and rats. A wide variety of behavioral tests were conducted in rats and mice; alterations in motor function were the most consistently observed effects. Decreases in forelimb and/or hindlimb grip strength have been observed in adult mice exposed to 195 mg Al/kg/day as aluminum lactate in the diet for 90 days (Golub et al. 1992b), mice (6 weeks of age at study beginning) exposed to 195 mg Al/kg/day as aluminum lactate in the diet for 5–7 weeks (Oteiza et al. 1993), the offspring of mice exposed on gestation day 1 through lactation day 21 to 155 mg Al/kg/day (Donald et al. 1989; Golub et al. 1995) or 250 mg Al/kg/day (Golub et al. 1995) as aluminum lactate, and the offspring of rats exposed to 103 mg Al/kg/day as aluminum nitrate in drinking water (with added citric acid) for 15 days prior to mating and on gestation day 1 through lactation day 21 (Colomina et al. 2005). Decreases in spontaneous motor activity were observed in mice exposed to 130 mg Al/kg/day for 6 weeks (Golub et al. 1989) or 195 mg Al/kg/day for 90 days (Golub et al. 1992b). Motor impairments have also been detected in mice in the wire suspension test in which offspring exposed to 130 mg Al/kg/day had a shorter latency to fall from the wire and in the rotorod test in which offspring exposed to 260 mg Al/kg/day had a higher number of rotations (which occur when the animals lost its footing, clung to the rod, and rotated with it for a full turn) (Golub and Germann 2001). Neurobehavioral alterations that have occurred at similar dose levels include decreased responsiveness to auditory or air-puff startle (Golub et al. 1992b, 1995), decreased thermal sensitivity (Golub et al. 1992a), increased negative geotaxis latency (Golub et al. 1992a), and increased foot splay (Donald et al. 1989). Additionally, one study found significant impairment in performance of the water maze test in offspring of mice exposed to 130 mg Al/kg/day on gestation day 1 through lactation day 21 (Golub and Germann 2001). Colomina et al. (2005) did not find alterations in this test in rats exposed to 53 mg Al/kg/day; however, this study did not run probe tests, which showed significant alterations in the Golub and Germann (2001) study. Other studies have utilized passive avoidance tests or operant training tests to evaluate potential impairment of cognitive function. However, the interpretation of the results of these tests is complicated by an increase in food motivation in aluminum exposed mice (Golub and Germann 1998).

In addition to the neurodevelopmental effects, there is also strong evidence that gestational and/or lactational exposure can cause other developmental effects. Aluminum does not appear to result in an increase in the occurrence of malformations and anomalies and does not typically affect birth weight. Gestation and/or lactation exposure can result in significant decreases in pup body weight gain in rats and mice (Colomina et al. 2005; Golub and Germann 2001; Golub et al. 1992a). The decreases in pup body weight are often associated with decreases in maternal body weight during the lactation phase of the study; however, decreases in body weight have also been observed in a cross-fostering study when gestation-exposed pups were nursed by control mice (Golub et al. 1992a). Other studies involving gestation and lactation exposure to aluminum did not find changes in pup growth in mice (Donald et al. 1989; Golub and Germann 1998; Golub et al. 1995). In rats, a delay in physical maturation, particularly delays in vagina opening, testes descent, and incisor eruption, has been reported at 53 mg Al/kg/day (Colomina et al. 2005).

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MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Aluminum
CAS Numbers: 7429-90-5
Date: June 2008
Profile Status: Final
Route: Inhalation Oral
Duration: Acute Intermediate Chronic
Graph Key: 56
Species: Mouse

Minimal Risk Level: 1 mg/kg/day ppm

Reference: Golub MS, Germann SL, Han B, et al. 2000. Lifelong feeding of a high aluminum diet to mice. *Toxicology* 150:107-117.

Experimental design: Groups of 8 male and 10 female Swiss Webster mice were exposed to 7 or 1,000 $\mu\text{g Al/g}$ diet as aluminum lactate in a purified diet. The investigators estimated adult doses of <1 and 100 mg/kg/day. The mice were exposed to aluminum from conception (via feeding the dams) through 24 months of age. Body weight, food intake, and clinical signs were determined during the last 6 months of the study. Neurobehavioral test battery (foot splay, temperature sensitivity, negative geotaxis, and grip strength), 1 hour spontaneous activity, and auditory startle tests were conducted at 18 and 24 months.

In a companion study, groups of 6–9 male and female Swiss Webster mice or 7 male and female C57BL/6J mice (number per sex were not reported) were exposed to 7 or 1,000 $\mu\text{g Al/g}$ diet as aluminum lactate in a purified diet (<1 and 100 mg/kg/day) from conception (via feeding the dams) through 24 months of age. Body weight, food intake, and clinical signs were determined during the last 6 months of the study. Neurobehavioral test battery (foot splay, temperature sensitivity, negative geotaxis, and grip strength) and Morris maze testing were at 22–23 months of age.

