APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99–499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that

are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology and Human Health Sciences (proposed), 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 Human Health Sciences (proposed), 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: Manganese (inorganic manganese compounds)
CAS Number: 7439-96-5
Date: September, 2012
Profile Status: Final Post-Public Comment Draft
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Graph Key: 61
Species: Human

Minimal Risk Level: 0.0003 mg respirable manganese/m^3 (0.3 $\mu g/m^3$)

Reference: Roels HA, Ghyselen P, Buchet JP, et al. 1992. Assessment of the permissible exposure level to manganese in workers exposed to manganese dioxide dust. Br J Ind Med 49:25-34.

Experimental design: Neurological effects of manganese exposure were evaluated in 92 male workers in a dry alkaline battery factory. The control group was 101 age- and area-matched workers not occupationally exposed to manganese but with similar work schedules and workloads. Total and respirable manganese dust concentrations were measured using personal air sampling in different occupational areas within the factory. Each worker's personal exposure was determined by the measured concentration characteristic for their particular job and the number of years employed. Workers were exposed for an average duration of 5.3 years (range 0.2–17.7 years) to average (geometric mean) concentrations of 0.215 and 0.948 mg manganese/m^3 in respirable and total dust, respectively. The authors noted that the work processes had not changed significantly in the last 15 years, indicating that past exposures should be comparable to those measured in the study. Neurological function was measured using an audioverbal short term memory test, a simple visual reaction time test using a chronoscope, and three manual tests of hand steadiness, coordination, and dexterity. This report provided good documentation of individual exposure data and characterization of the population studied.

Effects noted in study and corresponding doses: Manganese-exposed workers performed significantly worse than the controls on the neurobehavioral tests, with particular differences in simple reaction time, eye-hand coordination, and hand steadiness. Dr. Harry Roels provided the data on the manganese-exposed group evaluated in this study. These data included individual exposure levels and whether the individual had an abnormal performance in the neurobehavioral tests (scores below the 5^{th} percentile score of the control group). Actual scores on the tests for each individual were not provided by Dr. Roels. Percent precision score in the eye-hand coordination test was the most sensitive end point among the end points showing statistically significantly elevated incidences of abnormal scores and was selected as the basis of the MRL. Average exposure concentration for each worker was calculated by dividing the individual lifetime integrated respirable concentration (LIRD; calculated by Dr. Roels from occupational histories and measurements of workplace air manganese concentrations) by the individual's total number of years working in the factory. Individuals were grouped into six exposed groups and the control group, and the average of the range in each group was used in BMD modeling of the incidence data for number of workers with abnormal percent precision eye-hand coordination scores (Table A-1).

Table A-1. Incidence Data for Abnormal Eye-Hand Coordination Scores in Workers Exposed to Respirable Manganese[a]

Group[b]	Range of manganese (respirable) exposure concentrations[c] (µg/m^3)	Average manganese (respirable) exposure concentration (µg/m^3)	Number of workers with abnormal eye-hand coordination score[d]	Total number of workers	% affected
1	Control	0	5	101	5
2	1.0–99	33	1	7	14
3	100–199	174	6	39	15
4	200–299	224	4	28	11
5	300–399	307	2	3	67
6	400–499	451	4	9	44
7	>500 (523–650)	565	4	6	67

[a]Based on individual exposure and dichotomized response data collected by Roels et al. (1992).
[b]Individuals were sorted into 7 groups, based on manganese exposure, for use in BMD modeling
[c]For each individual, the time-weighted average exposure concentration (respirable manganese) was calculated by dividing the individual lifetime integrated respirable concentrations (LIRD) by the individual's respective total number of years exposed.
[d]An abnormal eye-hand coordination score was defined by Roels as a score below the 5th percentile score in the control group for percent precision (52.4) in the eye-hand coordination test.

