8. REGULATIONS, ADVISORIES, AND GUIDELINES

MRLs are substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors and other responders to identify contaminants and potential health effects that may be of concern at hazardous waste sites.

An MRL of 0.0003 mg manganese/m^3 (0.3 µg manganese/m^3) in respirable dust has been derived for chronic inhalation exposure to manganese. As discussed in Appendix A, dichotomous models in the EPA BMDS were fit to the incidence data for abnormal eye-hand coordination scores in battery workers exposed to respirable manganese (Roels et al. 1992). $BMCL_{10}$ 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.

The MRL of 0.3 µg respirable manganese/m^3 was derived by adjusting the POD to a continuous exposure basis (142 x 5/7 x 8/24) and dividing by an uncertainty factor of 100. An uncertainty factor of 10 was used 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.

An uncertainty factor of 10 was applied 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. 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.

No oral MRLs were derived for acute-, intermediate-, or chronic-duration oral exposure to manganese, but an interim guidance value of 0.16 mg manganese/kg/day, based on the Tolerable Upper Intake Level (UL) for adults of 11 mg manganese/day (established by FNB/IOM [2001]) is recommended to be used for ATSDR public health assessments of oral exposure to inorganic forms of manganese. The interim guidance value is necessary because of the prevalence of manganese at hazardous waste sites and the fact that manganese is an essential nutrient. It is recommended to be used until more information on actual intake levels across environmental media can be obtained.

The EPA derived a chronic inhalation RfC of 5x10^{-5} mg/m^3 for respirable manganese (IRIS 2011). This value is based on the LOAEL of 0.15 mg/m^3 from a study of battery workers exposed to manganese dioxide (Roels et al. 1992). EPA verified this assessment in 1993. The LOAEL was calculated by

dividing the geometric mean concentration of the lifetime-integrated respirable dust concentration for the exposed workers by the average duration of employment in the facility. EPA calculated the RfC by adjusting for continuous exposure and dividing by an uncertainty factor of 1,000 (10 for use of a LOAEL, 10 to protect sensitive individuals, and 10 for database limitations reflecting both the less-than-chronic periods of exposure and the lack of developmental data, as well as potential, but unquantified, differences in the toxicity of different forms of manganese). The estimated breathing rate in the exposed workers was assumed to be 10 m^3/workday.

The EPA (IRIS 2011) derived an oral reference dose (RfD) value of 0.14 mg/kg/day manganese from all oral exposures. As of August 2008, this value was last updated in May 1996. The agency suggested using a modifying factor of 1 if the manganese is ingested in food and a modifying factor of 3 if the element is ingested in water or soil. The RfD was developed using a previous determination of the upper range of total dietary intake of 10 mg/day. The modifying factor of 1 was based on composite data on chronic human NOAELs from the World Health Organization (WHO 1973) (0.11–0.13 mg/kg/day), the National Academy of Sciences/National Research Council (1989) "safe and adequate level" (0.04–0.07 mg/kg/day), and a study by Freedland-Graves et al. (1994) concerning nutritional requirements for manganese. The FNB/IOM (2001) re-established an Adequate Intake (AI) value for manganese for men and women at 2.3 and 1.8 mg manganese/day, respectively (for 70-kg individuals, this would result in exposures of 0.033 and 0.026 mg manganese/kg/day, respectively). The UL of 11 mg/day was also set by the FNB/IOM (2001) for adults based on a NOAEL for Western diets (approximately 0.16 mg manganese/kg/day assuming a 70-kg body weight).

The international and national regulations, advisories, and guidelines regarding manganese in air, water, and other media are summarized in Table 8-1.

Table 8-1. Regulations, Advisories, and Guidelines Applicable to Manganese

Agency	Description	Information	Reference
INTERNATIONAL			
Guidelines:			
IARC	Carcinogenicity classification	No data	IARC 2008
WHO	Air quality guidelines		WHO 2000a
	Manganese[a]	0.15 µg/m^3	
	Drinking water quality guidelines		WHO 2004a
	Manganese[b]	0.4 mg/L	
NATIONAL			
Regulations and Guidelines:			
a. Air			
ACGIH	TLV (8-hour TWA)		ACGIH 2007
	Manganese	0.2 mg/m^3	
	MMT[c]	0.2 mg/m^3	
	TLV basis (critical effects)		
	Manganese	Central nervous system impairment	
	MMT	Central nervous system impairment, lung, liver, and kidney damage	
EPA	Second list of AEGL priority chemicals for guideline development		EPA 2008a
	Manganese	Yes	
	MMT	Yes	
NIOSH	Category of pesticides		NIOSH 1992
	Potassium permanganate	Group 1 pesticide	
	REL (10-hour TWA)		NIOSH 2005
	Manganese	1 mg/m^3	
	Manganese (II,III) oxide[d]	Not established	
	MMT[e]	0.2 mg/m^3	
	STEL (15-minute TWA)		
	Manganese	3 mg/m^3	
	IDLH		
	Manganese	500 mg/m^3	
	Target organs		
	Manganese	Respiratory system, central nervous system, blood, and kidneys	

