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 and Environmental Medicine, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-62, Atlanta, Georgia 30333.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Boron and Compounds
CAS Number: 7440-42-8
Date: August 2009
Profile Status: Final Draft Post-Public Comment
Route: [X] Inhalation [ ] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Graph Key: 2
Species: Human

Minimal Risk Level: 0.3 [X] mg/m^3 [ ] ppm

Reference: Cain WS, Jalowayski AA, Kleinman M, et al. 2004. Sensory and associated reactions to mineral dusts: Sodium borate, calcium oxide, and calcium sulfate. J Occup Environ Hyg 1:222-236.

Cain WS, Jalowayski AA, Schmidt R, et al. 2008. Chemesthetic responses to airborne mineral dusts: boric acid compared to alkaline materials. Int Arch Occup Environ Health 81:337-345.

Experimental design: Male and female volunteers were trained to recognize the difference in chemesthetic feel (pungency or irritancy) of various levels of CO_2 offered to the eyes, nose, and throat. Exposures of ≥17.7% CO_2 resulted in a "feel" described by the volunteers as irritating. Twelve male volunteers were exposed to 0, 0.8, 1.5, 3.0, 4.5, or 6.0 mg boron/m^3 (0, 5, 10, 20, 30, or 40 mg sodium borate pentahydrate/m^3) for 20 minutes while performing light exercise (Cain et al. 2004). At 5-minute intervals, they reported the magnitude of "feel" of borate dust in terms of equivalent CO_2 irritancy. They were also observed for changes in nasal secretions (by mass) and nasal airway resistance relative to pre-exposure measurements. Data were reported as means of all responses at each concentration and time point.

In a similar fashion, six male and six female volunteers were exposed to 1.5 mg boron/m^3 (10 mg sodium borate/m^3) or 1.8 mg boron/m^3 (10 mg boric acid/m^3) for 47 minutes while exercising. They reported the magnitude of "feel" of boric acid and borate dusts in terms of equivalent CO_2 irritancy. They were also observed for changes in nasal secretions (by mass), nasal airway resistance, and respiration frequency.

Effects noted in study and corresponding doses: Male volunteers exposed to ≤3.0 mg boron/m^3 (≤20 mg sodium borate/m^3) for 20 minutes reported increasingly higher magnitude of feel of the dust in eyes, nose, and throat. However, the mean reported level of feel, compared to equivalent CO_2 levels, was not considered irritating by the study subjects. The mean reported perception of feel at ≥4.5 mg boron/m^3 (≥30 sodium borate/m^3) was reported to feel irritating to the nose (Cain et al. 2004). Significantly increased nasal secretions (by mass) occurred at 1.5 mg boron/m^3 (10 mg sodium borate/m^3), but not 0.8 mg boron/m^3 (5 mg sodium borate/m^3) (Cain et al. 2004). Similarly, male and female volunteers exposed to 1.5 mg boron/m^3 (10 mg sodium borate/m^3) or 1.8 mg boron/m^3 (10 mg boric acid/m^3) for 47 minutes while exercising reported a mean sense of feel that initially increased and peaked at the equivalent of slightly <17.7% CO_2. Boron exposures with a mean reported feel equivalent to less than 17.7% CO_2 are considered non-irritating, although increases in nasal secretions were observed at 1.8 mg boron/mg^3 (10 mg boric acid/m^3), but not at 0.9 mg boron/mg^3 (5 mg boric acid/m^3) (Cain et al. 2008). Nasal airway resistance decreased, then increased, as a result of exercise, but did not change in a dose-related manner.

Dose and end point used for MRL derivation: A NOAEL of 0.8 mg/m^3 associated with a minimal LOAEL of 1.5 mg/m^3 for significantly increased volume of nasal secretions.

[X] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[ ] 10 for extrapolation from animals to humans
[X] 3 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: Not applicable.

Other additional studies or pertinent information that lend support to this MRL: In an early cross-sectional study of sodium borate workers, past occurrence of symptoms of respiratory irritation such as dryness of the mouth, nose, or throat, dry cough, nose bleeds, and sore throat were reported at elevated frequencies in workers in areas with mean dust concentrations of 8.4 and 14.6 mg particulates/m^3 (1.8 and 3.1 mg boron/m^3, respectively), compared with workers in areas with lower mean dust levels of 4.0 and 1.1 mg particulate/m^3 (0.9 and 0.2 mg boron/m^3) (Garabrant et al. 1984, 1985). In addition, a reduction in forced expiratory volume in 1 second (FEV_1) was measured in a subgroup of smoking workers with estimated high cumulative exposure ($\geq$80 mg particulate/m^3, $\geq$9 mg boron/m^3) to sodium borate dusts, but not in groups of less-exposed smoking workers or in nonsmoking workers. However, a subsequent survey of FEV_1 in 303 of the original 629 borax workers, 7 years after the original survey, found no exposure-related changes in FEV_1 over this period, when adjustments were made for the effects of age, height, and smoking on FEV_1 (Wegman et al. 1994). Acute-duration laboratory exposures of volunteers to sodium borate dust support the findings of respiratory irritation reported in the occupational studies.