Available dichotomous models in the EPA Benchmark Dose Software (version 1.4.1c) were fit to the incidence data for abnormal eye-hand coordination scores in workers exposed to respirable manganese (Roels et al. 1992, Table A-1). Results from the modeling are shown in Table A-2, including: (1) the BMC_{10} and the 95% lower confidence limit ($BMCL_{10}$) calculated as an estimate of the concentration associated with a 10% extra risk for an abnormal score; (2) BMC_{05} and $BMCL_{05}$ values; (3) the p-value for the chi-square goodness of fit statistic (adequate fit, $p>0.1$); and (4) AIC (lower AIC indicates better fit when comparing models, EPA [2000]). Based on the chi-square and AIC measures of fit, all of the models provided adequate and comparable fits to the data (the quantal linear and one-stage multistage models had the same parameter values). $BMCL_{10}$ estimates from the different models showed an approximate 2-fold range from 73 µg/m^3 from a one-stage multistage model to 142 µg/m^3 from the logistic model. The logistic model was indicated as the best fitting model by the AIC measure (Table A-2) and was used to provide the POD for the MRL. Figure A-1 plots predicted risks for abnormal scores from the multistage model and observed incidence values calculated from data in Table A-1.

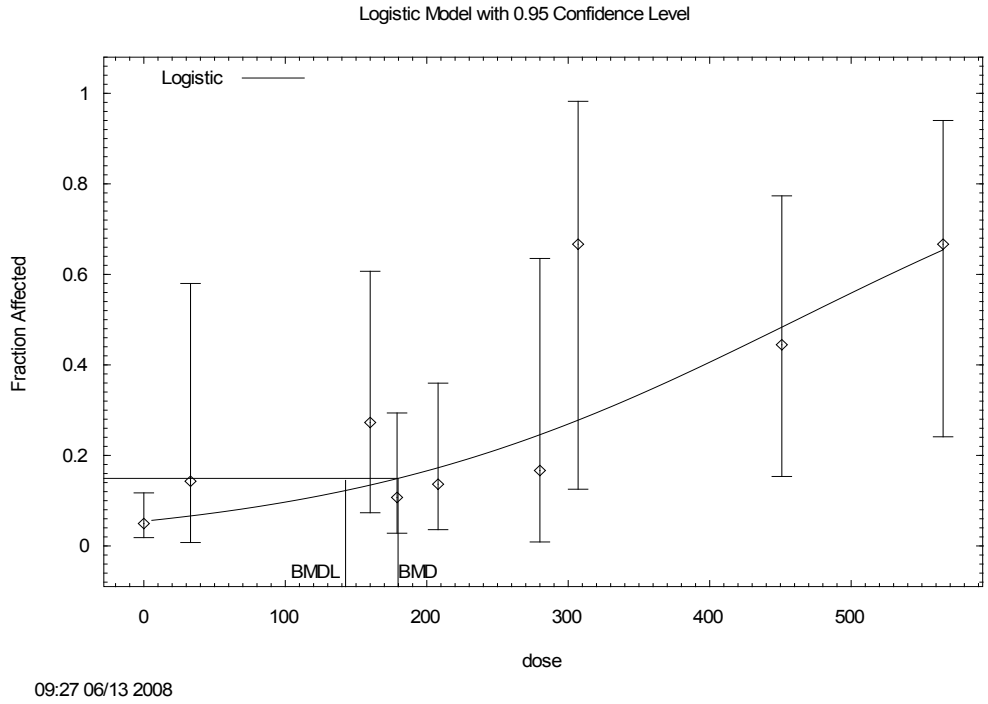
Table A-2. Modeling Results for Incidences of Abnormal Eye-Hand Coordination Scores in Workers Exposed to Respirable Manganese

Model	BMC_{10} ($\mu g/m^3$)	$BMCL_{10}$ ($\mu g/m^3$)	BMC_{05} ($\mu g/m^3$)	$BMCL_{05}$ ($\mu g/m^3$)	x^2 p-value	AIC
Gamma[a]	185.46	90.53	134.95	44.07	0.46	134.99
Logistic	179.03	142.14	109.00	83.96	0.64	132.81
Log-logistic[b]	186.37	98.40	136.04	46.67	0.47	134.98
Multi-stage[c]	110.42	73.21	53.75	35.64	0.36	135.13
Probit	165.97	131.31	98.50	76.01	0.64	132.85
Log-probit[b]	188.64	124.37	145.64	86.48	0.46	135.05
Weibull[a]	182.58	91.23	126.65	44.41	0.47	134.94

[a]Restrict power ≥1
[b]Slope restricted to >1
[c]Restrict betas ≥0; lowest degree polynomial with an adequate fit is reported; degree of polynomial=1

Source: Roels et al. 1992

Figure A-1. Predicted (Logistic Model) and Observed Incidence of Abnormal Eye-Hand Coordination Scores in Workers Exposed to Respirable Manganese (Roels et al. 1992)*



*BMD=BMC, BMDL=BMCL; BMDs and BMDLs indicated are associated with a 10% extra risk change from the control, and are in units of $\mu g/m^3$.

