

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 3×10^{-4} mg manganese/m³ (0.3 µg manganese/m³) in respirable dust has been derived for chronic inhalation exposure to manganese. As discussed in Appendix A, dichotomous models in the EPA Benchmark Dose software were fit to the incidence data for abnormal eye-hand coordination scores in battery workers exposed to respirable manganese (Roels et al. 1992). The model with the lowest AIC was selected as the best fitting model, and the BMCL₁₀ from this model, 142 µg respirable manganese/m³, was selected as the point of departure for the chronic inhalation MRL. The MRL of 0.3 µg respirable manganese/m³ was derived by adjusting the point of departure to a continuous exposure basis ($142 \times 5/7 \times 8/24$) and dividing by an uncertainty factor of 100:

- 10 for uncertainty about human variability including possibly enhanced susceptibility of the elderly, infants, and children; individuals with chronic liver disease or diminished hepatobiliary function; and females and individuals with iron deficiency; and
- 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 and the uncertainty that a factor of 10 for human variability will provide enough protection for manganese effects on brain development in children. 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 target organ for effects from 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 for adults of 11 mg manganese/day (established by the U.S. Food and Nutrition Board/Institute of Medicine [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.

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The EPA derived a chronic inhalation RfC of 5×10^{-5} mg/m³ for respirable manganese (IRIS 2008). This value is based on the LOAEL of 0.15 mg/m³ 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 m³/workday.

The EPA (IRIS 2008) 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). A Tolerable Upper Intake Level (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.

8. REGULATIONS, ADVISORIES, AND GUIDELINES

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

| Agency | Description | Information | Reference |
|-----------------------------|--|---|------------|
| <u>INTERNATIONAL</u> | | | |
| Guidelines: | | | |
| IARC | Carcinogenicity classification | No data | IARC 2008 |
| WHO | Air quality guidelines Manganese ^a | 0.15 µg/m ³ | WHO 2000a |
| | Drinking water quality guidelines Manganese ^b | 0.4 mg/L | WHO 2004a |
| <u>NATIONAL</u> | | | |
| 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 | |
| | Manganese (II,III) oxide | Respiratory system, central nervous system, blood, and kidneys | |

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| Agency | Description | Information | Reference |
|---|---|--|---|
| 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 | |
| OSHA | 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 |
| 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 | | |

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|--|---|--------------------------------------|----------------|
| 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 | |
| FDA | Potassium permanganate | Yes | |
| | Bottled drinking water | | FDA 2007a |
| | Manganese | 0.05 mg/L | 21 CFR 165.110 |
| | EAFUS ⁿ | | FDA 2008 |
| | Potassium permanganate | Yes | |
| | Indirect food additives: adhesives and components of coatings | | FDA 2007b |
| | Potassium permanganate | Yes | 21 CFR 175.105 |
| | | | |
| d. Other | | | |
| ACGIH | Carcinogenicity classification | | ACGIH 2007 |
| | Manganese | No data | |
| | MMT | No data | |
| DEA | Records and reports of listed chemicals | | DEA 2007 |
| | Potassium permanganate | List II chemical | 21 CFR 1310.02 |
| EPA | Carcinogenicity classification | | IRIS 2008 |
| | Manganese | Group D ^l | |
| | 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 |
| | Manganese ^l | Yes | 40 CFR 302.4 |
| | Potassium permanganate ^k | Yes | |
| Reportable quantity | | | |
| Manganese | None ^l | | |
| Potassium permanganate | 100 pounds | | |
| Effective date of toxic chemical release reporting | | EPA 2008g | |
| Manganese | 01/01/1987 | 40 CFR 372.65 | |

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|----------------------------------|---|-------------|--|
| NATIONAL (<i>cont.</i>) | | | |
| EPA | Superfund, emergency planning, and community right-to-know Extremely Hazardous Substances MMT | | EPA 2008f 40 CFR 355, Appendix A |
| | Reportable quantity | 100 pounds | |
| | Threshold planning quantity | 100 pounds | |
| NTP | Carcinogenicity classification | No data | NTP 2005 |

^aTWA based on effects other than cancer or odor/annoyance using an averaging time of 1 year.

^bConcentrations 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.

^cSkin 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.

^dNIOSH 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/m³) was adequate enough to protect workers from potential health hazards (NIOSH 2005).

^eSkin 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.

^fThe 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.

^gNational 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.

^hThe EAFUS list of substances contains ingredients added directly to food that FDA has either approved as food additives or listed or affirmed as GRAS.

ⁱGroup D: not classifiable as to human carcinogenicity.

^jDesignated CERCLA hazardous substance pursuant to Section 112 of the Clean Air Act.

^kDesignated CERCLA hazardous substance pursuant to Section 311(b)(2) of the Clean Water Act.

^lNo 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 exposure limit; TLV = threshold limit values; TWA = time-weighted average; WHO = World Health Organization