The occurrence of acute respiratory symptoms as a possible consequence of acute exposure to dusts of sodium borate (the decahydrate, pentahydrate, and anhydrous tetraborates) was studied in a later study by interviewing workers about acute irritation symptoms before the work shift began and at regular hourly intervals during the work shift, and by measuring personal air concentrations of particulates at concurrent intervals for 4 consecutive days (Hu et al. 1992; Wegman et al. 1991, 1994). Seventy-nine exposed production workers and 27 nonexposed workers were included in the study. In the latest analysis of the collected data, the incidence rates for irritation symptoms in exposed workers were statistically significantly higher than those in nonexposed workers, with exposed workers 9-, 5-, and 3-fold more likely to report incidents of nasal, eye, and throat irritation, respectively, than comparison workers (Hu et al. 1992; Wegman et al. 1991, 1994). For the unexposed groups, the arithmetic means of the 6-hour TWA daily dust concentration was 0.45 mg particulates/m^3 (0.02 mg boron/m^3), with 100% of samples $\leq$1.0 mg particulates/m^3 and about 90% of samples $\leq$0.5 mg particulates/m^3. The arithmetic mean of the 6-hour TWA daily dust concentrations for the exposed group was 5.72 mg particulates/m^3 (0.44 mg boron/m^3), with a majority of air concentrations between 1.0 and 10.0 mg particulates/m^3 (Wegman et al. 1991, 1994). Several factors make it difficult to identify a NOAEL or LOAEL for this study, precluding inclusion of this study in Figure and Table 3-1. Study participants rated their perception of individual episodes of eye, throat, and nasal irritancy on a scale of 0 (not at all) to 10 (very, very much), with ratings of 1, 2, and 3 representing “very little”, “fairly little”, and “moderate” irritation, respectively. Unexposed responders to the pre-shift survey reported a mean rating of 1.9 for all symptoms, while the mean rating for nasal irritation (the most commonly reported effect) among exposed workers was just slightly higher at 2.2. Thus, the cutoff for boron dust-induced effects is likely to be for ratings of $\geq$3. In the exposed

group, 91% of reported symptoms were rated with severity scores ≤3 and 96% of symptoms were rated with severity scores of ≤4 ("pretty much"). For incidences in which the workers depressed a counter button to record time of symptom onset, and the study surveyor recorded an occurrence of effect, the probability of reporting an effect did not change markedly until 0.25-hour TWA exposure levels reached 0.8–1.2 mg boron/m^3 (Wegman et al. 1991). There was no significant difference in reporting of symptoms based on the type of borate dust, which differ in boron content by almost a factor of two (i.e., 4.7 mg anhydrous borax/m^3 and 8.8 mg/m^3 of the decahydrate provide 1 mg boron/m^3). Finally, the data do not indicate a temporal increase in effect intensity, as would be expected for a local irritant.

An uncertainty factor of 3 for human variability was based on the fact that inhaled borates and boric acid exert their adverse effects on respiratory tract tissues as portal-of-entry irritants. For portal-of-entry inhalation toxicants, the variability between humans in pharmacokinetics (i.e., toxicant deposition in the respiratory tract) is minimal. Thus, half ($10^{0.5}$, or 3) of the composite uncertainty factor for pharmacokinetic and pharmacodynamic variability in humans should be applied to the identified NOAEL.

Agency Contacts (Chemical Managers): Malcolm Williams

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Boron and Compounds
CAS Number: 7440-42-8
Date: August 2009
Profile Status: Final Draft Post-Public Comment
Route: [ ] Inhalation [X] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Graph Key: 22
Species: Rabbit

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

Reference: Price CJ, Marr MC, Myers CB, et al. 1996b. The developmental toxicity of boric acid in rabbits. Fundam Appl Toxicol 34:176-187.

The results of this study have also been reported in the following references:

Heindel JJ, Price CJ, Schwetz BA. 1994. The developmental toxicity of boric acid in mice, rats, and rabbits. Environ Health Perspect Suppl 102(7):107-112.

NTP. 1991. Final report on the developmental toxicity of boric acid (CAS No. 10043-35-3) in New Zealand white rabbits. Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service, National Toxicology Program. PB92129550.