Dose and end point used for MRL derivation:

[ ] NOAEL [ ] LOAEL [X] Other $BMCL_{10}$ for incidence of workers with abnormal scores on an eye-hand coordination test (142 μg/m^3 from the Logistic Model)

Uncertainty and modifying factors used in MRL derivation:

[ ] 10 for the use of a LOAEL
[ ] 10 for extrapolation from animals to humans
[X] 10 for human variability including possibly enhanced susceptibility of the elderly, infants, and children; individuals with chronic liver disease or parenteral nutrition; and females and individuals with iron deficiency. The current assessment does not use an additional modifying factor of 5 for potentially increased susceptibility in children based on differential kinetics in the young (which was used in the Agency for Toxic Substances and Disease Registry [2000] assessment), because recent toxicokinetic studies in lactating rats and their offspring exposed to manganese by the oral or inhalation routes suggest that the human variability factor of 10 provides sufficient protection for differential kinetics in children and adults. For example, in neonatal rats orally exposed to 25 or 50 mg manganese/kg/day manganese chloride from PND 1 through 21, manganese concentrations in various brain regions were about 2-fold higher than brain manganese concentrations in adult rats exposed to the same oral dose levels for 21 days (Dorman et al. 2000). Similarly, 18-day-old neonatal rats exposed from birth to aerosols of manganese sulfate at 1 mg manganese/m^3, 6 hours/day showed a 2.6-fold increase in striatum manganese concentrations, compared with controls, while lactating adults exposed to the same aerosol concentration showed a 1.7-fold increase compared with controls (Dorman et al. 2005a). Likewise, simulations with PBPK models for inhaled manganese in lactating rat dams and offspring indicate that manganese concentrations in the striatum and olfactory bulb of the brains of PND 19 offspring begin to increase when air concentrations exceed 50–100 μg manganese/m^3, whereas maternal concentrations begin to increase at air concentrations between 100 and 300 μg manganese/m^3 (Yoon et al. 2009b). These results indicate that at air concentrations above about 0.05–0.1 mg/m^3, brain concentrations in neonates may be elevated, compared with controls, to a greater degree than in lactating dams, but the age-specific difference in the tested air concentration range does not appear to be large. Simulations from a human PBPK model for inhaled manganese in lactating mothers and their offspring indicate that average daily AUCs for manganese concentrations in the globus pallidus of the fetus, suckling neonate, and 3-year-old child from manganese air concentrations increased beyond 10% of background concentrations in fetuses and 3-year-old children when air concentrations exceeded 0.01 mg/m^3 (10 μg/m^3) and in suckling neonates when air concentrations exceeded 0.001 mg/m^3 (1 μg/m^3) (Yoon et al. 2011). Thus, the inhalation MRL derived herein, 0.3 μg/m^3, is below air concentrations at which brain concentrations in human fetuses (10 μg/m^3) and nursing infants (1 μg/m^3) are predicted to begin to rise under normal dietary manganese exposure conditions.

[X] 10 for limitations/uncertainties in the database including the lack of epidemiological data for humans chronically exposed to soluble forms of manganese and the concern that the general population may be exposed to more soluble forms of manganese than most of the manganese-exposed workers in the principal and supporting studies. Evidence from several rat studies indicate that inhalation of more soluble forms of manganese (e.g., manganese sulfate and manganese chloride) results in higher manganese concentrations in brains than inhalation of less soluble forms, such as manganese phosphate, manganese tetroxide, or manganese dioxide (Dorman et al. 2001a, 2004a; Roels et al. 1997). In addition, data on developmental toxicity for this route and duration of exposure are lacking. There is limited information on reproductive effects in females (one study in rat dams) and reported effects on male reproductive organs have not been clearly associated with decreased reproductive function. Though it is clear that the

neurological system is the most sensitive identified target organ for effects from subchronic- to chronic-duration inhalation exposure to manganese, data are lacking to fully characterize the potential risk for all organ systems from chronic inhalation exposure.

