Manganese

TEACH Chemical Summary

U.S. EPA, Toxicity and Exposure Assessment for Children's Health

This TEACH Chemical Summary is a compilation of information derived primarily from U.S. EPA and ATSDR resources, and the TEACH Database. The TEACH Database contains summaries of research studies pertaining to developmental exposure and/or health effects for each chemical or chemical group. TEACH does not perform any evaluation of the validity or quality of these research studies. Research studies that are specific for adults are not included in the TEACH Database, and typically are not described in the TEACH Chemical Summary.

I. INTRODUCTION

Manganese is a naturally-occurring metal that, in pure form, is silver-colored with no taste or smell. Manganese is normally encountered in the environment as a compound with oxygen, sulfur, or chlorine (1). Manganese is an essential nutrient, required in trace amounts for human health. Intake is normally sufficient with a balanced diet. While adverse developmental effects due to insufficient (too low) levels of manganese in the diet have been evaluated, these studies are not covered in TEACH. Exposure to high concentrations of manganese exposure can be detrimental to health (1), and such studies are discussed in this TEACH Chemical Summary.

There are two forms of manganese in the environment. Inorganic manganese compounds are used in the production of steel, batteries, ceramics, and dietary supplements. These manganese compounds are also generated as combustion products from motor vehicles and coal-burning industrial plants. Organic manganese compounds are used in some pesticides, fertilizers, and in a gasoline additive called methlcyclopentadienyl manganese tricarbonyl (MMT) (1). Manganese compounds can be present as dust particles in the air, and dissolved in ground water or drinking water (1).

Infants and children are exposed to manganese primarily via diet, including breast milk and infant formula, but can also be exposed via air and drinking water (1-12). Manganese concentrations in these media are usually not at levels of concern, though children with certain types of liver disease, and children on parenteral (intravenous) nutrition are sub-populations that may be at higher risk for over-exposure to manganese (1).

The primary targets of manganese toxicity are the brain and central nervous system (1). Manganese has been shown to be deposited in certain regions of the brain, and exposure to high concentrations in occupational studies was associated with permanent damage, with symptoms of impaired neurological and neuromuscular control, mental and emotional disturbances, muscle stiffness, lack of coordination, tremors, difficulties with breathing or swallowing, and other neuromuscular problems (1). Exposure to very high doses of manganese in experimental animal studies has resulted in impaired male fertility, and birth defects in offspring including cleft palate, impaired bone development, and other effects (13-33).

II. EXPOSURE MEDIA AND POTENTIAL FOR CHILDREN'S EXPOSURE[1]

Exposure Media	Relative Potential for Children's Exposure[2,3]	Basis[4]
Diet	Higher	Manganese may be found in infant formulas and breast milk, as well as some cereals, leafy vegetables, fruits, and fruit juices. Manganese is an essential nutrient. Elevated intake of manganese above recommended amounts may be of concern in some dietary situations.
Ambient Air	Medium	Manganese uptake via inhalation is of greater concern for toxicity than uptake via ingestion. Manganese can be found in ambient air, though it is generally not at levels of concern for exposure. However, air concentrations can be of higher concern near industries processing or using manganese (e.g., mining operations, metal processing plants, coke ovens, power plants, and certain pesticide producers). Use of the manganese-containing additive MMT in gasoline contributes to ambient air contamination, though MMT use in the U.S. is uncommon.
Ground Water	Lower	Manganese is a common natural constituent of ground water. Elevated concentrations of manganese may exist in some ground water due to certain bedrock formations or pollution sources.
Drinking Water	Lower	Elevated concentrations of manganese may exist in some drinking water due to certain bedrock formations or pollution sources.
Surface Water	Lower	Manganese is not generally found at elevated concentrations in surface water.
Indoor Air	Lower	Manganese is not generally found in indoor air.
Soil	Lower	Manganese can be found in soil, but is not likely to be a significant contributor to exposure for most children.

[1] For more information about child-specific exposure factors, please refer to the Child-Specific Exposure Factors Handbook (http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=55145).

[2] The Relative Potential for Children's Exposure category reflects a judgment by the TEACH Workgroup, U.S. EPA, that incorporates potential exposure pathways, frequency of exposure, level of exposure, and current state of knowledge. Site-specific conditions may vary and influence the relative potential for exposure. For more information on how these determinations were made, go to http://www.epa.gov/teach/teachprotocols_chemsumm.html.

[3] Childhood represents a lifestage rather than a subpopulation, the distinction being that a subpopulation refers to a portion of the population, whereas a lifestage is inclusive of the entire population.