Experimental design: Groups of 30 pregnant New Zealand white rabbits were given gavage doses of 0, 62.5, 125, or 250 mg boric acid/kg/day (0, 11, 22, or 44 mg boron/kg/day) on gestation days 6–19. Observations were made for clinical signs, maternal and fetal body weight, number of implantations, resorptions, number of live and dead fetuses, and fetal external, visceral, and skeletal defects.

Effects noted in study and corresponding doses: No adverse maternal effects were observed in the 11 or 22 mg boron/kg/day groups. At 44 mg boron/kg/day, decreases in maternal body weight, relative kidney weight, and food consumption were observed. During the treatment period, the rabbits lost 137 g body weight compared to a weight gain of 93 g in controls. No differences in the number of implantation sites per litter were observed; however, there were significant increases in the percent resorptions per litter (6.3, 5.9, 7.7, and 89.9% in the 0, 11, 22, and 44 mg boron/kg/day groups, respectively), percent of litters with one or more resorptions (39, 39, 45, and 95%), and percent of litters with 100% resorption (0, 0, 0, and 73%). The number of live litters was 18, 23, 20, and 6 in the 0, 11, 22, and 44 mg boron/kg/day groups, respectively, and the number of live fetuses was 159, 175, 153, and 14, respectively. A decrease in fetal body weights (92% of controls) was observed at 44 mg boron/kg/day; although the body weight was not significantly different from controls, the effect was considered biologically significant. Significant increases in the percent of fetuses per litter with external (0.8, 1.4, 1.0, and 11.1% in the 0, 11, 22, and 44 mg boron/kg/day groups, respectively), visceral (7.3, 5.9, 7.4, and 80.6%), cardiovascular malformations (2.7, 3.1, 4.2, and 72.2%) and cardiovascular variations (10.6, 5.7, 7.2, and 63.9%) were observed. Although the overall incidence of external malformations was increased at 44 mg boron/kg/day, there were no increases in a specific malformation. The visceral malformations primarily consisted of cardiovascular malformations, particularly interventricular septal defect, enlarged aorta, papillary muscle malformation, and double outlet right ventricle. The cardiovascular variations consisted of abnormal number of cardiac papillary muscles.

Dose and end point used for MRL derivation: NOAEL of 22 mg boron/kg/day as boric acid associated with a LOAEL of 44 mg boron/kg/day as boric acid for developmental effects

[X] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

[ ] 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: Not applicable.

Other additional studies or pertinent information that lend support to this MRL: A series of studies conducted by Cherrington and Chernoff (2002) also examined the developmental toxicity of boron. A variety of skeletal malformations (including rib agenesis, cervical rib, and fused ribs) were observed in the fetuses of mice receiving two gavage doses of 70 mg boron/kg on gestation day 8 or gestation days 6–8, once daily dose of 88 mg boron/kg/day on gestation days 6–10, or one dose of 131 mg boron/kg on gestation day 8. Multiple thoracic skeletal malformations were observed in the fetuses of mice receiving two doses of 131 mg boron/kg on gestation day 8. Decreases in fetal body weight were also observed in these studies and in studies of mice receiving two gavage doses of 70 mg boron/kg on gestation day 6, 7, 9, or 10.

Developmental effects have also been observed in intermediate-duration studies. Decreases in fetal body weight were observed in rats exposed to 13 or 13.6 mg boron/kg/day on gestation days 0–20 (Heindel et al. 1992; Price et al. 1996a), increases in skeletal abnormalities were observed in rats exposed to 13 mg boron/kg/day on gestation days 0–20 (Price et al. 1996a), and rib cage defects and enlargement of the brain lateral ventricles were observed in rats exposed to 28.4 mg boron/kg/day on gestation days 0–20 (Heindel et al. 1992). In mice exposed to boric acid on gestation days 0–17, reduced fetal body weight and increased skeletal defects were observed at 79 and 175.3 mg boron/kg/day, respectively.

Agency Contacts (Chemical Managers): Malcolm Williams

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Boron and Compounds
CAS Number: 7440-42-8
Date: August 2009
Profile Status: Final Draft Post-Public Comment
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 60, 61
Species: Rat

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

Reference: Heindel JJ, Price CJ, Field EA, et al. 1992. Developmental toxicity of boric acid in mice and rats. Fundam Appl Toxicol 18:266-277.