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.

Was a conversion used from intermittent to continuous exposure?

[X] 5/7 to account for intermittent exposure (5 days/week)
[X] 8/24 to account for intermittent exposure (8 hours/day)

MRL = 142 µg respirable manganese/m^3 x 5d/7d x 8h/24h x 1/100 = 0.3 µg respirable manganese/m^3.

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

Previous BMD analyses of exposure data and incidence data for abnormal eye-hand coordination test scores from the Roels et al. (1992) study used a quantal linear model to arrive at a $BMCL_{10}$ value of about 74 µg respirable manganese/m^3 (Agency for Toxic Substances and Disease Registry 2000; EPA 1994c; WHO 2001). This value is virtually the same as the $BMCL_{10}$ of 73.2 µg manganese/m^3 obtained from a one-stage multistage model in the current analysis (Table A-2).

Several BMD analyses of results from other epidemiological studies of neurobehavioral end points in manganese-exposed workers provide support for the MRL (Clewell and Crump 1999; Clewell et al. 2003; Health Canada 2010). Estimated $BMCL_{10}$ values in these analyses were within 2–3-fold of the POD (142 µg manganese/m^3) selected for the chronic inhalation MRL herein.

Dr. Anders Iregren provided ATSDR with individual worker data on total dust manganese exposure and performance on neurobehavioral tests for the occupational cohort that participated in his study (Iregren 1990; Wennberg et al. 1991). A BMD analysis was performed with these data under contract with ATSDR (Clewell and Crump 1999) and the lowest $BMCL_{10}$ value among the end points analyzed was 0.07 mg respirable manganese/m^3 for a 10% change in simple reaction time. The BMD analysis applied K-power and Weibull models to continuous variable data (from 11 different test scores collected by Dr. Iregren) using current respirable manganese exposure estimates, age, and vocabulary test results as explanatory variables, an assumption that 5% of unexposed subjects had adverse responses, and a benchmark response of 10% change from unexposed mean scores. For each dataset, $BMCL_{10}$ values from the Weibull model were lower (by 2–3-fold at the most) than $BMCL_{10}$ values from the K-Power model. Weibull $BMCL_{10}$ values for the different test score datasets ranged from 0.07 to 0.67 mg respirable manganese//m^3. Thus, the lowest $BMCL_{10}$ value from this analysis of test score data from manganese-exposed workers collected by Iregren (1990; Wennberg et al. 1991) is within 2-fold of the POD of 142 µg manganese/m^3 for the MRL.

Clewell et al. (2003) conducted BMD analyses on data from three neuromotor tests in the Roels et al. (1992) study (visual reaction time, eye-hand coordination, and hand steadiness) and from five neuromotor tests in the Gibbs et al. (1999) study (hole 6 of the hand steadiness test, percent precision of the eye-hand coordination test, reaction time in the complex reaction test, root mean square amplitude in the steady test, and tap time). Exposure measures in these analyses were recent measures of manganese concentrations in respirable dust. $BMCL_{10}$ values were 0.257, 0.099, and 0.202 mg manganese/m^3 for the visual reaction time, eye-hand coordination, and hand steadiness data from the Roels et al. (1992) study;

these results were obtained after fitting incidence data for abnormal scores in these tests to a Weibull model for dichotomous data. The reported $BMCL_{10}$ value of 0.099 mg manganese/m^3 for the eye-hand coordination test is similar to the $BMCL_{10}$ value of 0.091 mg manganese/m^3 obtained with the Weibull model in the current ATSDR analysis (Table A-2). $BMCL_{10}$ values from the analyses of outcomes from the Gibbs et al. (1999) study ranged from 0.09 to 0.27 mg manganese/m^3 (averaging the BMCLs within end points across different BMD models applied to the data). Clewell et al. (2003) did not have individual worker data from the Iregren (1990) or Mergler et al. (1994) studies, but, based on some assumptions about exposures (e.g., all exposed workers were exposed to average concentrations for the facilities and respirable manganese concentrations were calculated for the Iregren workers based on an assumption that 50% of total dust manganese was respirable), they calculated $BMCL_{10}$ values for six end points from the Mergler et al. (1994) study and the simple reaction time end point in the Iregren (1990) study. $BMCL_{10}$ values ranged from about 0.1 to 0.3 mg manganese/m^3 from the Mergler et al. (1994) study end points to 0.1 mg manganese/m^3 for the reaction time end point in the Iregren (1990) study.