Table 8-1. Regulations, Advisories, and Guidelines Applicable to Manganese

Agency	Description	Information	Reference
	Manganese (II,III) oxide	Respiratory system, central nervous system, blood, and kidneys	
NATIONAL *(cont.)*			
NIOSH	Target organs *(cont.)*		
	MMT	Eyes, central nervous system, liver, and kidneys	
OSHA	PEL (8-hour TWA) for general industry (ceiling limit)		OSHA 2007c 29 CFR 1910.1000, Table Z-2
	Manganese (compounds and fume)	5 mg/m^3	
	PEL (8-hour TWA) for shipyard industry (ceiling limit)		OSHA 2007a 29 CFR 1915.1000
	Manganese (compounds and fume)	5 mg/m^3	
	PEL (8-hour TWA) for construction industry (ceiling limit)		OSHA 2007b 29 CFR 1926.55, Appendix A
	Manganese (compounds and fume)	5 mg/m^3	
b. Water			
EPA	Designated as hazardous substances in accordance with Section 311(b)(2)(A) of the Clean Water Act		EPA 2008b 40 CFR 116.4
	Potassium permanganate	Yes	
	Drinking water contaminant candidate list		EPA 1998
	Manganese	Yes	
	Drinking water standards and health advisories		EPA 2006a
	Manganese		
	1-Day health advisory for a 10-kg child	1 mg/L	
	10-Day health advisory for a 10-kg child	1 mg/L	
	DWEL	1.6 mg/L	
	Lifetime	0.3 mg/L	
	National recommended water quality criteria		EPA 2006c
	Manganese[f]		
	Human health for consumption of water + organism	0.05 mg/L	
	Human health for consumption of organism only	0.1 mg/L	
	National secondary drinking water standards		EPA 2003b

Table 8-1. Regulations, Advisories, and Guidelines Applicable to Manganese

Agency	Description	Information	Reference
	Manganese[g]	0.05 mg/L	
	Reportable quantities of hazardous substances designated pursuant to Section 311 of the Clean Water Act		EPA 2008d 40 CFR 117.3
	Potassium permanganate	100 pounds	
NATIONAL *(cont.)*			
c. Food			
EPA	Inert ingredients permitted for use in nonfood use pesticide products		EPA 2008e
	Mn(II) carbonate	Yes	
	Manganese dioxide	Yes	
	Manganese sulfate	Yes	
	Potassium permanganate	Yes	
FDA	Bottled drinking water		FDA 2007a 21 CFR 165.110
	Manganese	0.05 mg/L	
	EAFUS[h]		FDA 2008
	Potassium permanganate	Yes	
	Indirect food additives: adhesives and components of coatings		FDA 2007b 21 CFR 175.105
	Potassium permanganate	Yes	
d. Other			
ACGIH	Carcinogenicity classification		ACGIH 2007
	Manganese	No data	
	MMT	No data	
DEA	Records and reports of listed chemicals		DEA 2007 21 CFR 1310.02
	Potassium permanganate	List II chemical	
EPA	Carcinogenicity classification		IRIS 2011
	Manganese	Group D[i]	
	RfC		
	Manganese	$5x10^{-5}$ mg/m^3	
	RfD		
	Manganese	0.14 mg/kg/day	
	Superfund, emergency planning, and community right-to-know		
	Designated CERCLA hazardous substance		EPA 2008c 40 CFR 302.4
	Manganese[j]	Yes	
	Potassium permanganate[k]	Yes	
	Reportable quantity		
	Manganese	None[l]	
	Potassium permanganate	100 pounds	

Table 8-1. Regulations, Advisories, and Guidelines Applicable to Manganese

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
	Effective date of toxic chemical release reporting		EPA 2008g 40 CFR 372.65
	Manganese	01/01/1987	
EPA	Superfund, emergency planning, and community right-to-know		
	Extremely Hazardous Substances		EPA 2008f 40 CFR 355, Appendix A
	MMT		
	Reportable quantity	100 pounds	
	Threshold planning quantity	100 pounds	
NTP	Carcinogenicity classification	No data	NTP 2005

[a]TWA based on effects other than cancer or odor/annoyance using an averaging time of 1 year.
[b]Concentrations of the substance at or below the health-based guideline value may affect the appearance, taste, or odor of the water, resulting in consumer complaints.
[c]Skin designation refers to the potential significant contribution to the overall exposure by the cutaneous route, including mucous membranes and the eyes, by contact with vapors, liquids, and solids.
[d]NIOSH has not established a REL for magnesium oxide fume under the “Proposed Rule on Air Contaminants" (29 CFR 1910, Docket No. H-020) in which NIOSH questioned whether the OSHA PEL for magnesium oxide fume (1 mg/m^3) was adequate enough to protect workers from potential health hazards (NIOSH 2005).
[e]Skin designation indicates the potential for dermal absorption; skin exposure should be prevented as necessary through the use of good work practices, gloves, coveralls, goggles, and other appropriate equipment.
[f]The human health criteria are based on carcinogenicity of 10^{-6} risk. This criterion for manganese is not based on toxic effects, but rather is intended to minimize objectionable qualities such as laundry stains and objectionable tastes in beverages.
[g]National Secondary Drinking Water Standards are non-enforceable guidelines regulating contaminants that may cause cosmetic effects (such as skin or tooth discoloration) or aesthetic effects (such as taste, odor, or color) in drinking water.
[h]The EAFUS list of substances contains ingredients added directly to food that FDA has either approved as food additives or listed or affirmed as GRAS.
[i]Group D: not classifiable as to human carcinogenicity.
[j]Designated CERCLA hazardous substance pursuant to Section 112 of the Clean Air Act.
[k]Designated CERCLA hazardous substance pursuant to Section 311(b)(2) of the Clean Water Act.
[l]No reportable quantity is being assigned to the generic or broad class.

ACGIH = American Conference of Governmental Industrial Hygienists; AEGL = acute exposure guideline levels; CERCLA = Comprehensive Environmental Response, Compensation, and Liability Act; CFR = Code of Federal Regulations; DEA = Drug Enforcement Administration; DWEL = drinking water equivalent level; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; GRAS = Generally Recognized As Safe; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information System; MMT = methylcyclopentadienyl manganese tricarbonyl; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; STEL = short-term expsoure limit; TLV = threshold limit values; TWA = time-weighted average; WHO = World Health Organization