Experimental design: Groups of 26–28 pregnant Sprague-Dawley rats and Swiss mice were exposed to 0, 0.1, 0.2, or 0.4% boric acid in the diet on gestation days 0–20. Estimated boron doses are 0, 13.6, 28.5, or 57.7 mg boron/kg/day (0, 78, 163, or 330 mg boric acid/kg/day) for rats and 0, 43, 79, or 176 mg boron/kg/day (0, 248, 452, or 1,003 mg boric acid/kg/day) for mice. Daily observations were made for clinical signs and food and water consumption. At death, body and organ weights were recorded. Maternal kidneys were examined microscopically. Live fetuses were excised, anesthetized, weighed, and examined for skeletal malformations.

Effects noted in study and corresponding doses: Decreased maternal weight gain was observed in the 57.7 mg boron /kg/day group of rats, but not when corrected for gravid uterine weight. Decreased relative kidney and liver weights were seen in the 28.4 mg boron/kg/day group. The incidence and severity of the minimal maternal nephropathy was not dose-related. Mean fetal body weight per litter was significantly reduced (7–15%) in all treated groups. Significant increases in the percentage of malformed fetuses/litter or litter with one or more malformed fetuses was observed at doses $\geq$28.5 mg boron/kg/day. Noted malformations included anomalies of the eye, central nervous system, cardiovascular system, and axial skeleton. Enlarged lateral ventricles of the brain and agenesis or shortening of the 13th rib were seen in the 57.7 mg boron/kg/day group.

Reference: Price PJ, Strong PL, Marr MC, et al. 1996a. Developmental toxicity NOAEL and postnatal recovery in rats fed boric acid during gestation. Fundam Appl Toxicol 32:179-193.

Experimental design: Groups of 60 female Sprague-Dawley rats were exposed to 0, 0.025, 0.050, 0.075, 0.100, or 0.200% boric acid in the diet on gestation days 0–20. Observations were made for body weight, clinical signs, and food and water consumption. The study was performed in two phases; offspring were evaluated in both phases for post-implantation mortality, body weight, and external, visceral, and skeletal morphology. Phase I was terminated on gestation day 20. The calculated average maternal dose of boron was 0, 3.3, 6.3, 10, 13, or 25 mg boron/kg/day (0, 19, 36, 55, 76, or 143 mg boric acid/kg/day). Phase II dams were allowed to litter and rear their pups until postnatal day (pnd) 21. For these dams, the calculated average doses of boron were 0, 0.2, 6.5, 9.7, 12.9, and 25.3 mg/kg/day (0, 19, 37, 56, 74, and 145 mg boric acid/kg/day). During this phase, the incidence of skeletal defects in control and exposed pups was evaluated at the end of the first 21 postnatal days.

Effects noted in study and corresponding doses: During Phase I of the study, no maternal deaths or clinical signs were associated with boric acid treatment. When corrected for gravid uterine weight,

maternal weight gain was not affected. However, reduced gravid uterine weight resulted in significant trend tests for decreased maternal body weight (gestation days19 and 20) and decreased maternal body weight gain (gestation days 15–18 and 0–20). Dams in the 25 mg boron/kg/day group had a 10% reduction (statistically significant in the trend test, $p<0.05$) in gravid uterine weight compared with controls. Fetal body weights were significantly decreased in the 13 and 25 mg boron/kg/day groups (6 and 12% less than controls) on gestation day 20. Incidences of external or visceral malformations or variations were not treatment-related. However, a significant increase was observed for percentage of fetuses with skeletal malformations (short rib XIII) per litter and variations (wavy rib or wavy rib cartilage) in the 13 and 25 mg boron/kg/day groups. A significant trend test ($p<0.05$) resulted for decrease in rudimentary extra rib on lumbar I (a variation). The LOAEL for Phase I of this study was identified as 13 mg boron/kg/day, based on decreased fetal body weight and skeletal malformations. The NOAEL for this phase was identified as 10 mg boron/kg/day.

In the Phase II study, a significant trend for increased number and percent of dead pups was seen between pnd 0 and 4, but not between pnd 4 and 21. This appeared to be due to the non-significant early postnatal mortality in the 25.3 mg boron/kg/day group. There were no effects of boric acid on the pup body weight from pnd 0 to 21; therefore, fetal body weight deficits (identified in Phase I) did not continue into the postnatal period (Phase II). The percentage of pups per litter with short rib XIII was increased on pnd 21 in the 25.3 mg boron/kg/day group. A LOAEL of 25.3 mg boron/kg/day, with an associated NOAEL of 12.9 mg boron/kg/day, was identified for skeletal malformations in Phase II of this study.