[4] Information described in this column was derived from several resources (e.g., 1, 2) including studies listed in the TEACH Database (http://www.epa.gov/teach).

III. TOXICITY SUMMARY[5, 6]

Manganese is an essential nutrient that is important for normal processes in the body, though adverse health effects have been noted at higher doses (1). Excessive manganese exposure, predominantly reported in adults exposed occupationally via inhalation, has been associated with adverse central nervous system effects (1). "Manganism" refers to a set of symptoms associated with relatively high exposure to manganese, reported in adult occupational exposure studies, and includes muscle stiffness, lack of coordination, tremors, difficulties with breathing or swallowing, and other neuromuscular problems (1). Manganism has symptoms similar to Parkinson's Disease, and in adults, manganese-induced Parkinsonism has been reported to continue for at least ten years after the cessation of exposure to manganese (1). More subtle effects on neuromotor function were associated with residential Mn exposures (34).

Manganese toxicity varies with exposure route. When ingested, manganese may be among the least toxic of the trace elements (35). Inhaled manganese bypasses the gut and can enter the brain in two ways: by olfactory (nasal airway) neural pathways that provide a direct path to brain tissue, and by lung uptake and long residence time that could provide a source of continuing exposure (36).

In children, higher manganese concentrations in hair or blood have been associated with learning disabilities (5, 37) and neuromuscular effects (38-40). Some subpopulations of children are at higher risk for overexposure to manganese via diet, including children with choleastatic liver disease (with decreased liver function) (38), and children who receive parenteral nutrition (intravenous feeding) (39, 41-44). Deposition of manganese in the basal ganglia of the central nervous system has been measured in some of these studies (39, 41, 43).

In experimental animal studies, very high doses of manganese were shown to impair male fertility (13-15) and result in fetal toxicity (15-17). In some studies, manganese exposure was shown to be teratogenic (cause birth defects), including short tail, excess toes, cleft palate, low external ears, hydrocephaly, delayed bone hardening, and decreased birth weight (16-20). Studies of neonatal and early life manganese exposure reported neurochemical and neurobehavioral changes in rats, e.g. increased spontaneous motor activity and increased brain dopamine levels (21-33).

Carcinogenicity weight-of-evidence classification[7]: The U.S. EPA classified manganese as "not classifiable as a human carcinogen" because existing studies were inadequate to assess the carcinogenicity of manganese (www.epa.gov/iris/subst/0373.htm, II.A.1) (35). The World Health Organization International Agency for Research on Cancer (IARC) has not classified manganese as to its carcinogenicity (http://monographs.iarc.fr/ENG/Classification/index.php) (45).

[5] Please refer to research article summaries listed in the TEACH Database for details about study design considerations (e.g., dose, sample size, exposure measurements).

[6] This toxicity summary is likely to include information from workplace or other studies of mature (adult) humans or experimental animals if child-specific information is lacking for the chemical of interest. Summaries of articles focusing solely on adults are not listed in the TEACH Database because the TEACH Database contains summaries of articles pertaining to developing organisms.

[7] For recent information pertaining to carcinogen risk assessment during development, consult Guidelines for Carcinogen Risk Assessment and Supplemental Guidance on Risks from Early Life Exposure at *http://www.epa.gov/cancerguidelines*.

IV. EXPOSURE AND TOXICITY STUDIES FROM THE TEACH DATABASE

This section provides a brief description of human and animal studies listed in the TEACH Database. For more details about study design parameters, e.g., doses and exposure information, please refer to article summaries in the TEACH Database. Any consideration should include an understanding that exposure levels in animal studies, in many cases, are greater than exposure levels normally encountered by humans.