Health Canada (2010) published a human health risk assessment for inhaled manganese in which BMD analyses were conducted on data for neurobehavioral end points from the study of manganese alloy workers by Lucchini et al. (1999). Dose-response data for six tests of fine motor control, two aspects of memory tests, one test of mental arithmetic, and measured serum prolactin levels were fit to linear models, using exposure metrics based on an average over all occupational history (ARE) or an average over the latest five years of occupation (ARE5). Using a linear model, $BMCL_{10}$ values for the various end points were 32–59 and 85–98 µg manganese/m^3 for the ARE5 and ARE exposure metrics, respectively. Regardless of exposure metric, the values are within a 2–4-fold range of the selected POD of 142 µg manganese/m^3, based on eye-hand coordination test scores in workers in the Roels et al. (1992) study.

Neurological effects from repeated inhalation exposure to manganese are well recognized as effects of high concern based on case reports and epidemiological studies of groups of occupationally exposed workers. A number of epidemiological studies have used batteries of neurobehavioral tests of neuromotor, cognition, and mood states to study the psychological or neurological effects of exposure to low levels of manganese in the workplace (Bast-Pettersen et al. 2004; Beuter et al. 1999; Blond and Netterstrom 2007; Blond et al. 2007; Bouchard et al. 2003, 2005, 2007a, 2007b; Chia et al. 1993a, 1995; Crump and Rousseau 1999; Deschamps et al. 2001; Gibbs et al. 1999; Iregren 1990; Lucchini et al. 1995, 1999; Mergler et al. 1994; Myers et al. 2003a, 2003b; Roels et al. 1987a, 1992, 1999; Summers et al. 2011; Wennberg et al. 1991). Some of these studies have found statistically significant differences between exposed and non-exposed groups or significant associations between exposure indices and neurological effects (Bast-Pettersen et al. 2004; Chia et al. 1993a; Iregren 1990; Lucchini et al. 1995, 1999; Mergler et al. 1994; Roels et al. 1987a, 1992; Wennberg et al. 1991), whereas others have not found significant associations (Deschamps et al. 2001; Gibbs et al. 1999; Myers et al. 2003a, 2003b; Summers et al. 2011; Young et al. 2005). Table A-3 summarizes results from these studies. Comparison of the effect levels in these studies provides support for selection of the Roels et al. (1992) as the basis of the MRL. The advantage of the Roels et al. (1992) study is that individual worker data were available to support a BMD analysis, but, as discussed above, BMD analyses of other epidemiological data for performance on tests of neurobehavior provided potential PODs within 2–4-fold of the POD selected as the basis of the MRL.

Table A-3. Epidemiological Studies of Neurological End Points in Workers Exposed to Low Levels of Inorganic Manganese in Workplace Air

Reference	Place of work	Estimated exposure (mg manganese/m^3)[a]	Years worked[b]	Number of exposed	Number of control	Effects
Chia et al. 1993a	Mn ore process	1.59	7.4	17	17	↓ finger tapping, digit symbol, pursuit aiming
Roels et al. 1987a	Mn salt and oxide plant	0.97	7.1	141	104	↓ reaction time, short-term memory, eye-hand coordination, hand steadiness
Roels et al. 1992, 1999	Dry alkaline battery plant	0.948 (0.215)	5.3	92	37	↓ reaction time, short-term memory, eye-hand coordination, hand steadiness
Iregren 1990; Wennberg et al. 1991	Mn foundry	0.14	9.9	30	60	↓ finger tapping, reaction time
Lucchini et al. 1995	Mn alloy plant	0.149	13	58	None	↓ finger tapping, short-term memory with increasing exposure indices
Lucchini et al. 1999	Mn alloy plant	0.097 (0.038)	11.5	61	87	↓ hand movements, finger tapping, short-term memory
Mergler et al. 1994	Mn alloy plant	0.23 (0.04)	16.7	115	115	↓ rapid hand movements, cognitive flexibility; ↑ indices for tension, anger, fatigue, confusion
Gibbs et al. 1999	Mn process plant	0.18 (0.051)	12.7	75	75	No effects on neuromotor tests or self-reported symptoms
Deschamps et al. 2001	Enamels production plant	2.05 (0.035)	19.7	134	137	No effects on self-reported symptoms or several cognitive tests; no neuromotor tests given.
Myers et al. 2003a	Mn mines	0.21	10.8	489	None	No associations between indices of exposure and outcomes from tests of neuromotor and cognitive functions or self-reported symptoms
Myers et al. 2003b; Young et al. 2005	Mn smelter	0.85 (0.58)	18.2	509	67	Neurobehavioral test batteries showed significant effects in only a few of the many end points evaluated