Dose and end point used for MRL derivation: $BMDL_{05}$ of 10.3 mg/kg/day for reduced fetal body weight

[ ] NOAEL [ ] LOAEL [X] $BMDL_{05}$

Allen et al. (1996) performed multiple benchmark dose (BMD) analyses on single-study or combined data from Heindel et al. (1992) and Price et al. (1996a) for all statistically significant developmental end points (Table A-1). Fetal body weight changes were analyzed using the average fetal weight for each litter with live fetuses. The modeling of rib effects aimed to differentiate whether treatment-related differences in the lumbar rib were variations or malformations. Thus, a weighting scheme was applied to represent three possible interpretations of severity of this effect; that is, a missing rib is: (a) trivially different from "normal" (1/6 weighting), (b) intermediate between a trivial or frank malformation (1/2 weighting), or (c) considered a frank malformation (5/6 weighting). Rib count analysis involved adjusting up (if rudimentary or full lumbar ribs present) or down (shortened rib XIII or rib agenesis) the base count of 13 rib pairs for each fetus analyzed. Benchmark responses (BMRs) were chosen for each end point. The BMD expected to result in the BMR, while the $BMDL_{05}$ was defined as the 95% lower bound on the BMD. The data were modeled with a continuous power model using an F-test evaluation of goodness of fit.

Table A-1. Benchmark Dose Modeling of Developmental Effects of Oral Boric Acid Exposure to Rats

End point	Study data	Goodness-of-fit p-value[a]	BMD[b] (mg boron/ kg/day)	Lower bound on BMD[c] (mg boron/ kg/day)
Fetal body weight as continuous data (BMR=5% reduction)	Heindel et al. 1994	0.24	14.0	9.8
	Price et al. 1996a	0.89	11.9	8.2
	Combined	0.58	13.7	10.3
Fetal body weight as continuous data (BMR=1/2 standard deviation below control)	Heindel et al. 1994	0.24	12.8	8.4
	Price et al. 1996a	0.89	8.6	5.4
	Combined	0.58	11.4	8.4
Fetal body weight as dichotomous incidence data (BMR=5% reduction)	Heindel et al. 1994	0.44	22.6	20.1
	Price et al. 1996a	0.01	8.2	5.4
	Combined	NA	NA	NA
Shortening or agenesis of rib XIII	Heindel et al. 1994	0.07	24.9	18.6
	Price et al. 1996a	0.64	29.9	21.5
	Combined	0.42	24.5	21.0
Missing lumbar ribs	Heindel et al. 1994	0.99	1.2	0.3
	Price et al. 1996a	0.78	1.5	0.6
	Combined	0.99	2.1	0.9
Rib effects analysis: 1/6 weighting for absence of lumbar rib	Heindel et al. 1994	0.27	21.2	16.5
	Price et al. 1996a	0.78	32.9	25.7
	Combined	NA	NA	NA
Rib effects analysis: 1/2 weighting for absence of lumbar rib	Heindel et al. 1994	0.02	13.5	10.2
	Price et al. 1996a	0.64	45.3	30.3
	Combined	NA	NA	NA
Rib effects analysis: 5/6 weighting for absence of lumbar rib	Heindel et al. 1994	<0.001	24.9	20.5
	Price et al. 1996a	0.53	53.7	31.2
	Combined	NA	NA	NA
Rib effects analysis: rib count for absence of lumbar rib	Heindel et al. 1994	0.002	16.5	12.8
	Price et al. 1996a	0.08	25.6	16.5
	Combined	NA	NA	NA

[a]p-values for assessing adequacy of the models for predicting the observed data of Heindel et al. (1992) and Price et al. (1996a)
[b]Benchmark dose: model estimated dose expected to result in the BMR
[c]95% lower bound on the BMD

BMR = benchmark response; NA = not applicable

Source: Heindel et al. 1992; Price et al. 1996a

A likelihood ratio test indicated that the response data from both studies could be modeled as a single dose-response function. Of the developmental end points modeled, the lowest resulting $BMDL_{05}$ was 10.3 mg boron/kg/day for fetal body weight (litter weight averages), which was similar to the NOAEL of 10 mg boron/kg/day from the Price et al. (1996a) study.

Uncertainty Factors used in MRL derivation: A total uncertainty factor of 66 was used.

[ ] 10 for use of a LOAEL
[X] 3.3 for extrapolation of toxicokinetics from animals to humans
[X] 3.16 for extrapolation of toxicodynamics from animals to humans
[X] 2.0 for human toxicokinetic variability
[X] 3.16 for human toxicodynamic variability

In deriving a reference dose (RfD) for chronic oral exposures to boron, the U.S. EPA applied chemical-specific uncertainty factors to the $BMDL_{05}$ of 10.3 mg boron/kg/day reported by Allen et al. (1996) (EPA 2004). Rather than using the default uncertainty factors of 10 for interspecies extrapolation and 10 for interindividual human variability, each uncertainty factor was further delineated into toxicokinetic and toxicodynamic components specific to boron. Since the critical effect (reduced fetal body weight in animals) and point of departure ($BMDL_{05}$ of 10.3 mg/kg/day) for intermediate oral exposure to boron are the same as those for chronic oral exposures, as identified by EPA (2004), the chemical-specific uncertainty factors derived by U.S. EPA to derive a chronic RfD are appropriate for use in deriving the intermediate-duration MRL.