Effect noted in study and corresponding doses: In the principal study, no significant alterations in mortality were observed. A significant decrease in body weight was observed in the female mice (approximately 20%). In the males, there was a significant increase in body weight (approximately 10%). No significant alterations in food intake were observed in either sex. However, food intake/g body weight was significantly higher in the aluminum exposed mice. No significant alterations in the occurrence of clinical signs or indications of neurodegenerative syndromes were found. Significant increases in relative spinal cord, heart, and kidney weights were found. Significant alterations in negative geotaxis and tail withdrawal time in the temperature sensitivity test (males only) were observed at 18 months. At 24 months, significant alterations in forelimb and hindlimb grip strength and temperature sensitivity were found in male and female mice. Forelimb and hindlimb grip strength was decreased and thermal sensitivity was decreased, as evidenced by an increase in tail withdrawal times. Auditory startle response tests could not be completed in the older mice. Similarly, vertical spontaneous movement could not be measured; no effect on horizontal movement was found.

In the companion study, no alterations in neurobehavioral battery test performance were observed; the investigators note that this may be due to the small number of animals per group. In general, aluminum-exposed mice performed better on the water maze test than controls.

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Dose and end point used for MRL derivation: A LOAEL of 100 mg Al/kg/day for decreased forelimb and hindlimb grip strength and decreased thermal sensitivity. A benchmark dose approach for deriving an MRL was not utilized because the Golub et al. (2000) study only tested one aluminum group.

[] NOAEL [X] LOAEL

Uncertainty Factors used in MRL derivation:

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

Modifying Factors used in MRL derivation:

- [X] 0.3 to account for possible differences in the bioavailability of the aluminum lactate used in the Golub and Germann (2001) study and the bioavailability of aluminum from drinking water and a typical U.S. diet.

No studies were identified that estimated the bioavailability of aluminum lactate following long-term dietary exposure; however, a bioavailability of 0.63% was estimated in rabbits receiving a single dose of aluminum lactate (Yokel and McNamara 1988). Yokel and McNamara (2001) and Powell and Thompson (1993) suggested that the bioavailability of aluminum from the typical U.S. diet was 0.1%; the bioavailability of aluminum from drinking water ranges from 0.07 to 0.39% (Hohl et al. 1994; Priest et al. 1998; Stauber et al. 1999; Steinhausen et al. 2004). These data suggest that aluminum lactate has a higher bioavailability than aluminum compounds typically found in drinking water or the diet.

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No (doses corresponding to food ppm levels were reported by investigators).

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: A small number of animal studies examined the chronic toxicity of aluminum. Schroeder and Mitchener (1975a, 1975b) examined the systemic toxicity of aluminum following lifetime exposure of rats and mice to very low doses of aluminum sulfate in the drinking water. Although the levels of aluminum in diet were not reported, they are assumed to be low because the animals were fed a low-metal diet in metal-free environmental conditions. Studies conducted by Roig et al. (2006) and Golub et al. (2000) primarily focused on the neurotoxicity of aluminum following lifetime exposure (gestation day 1 through 24 months of age). In the Golub et al. (2000) study, significant decreases in forelimb and hindlimb grip strength, and a decrease in thermal sensitivity were observed in mice exposed to 100 mg Al/kg/day; negative geotaxis was significantly altered at 18 months, but not at 24 months. No effect on horizontal activity was observed. A 10% increase in body weight and a 20% decrease in body weight were observed in the males and females, respectively. In a companion study by this group, no significant cognitive impairments were found in the Morris water maze test; in fact, aluminum-exposed mice performed better than controls in the learning tasks. Roig et al. (2006) also found no significant alterations in performance on the Morris water maze in rats exposed to 100 mg Al/kg/day as aluminum nitrate in the drinking water (with added citric acid). Although significant differences were found between the two aluminum groups

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(50 and 100 mg Al/kg/day), this was primarily due to the improved performance (as compared to controls, no significant differences) in the 50 mg Al/kg/day group. Roig et al. (2006) also found no significant alterations in open field activity.

Additional support for the selection of these end points, and neurotoxicity in general, comes from a number of intermediate-duration studies that indicate that this is one of most sensitive targets of aluminum toxicity (Colomina et al. 2005; Donald et al. 1989; Golub and Germann 2001; Golub et al. 1992a, 1995).

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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.

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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.

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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").

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- (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/m³ 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.