Table A-3. Epidemiological Studies of Neurological End Points in Workers Exposed to Low Levels of Inorganic Manganese in Workplace Air

Reference	Place of work	Estimated exposure (mg manganese/m^3)[a]	Years worked[b]	Number of exposed	Number of control	Effects
Summers et al. 2011	Mn smelter	0.384 (0.123)	10.6	143	None	Associations between decreasing deficits on tests of attention and executive function (but not tests of short-term memory span or information-processing speed) and increasing exposure. The magnitude of deficits were not expected by the study authors to be of clinical significance.
Bast-Pettersen et al. 2004	Mn alloy plant	0.753 (0.049)	20.2	100	100	↑ scores for hand tremor, but no effect on other neuromotor or cognitive tests or symptoms
Blond and Netterstrom 2007; Blond et al. 2007	Steel works	0.07	24	60–92	14–19	↓ fast hand and finger movement, but no effects on slow movements, reaction time, or cognitive end points

[a]Mean, median, or midpoint of reported ranges of manganese concentration in total dust. Values for respirable dust are noted in parentheses when they were available.
[b]Mean, median, or midpoint of reported ranges of years employed at the facility.

The neurological effects associated with prolonged low-level manganese exposure generally have been subtle changes including deficits in tests of neuromotor or cognitive functions and altered mood states; they have been referred to by various authors as preclinical or subclinical neurological effects. Manganese air concentrations associated with these effects in chronically exposed workers range from about 0.07 to 1.59 mg manganese/m^3 (manganese in total or inhalable dust measurements; values for manganese in respirable dust are noted in parentheses in Table A-3). For several of these work environments, values of concentrations of manganese in respirable dust (generally particulate diameters <10 μm) represented <20–80% of the total dust values.

Studies in communities surrounding manganese industries also have reported similar subclinical neurological effects in adults and children. In a study of men and women living close to a manganese alloy production plant, a blood manganese level-age interaction was observed, with the poorest performance on neurological tests occurring among those >50 years old who had the highest blood manganese levels (Baldwin et al. 1999; Beuter et al. 1999; Bowler et al. 1999; Mergler et al. 1999). Additional studies of environmentally exposed adults reported attention impairments, poorer postural stability, and subclinical motor impairments at environmental air exposures >0.1 μg manganese/m^3; however, other potential sources of environmental exposure were not accounted for (Kim et al. 2011; Rodríguez-Agudelo et al. 2006; Solís-Vivano et al. 2009; Standridge et al. 2008). In children living in a manganese mining area or close to a ferromanganese alloy plant, associations were found between manganese concentrations in blood or hair and deficits in intellectual functions or motor impairments, but the reported data are not useful for deriving an inhalation MRL for manganese (Hernández-Bonilla et al. 2011; Menezes-Filho et al. 2011; Riojas-Rodríguez et al. 2010).

The 2000 ATSDR Toxicological Profile for Manganese derived a chronic MRL for inorganic manganese of 0.00004 mg manganese/m^3 (manganese in respirable dust, 0.04 μg manganese/m^3), based on a $BMCL_{10}$ of 0.074 mg manganese/m^3 (manganese in respirable dust) for abnormal performance in tests of hand steadiness, eye-hand coordination, or reaction time in the same study of 92 male workers in a dry alkaline battery plant (Roels et al. 1992) used in the current assessment. The MRL was derived by adjustment of the $BMCL_{10}$ to a continuous exposure basis and division by an uncertainty factor of 500 (10 for human variability, 10 for database deficiencies and limitations, and a modifying factor of 5 for potentially increased susceptibility in children based on differential kinetics in the young). The current MRL of 0.3 μg manganese/m^3 replaces the old MRL.