Briefly, each uncertainty factor of 10 for extrapolation from animals to humans and human variability was initially separated into default toxicokinetic and toxicodynamic adjustment factors of 3.16 ($10^{0.5}$) each to account for species differences in toxicokinetic disposition and toxicodymanic responses to orally-ingested boron. The same division was made for the uncertainty factor of 10 for human variability. Thus, the composite uncertainty factor (UF_{TOTAL}) for the intermediate-duration oral MRL is defined as given by EPA (2004) as:

$$UF_{TOTAL} = (AF_{AK} \times AF_{AD} \times AF_{HK} \times AF_{HD} \times UF)$$

where:

AF_{AK} = interspecies toxicokinetic adjustment factor
AF_{AD} = interspecies toxicodynamic adjustment factor
AF_{HK} = interindividual toxicokinetic adjustment factor
AF_{HD} = interindividual toxicodynamic adjustment factor
UF = other uncertainty factors (e.g., use of a LOAEL instead of a NOAEL)

Since no data were available to adequately describe the mode(s) or mechanism(s) of action for boron toxicity in animals or humans, the default toxicodynamic adjustment factor of 3.16 was used to account for inter- and intraspecies uncertainties in toxicodynamics.

The pregnant female is considered to be a sensitive population for boron exposure, as fetal effects in rats are the most sensitive end point identified for boron toxicity. Since boron exhibits near first-order toxicokinetics, distributing freely between total body water and tissues (except for bone, in which it accumulates to approximately 4-fold that of plasma [Chapin et al. 1997]), variability between maternal and fetal kinetics should be essentially equal. Thus, maternal boron plasma concentration is an appropriate surrogate for fetal plasma levels. No data are available to relate rat and human plasma boron concentration. However, boron is not metabolized, but almost completely eliminated in the urine, making renal clearance an appropriate kinetic factor for comparison of toxicokinetic differences between rats and humans. Given the known distribution of boron to total body water and bone, two-compartment

pharmacokinetic models for boron in rats and humans can describe plasma concentration in terms of renal clearance. Boron's toxicity is likely to be related to a continuous exposure over an extended portion of fetal development in which a steady state of circulating boron is achieved. Under the assumption of steady-state plasma boron levels, and assuming approximately complete clearance of born to urine, the two-compartment model can be simplified to the following expression:

$$C_{SS} = (D_e \times f_a \times BW) / Cl$$

where:

D_e = external dose of ingested boron (mg boron/kg body weight/day)
f_a = fraction of ingested boron absorbed from the gut
BW = body weight (kg)
Cl = renal clearance (mL/minute)

Assuming that the ratio of 1 for internal, steady-state doses in rats and humans results in equivalent responses, the expressions for the plasma boron concentration in rats and humans can be expressed as the following ratio, which serves as the AF_{AK}:

$$AF_{AK} = (Cl_R \times f_{AH} \times BW_H) / (Cl_H \times f_{AR} \times BW_R)$$

where the subscripts R and H represent rats and humans. Values for mean renal clearance of 1.0 and 66.1 mL/minute in pregnant rats and humans, respectively, were derived from the studies of Vaziri et al. (2001), and Pahl et al. (2001), which also provided pregnant rat and human body weights of 0.303 and 67.6 kg, respectively. Using gastrointestinal absorption fractions of 0.92 (Schou et al. 1984) and 0.95 (Vanderpool et al. 1994) for f_{AH} and f_{AR}, respectively, AF_{AK} is derived as follows:

$$AF_{AK} = (1.00 \times 0.92 \times 67.6) / (66.1 \times 0.95 \times 0.303)$$
$$= 62.2 / 19.0$$
$$= 3.3$$

The assessment of human variability in boron toxicokinetics utilized glomerular filtration rate (GFR) as a surrogate for renal clearance. Pregnant women were considered the sensitive population, particularly those women with compromised renal function (3–5% preeclamptic women in the U.S. population). Using a modification of Dourson et al. (1998), data from women with normal renal function were used to define an AF_{HK} as:

$$AF_{HK} = GFR_{AVG} / (GFR_{AVG} - (3 \times SD_{GFR}))$$

where GFR_{AVG} and SD_{GFR} are mean and standard deviation of the GFR for healthy women. Three standard deviations below the mean GFR was chosen to account for the women with very low GFR. From the studies of Dunlop (1981), Krutzen et al. (1992), and Sturgiss et al. (1996), a mean GFR of 161.5 mL/minute and a mean GFR-$3SD_{GFR}$ of 85.8 mL/minute resulted in an AF_{HK} of 1.93. This number was rounded to 2.0 to account for uncertainties in human GFR.