A. *HUMAN EXPOSURE AND EFFECTS*

- Children are exposed to manganese in their diet as natural components of food. The main route of exposure for infants is ingestion of breast milk and infant formula, and manganese levels have been measured in both foods (2-9, 11, 46). One study reported that formula-fed infants tend to have higher levels of hair or blood manganese than breast-fed infants, though levels in both groups were within U.S. National Research Council (NRC) recommended ranges (5). Manganese can also be found in some cereals, fruits, and vegetables as natural components of the food or as residues of the pesticides maneb and mancozeb (47). Manganese concentrations were higher in soy and rice drinks, and in soy formulas, than in cow's milk formulas (8).
- Inhalation is another route of exposure for children. Levels of manganese in air have been measured in several cities, with particular interest in Canadian cities (48-51) where the gasoline additive MMT is used more extensively than in the U.S. (see Regulatory Issues). Some industrial releases are also sources of manganese in air (1). One study of teenagers in New York City detected manganese in personal air samples (52).
- Manganese concentrations have been measured in cord blood (51, 53-57), breast milk (4, 5, 9, 10, 12), children's hair (5, 58), and children's blood (4, 11, 39, 40, 43, 44, 58-61). Two larger studies described reference ranges for a healthy population (59, 60).
- Infants have been shown in one study to have increased absorption of manganese via the digestive tract, relative to adults (6). Formula-fed infants have been shown to absorb greater amounts of manganese than breast-fed infants (62, 63).
- Neurological effects of manganese exposure in children remain unclear. One case study of occupational exposure of a 17-year-old male described involuntary movement of one arm, one leg, and a lower portion of the face that resolved following manganese chelation therapy (40). In contrast, case reports of significant manganese deposition in the brains of children taking parenteral nutrition reported no observed neurological toxicity (41, 43). Two studies have shown that learning disabled and/or hyperactive children have more manganese in their hair than control children (5, 37). There have been limited reports of associations between increased manganese concentrations in drinking water and decreased scores on tests of memory or cognitive ability (58, 64). One recent California study reported that a modest increase in the incidence of autism was associated with the highest 25% of manganese air concentrations (65).

- Some subpopulations of children are at higher risk for overexposure to manganese. Children with choleastatic liver disease (decreased liver function) can accumulate manganese to a greater extent than other children (38). Children who receive parenteral nutrition (intravenous feeding) have experienced accumulation of high manganese concentrations in blood (39, 41-44). Deposition of manganese in the basal ganglia of the central nervous system has been measured in some of these studies (39, 43, 44). Careful regulation of the amount of manganese delivered in children's parenteral nutrition was found to be important for their long term health (39, 43, 44).

B. *ANIMAL EXPOSURE AND EFFECTS*

- Manganese has been shown to accumulate in maternal liver and to cross the placenta in rats (20, 66-68). Increased manganese in the diet of pregnant and lactating rats led to accumulation of manganese in the brains of their offspring, as well as altered concentrations of other metals in their brains (i.e., zinc and chromium) (69).
- Absorption of manganese in the gastrointestinal tract of developing rats and mice has been studied (66, 70-74). Manganese absorption was greater in neonatal rats than in adult rats, and this difference subsided by late suckling age (2 weeks after birth) (74).
- In adult males, exposure of rabbits to manganese via injection led to degeneration of the testicles, accompanied by a loss of spermatogenesis and complete infertility (13). Lifetime exposure (*in utero* through adulthood) of iron-deficient rats (14) or manganese exposure of adult mice (15) or via drinking water led to impaired spermatogenesis and fertility.
- Pregnant females exposed to high concentrations of manganese orally or by injection experienced fewer pregnancies in rats (14) or increased post-implantation losses (fetal deaths) in mice (15-17).
- Cleft palate, delayed ossification of bones and increased skeletal malformations were seen in offspring following injection of pregnant mice with inorganic manganese compounds (16, 17). One study found similar teratogenic effects in rats but not rabbits (75). Another study showed that, following exposure of pregnant rats during pregnancy and continuing through lactation, offspring had significantly reduced body weight and brain weight (68).
- Neurobehavioral effects of manganese exposure have been investigated. Following prenatal and lactational exposure of rats to high doses of manganese in drinking water, offspring demonstrated increased spontaneous motor activity (21). Oral administration of manganese to newborn rats also resulted in increased spontaneous motor activity (22, 23) and increased passive avoidance errors and other impairments in behavioral tests (28, 29). Infant monkeys fed formula with increasing amounts of manganese (with highest concentrations in soy formula supplemented with manganese) through 4 months of age showed significantly less growth and more gross motor activity at 8 months of age, as compared to monkeys fed formula (cow's milk formula) with less manganese (27).

- Neurochemical changes have been observed in offspring following prenatal and/or neonatal exposure of rats to high levels of manganese (21-33, 76). Reported effects included changes in dopamine and dopamine metabolite levels in striatal brain tissue (23, 28, 29); transient decreased choline acetyltransferase activity (24); and decreased hypothalamus dopamine levels and tyrosine hydroxylase activity (25, 26). Other reported neurochemical effects included increased glutathione levels (30), increased uptake of dopamine (31), and changes in glutamine synthetase and metallothionein levels in brain tissue (32). Two additional studies found no changes in measured monoamines levels in brains of pups orally exposed to similar or higher levels of manganese as in studies that found changes (21, 33).
- The nutritional state of rats has been shown to impact absorption of manganese and subsequent health effects. One study found that young rats fed a low protein diet were more likely to exhibit developmental neurological delays (eye opening and auditory startle) following exposure to manganese than control rats fed a balanced diet (77). Another study found that when fed a manganese-supplemented diet, iron-deficient pups absorbed more manganese and experienced greater weight loss than iron-sufficient controls (14).