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

SAMPLE

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

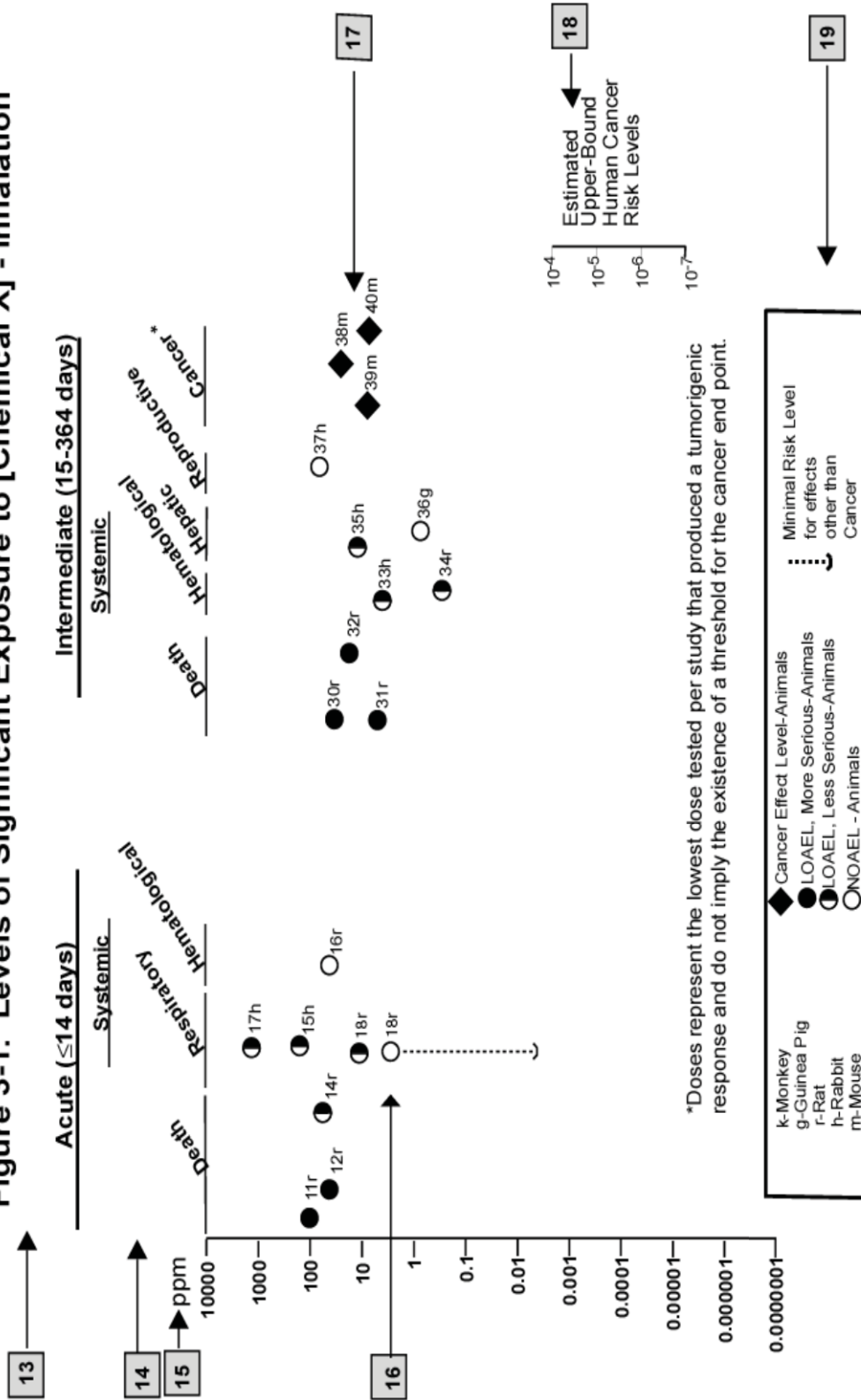
Key to figure ^a	Species	Exposure frequency/duration	System	NOAEL (ppm)	LOAEL (effect)			Reference
					Less serious (ppm)	Serious (ppm)		
1 →								
2 →	INTERMEDIATE EXPOSURE							
3 →	Systemic	↓	↓	↓	↓	↓	↓	↓
5		↓	↓	↓	↓	↓	↓	↓
6		↓	↓	↓	↓	↓	↓	↓
7		↓	↓	↓	↓	↓	↓	↓
8		↓	↓	↓	↓	↓	↓	↓
9		↓	↓	↓	↓	↓	↓	↓
10		↓	↓	↓	↓	↓	↓	↓
18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3 ^b	10 (hyperplasia)			Nitschke et al. 1981
4 →								
	CHRONIC EXPOSURE							
	Cancer							
38	Rat	18 mo 5 d/wk 7 hr/d						Wong et al. 1982
39	Rat	89–104 wk 5 d/wk 6 hr/d						NTP 1982
40	Mouse	79–103 wk 5 d/wk 6 hr/d						NTP 1982
11								
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 B

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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/	Department of Transportation/United Nations/
NA/IMDG	North America/Intergovernmental Maritime Dangerous Goods Code

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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
K _d	adsorption ratio
kg	kilogram
kgg	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	<i>trans,trans</i> -muconic acid
MAL	maximum allowable level
mCi	millicurie
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor

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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

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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

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>	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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