Based on these analyses, the total uncertainty factor applied to the $BMDL_{05}$ of 10.3 mg boron/kg is derived as:

$$UF_{TOTAL} = (AF_{AK} \times AF_{AD} \times AF_{HK} \times AF_{HD} \times UF)$$
$$= (3.3 \times 3.16 \times 2.0 \times 3.16 \times 1)$$
$$= 66$$

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: Not applicable.

Other additional studies or pertinent information that lend support to this MRL: Reproductive effects, including testicular atrophy and histopathology, sperm abnormalities, and reduced sperm production have been observed in mice, rats, and dogs after intermediate-duration ingestion of doses of 26 mg boron/kg/day (as boric acid or borax) and higher (Dixon et al. 1979; Fukuda et al. 2000; Harris et al. 1992; Ku et al. 1993a; Kudo et al. 2000; Seal and Weeth 1980; Treinen and Chapin 1991; Weir and Fisher 1972; Yoshizaki et al. 1999). Systemic effects have been observed in rats and dogs at higher doses. Hematological alterations (splenic extramedullary hematopoiesis and decreased hemoglobin levels) have been observed at 60.5 or 72 mg boron/kg/day (NTP 1987; Weir and Fisher 1972), desquamation of skin on paws and tail and inflamed eyes have been observed in rats exposed to 150 mg boron/kg/day (Weir and Fisher 1972), and hyperkeratosis and/or acanthosis of the stomach has been observed at 577 mg boron/kg/day (NTP 1987).

Agency Contacts (Chemical Managers): Malcolm Williams

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APPENDIX B. USER'S GUIDE

Chapter 1

Public Health Statement

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

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

Chapter 2

Relevance to Public Health

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

1. What effects are known to occur in humans?

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

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

The chapter covers end points in the same order that they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, and dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this chapter.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal Risk Levels (MRLs) for noncancer end points (if derived) and the end points from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Chapter 3 Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, ATSDR has derived MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

MRLs should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2, "Relevance to Public Health," contains basic information known about the substance. Other sections such as Chapter 3 Section 3.9, "Interactions with Other Substances," and Section 3.10, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables.

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, MRLs to humans for noncancer end points, and EPA's estimated range associated with an upper- bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 3-1 and Figure 3-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See Sample LSE Table 3-1 (page B-6)

(1) Route of Exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Tables 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures.

(2) Exposure Period. Three exposure periods—acute (less than 15 days), intermediate (15–364 days), and chronic (365 days or more)—are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Health Effect. The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) Key to Figure. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the two "18r" data points in sample Figure 3-1).

(5) Species. The test species, whether animal or human, are identified in this column. Chapter 2, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 3.4, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequency/Duration. The duration of the study and the weekly and daily exposure regimens are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to “Chemical x” via inhalation for 6 hours/day, 5 days/week, for 13 weeks. For a more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Nitschke et al. 1981).

(7) System. This column further defines the systemic effects. These systems include respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, one systemic effect (respiratory) was investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system, which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less Serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

(10) Reference. The complete reference citation is given in Chapter 9 of the profile.

(11) CEL. A CEL is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

(12) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates that the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

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

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure Period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the acute and intermediate exposure periods are illustrated.