Agency Contact (Chemical Manager): Malcolm Williams, DVM, Ph.D.

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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

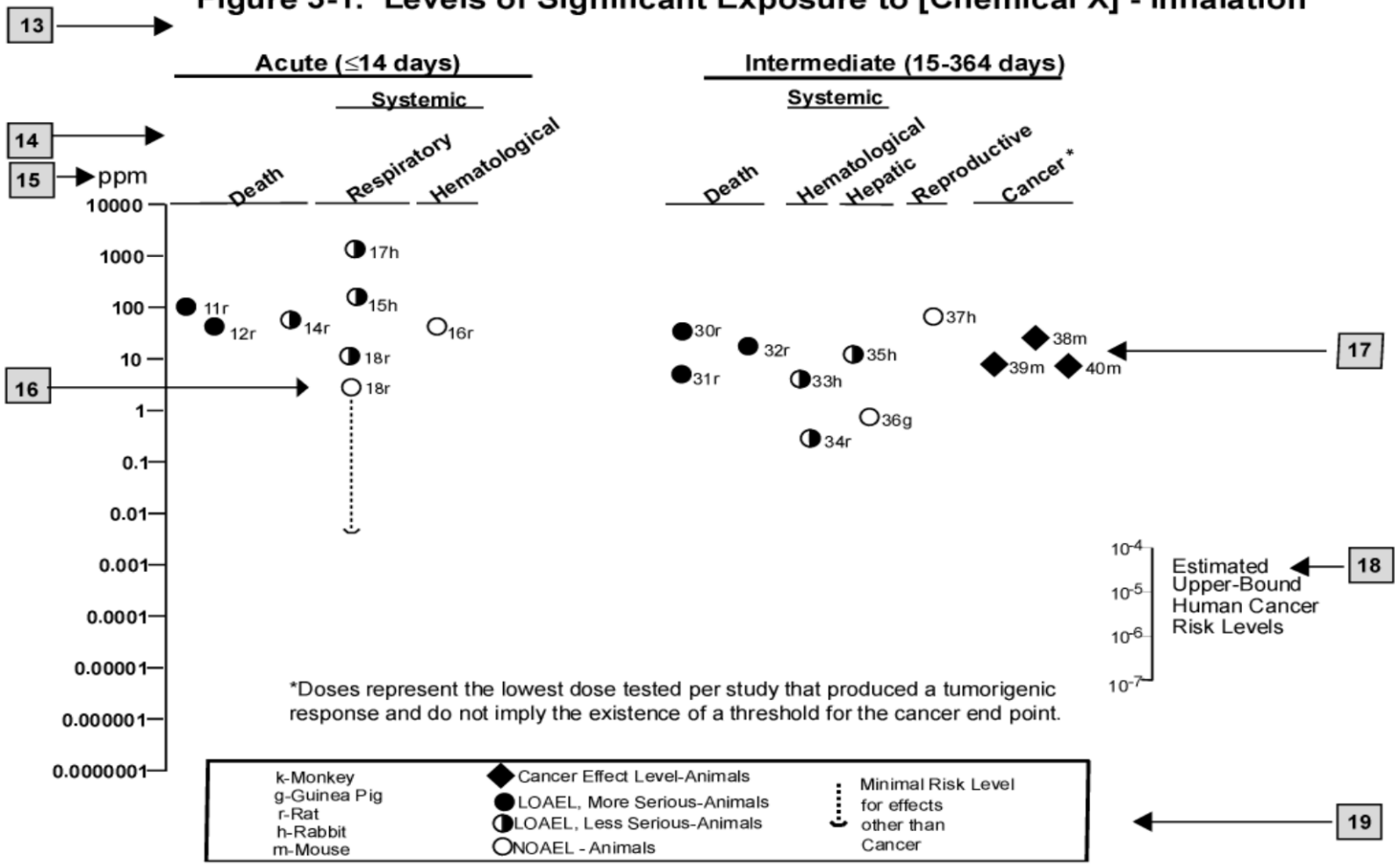
1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

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	↓	↓	↓	↓	↓		↓
18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
4 → 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