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

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

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

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

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

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

SAMPLE

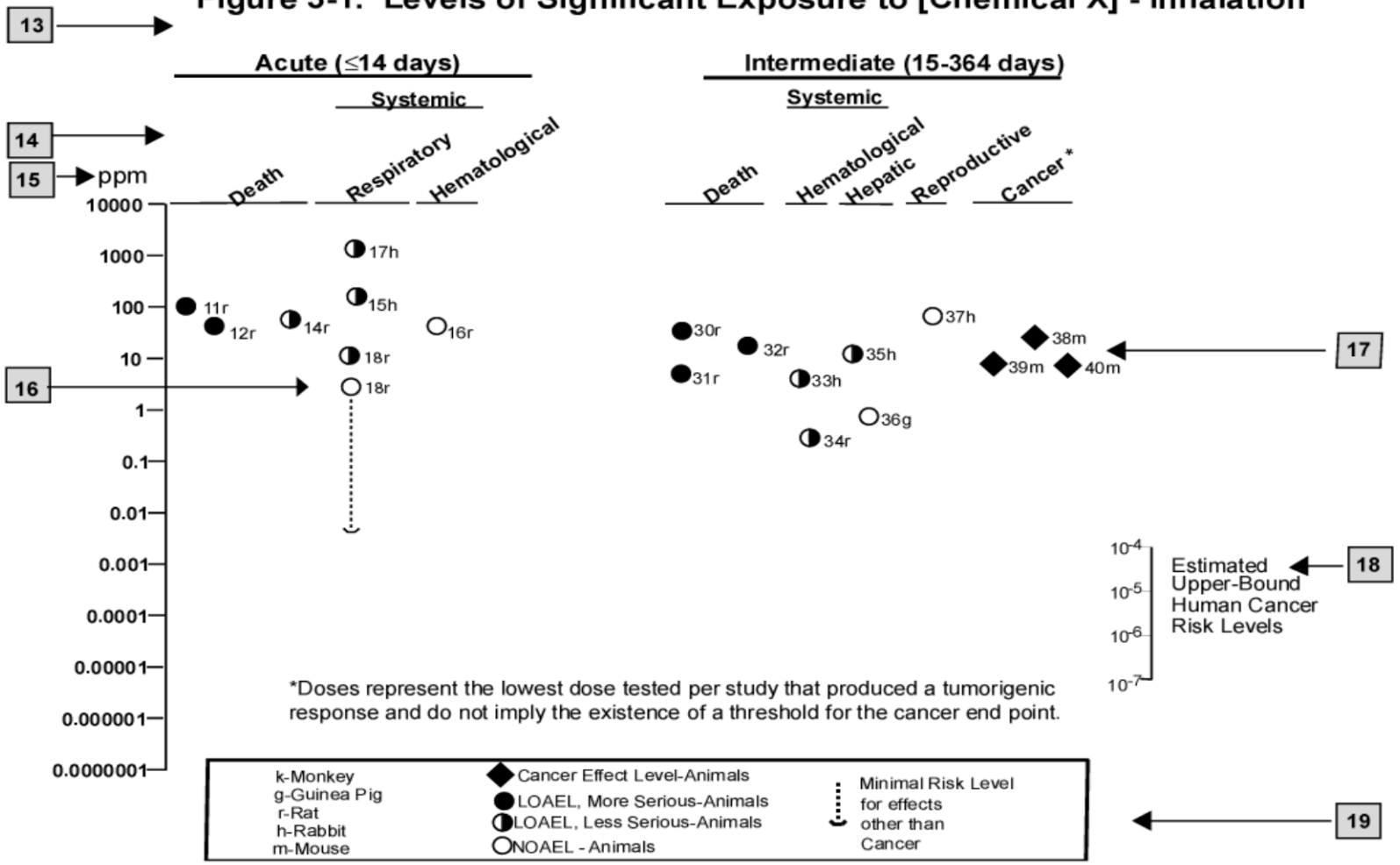
1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

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

12 → [a] The number corresponds to entries in Figure 3-1.
[b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of $5x10^{-3}$ ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

SAMPLE

Figure 3-1. Levels of Significant Exposure to [Chemical X] - Inhalation



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APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
APHA	American Public Health Association
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	best available technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BMD/C	benchmark dose or benchmark concentration
BMD_X	dose that produces a X% change in response rate of an adverse effect
$BMDL_X$	95% lower confidence limit on the BMD_X
BMDS	Benchmark Dose Software
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/IMDG	Department of Transportation/United Nations/ North America/Intergovernmental Maritime Dangerous Goods Code
DWEL	drinking water exposure level
ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F_1	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
FR	Federal Register
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
ILO	International Labor Organization
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
MA	*trans*,*trans*-muconic acid
MAL	maximum allowable level
mCi	millicurie

MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
MFO	mixed function oxidase
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCEH	National Center for Environmental Health
NCI	National Cancer Institute
ND	not detected
NFPA	National Fire Protection Association
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OR	odds ratio
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OTS	Office of Toxic Substances

OW	Office of Water
OWRS	Office of Water Regulations and Standards, EPA
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
pg	picogram
PHS	Public Health Service
PID	photo ionization detector
pmol	picomole
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	pretreatment standards for new sources
RBC	red blood cell
REL	recommended exposure level/limit
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
RQ	reportable quantity
RTECS	Registry of Toxic Effects of Chemical Substances
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SIC	standard industrial classification
SIM	selected ion monitoring
SMCL	secondary maximum contaminant level
SMR	standardized mortality ratio
SNARL	suggested no adverse response level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short term exposure limit
STORET	Storage and Retrieval
TD_{50}	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	total organic carbon
TPQ	threshold planning quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

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

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APPENDIX D. INDEX