V. CONSIDERATIONS FOR DECISION-MAKERS

This section contains information that may be useful to risk assessors, parents, caregivers, physicians, and other decision-makers who are interested in reducing the exposure and adverse health effects in children for this particular chemical. Information in this section focuses on ways to reduce exposure, assess possible exposure, and, for some chemicals, administer treatment.

- As an essential nutrient, the U.S. National Research Council (NRC) in 1989 set an "Estimated Safe and Adequate Daily Dietary Intake" (ESADDI) of manganese to be 0.3-0.6 mg/day for infants to 6 months, 0.6-1 mg/day for infants to 1 year, 1-1.5 mg/day for children 1-3 years old, 1-2 mg/day for children 4-10 years old, and 2-5 mg/day for children 10 years old and up. There currently is no Recommended Daily Allowance (RDA) for manganese (1). The Institute of Medicine (IOM) also issued dietary reference intakes for manganese which are similar to the NRC intakes, with the exception of infants 0-6 months old: the IOM recommends 0.003 mg/day for this age group (78, 79).
- The ESADDI for manganese (see bullet above) and the calculated toxicity value for manganese (U.S. EPA RfD) are close in value, suggesting that there may be a relatively narrow range of acceptable exposure to manganese (for example, an ESADDI of 1-2 mg, as compared to a recommended maximum daily intake of 3.5 mg, for an 8-year-old, 25 kg child based on the U.S. EPA RfD) (1).
- A well-balanced diet for children is important to avoid manganese toxicity since it is suggested from animal studies that iron-deficient and protein-deficient diets may increase the sensitivity of children to the toxic effects of manganese (14, 77).
- Elevated manganese levels are occasionally found in drinking water and specifically in well water (1). If tap water in homes with well water sources leaves black deposits or dark stains in sinks or other fixtures, families should consider getting their water tested for manganese levels (1).

- The pesticides maneb and mancozeb contain organic manganese compounds, and are known to be developmentally toxic (80-82). Many of the toxic effects following exposure to maneb and mancozeb may be due to ethylene thiourea (ETU), a major breakdown product of these thiocarbamate pesticides, though it is very difficult to separate out the manganese-related effects from the ETU-related effects; these issues are discussed in detail elsewhere (81, 82).
- A detailed compilation of information pertaining to exposure and health effects of manganese is available in the Toxicological Profile for Manganese (1). A Hazard Summary for Manganese is also available from the U.S. EPA (83).
- The U.S. EPA reported assessments of air concentrations of manganese compounds on a regional scale based on 1999 emissions data, and included risk assessments for the air toxics based on chronic exposure; manganese is one of 177 air pollutants included in this assessment (84).
- Manganese compounds, as a group, are listed as number 115 on the 2005 Priority List of Hazardous Substances for the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) section 104 (i), as amended by the Superfund Amendments and Reauthorization Act (SARA). This is a prioritized list ranking chemicals in order of concern for those most commonly found at sites listed on the National Priorities List (NPL); there are currently 275 substances on this list (85). The priority of concern is determined by considering the frequency of occurrence at NPL sites, the potential hazard to human health, and the potential for human exposure.
- Consult the U.S. EPA "Child-Specific Exposure Factors Handbook" (EPA-600-P-00-002B) for factors to assess children's dermal absorption and inhalation rates (86). An updated External Draft of the 2006 version of this handbook is available (87).

VI. TOXICITY REFERENCE VALUES

A. Oral/Ingestion

U.S. EPA Reference Dose (RfD) for Chronic Oral Exposure: 1.4E-1 (or 0.14) mg/kg/day (which equals 0.064 mg/lb/day), based on central nervous system effects in adults (www.epa.gov/iris/subst/0373.htm, I.A.1) (35). Last Workgroup Verification Date 5/12/95.

U.S. EPA Secondary Maximum Contaminant Level (MCL): 0.05 mg/L; recommended concentration and not enforceable, set for aesthetic or cosmetic reasons to avoid stains on plumbing and laundered clothes (http://www.epa.gov/safewater/contaminants/index.html) (88).

B. Inhalation

U.S. EPA Reference Concentration (RfC) for Chronic Inhalation Exposure: 5E-5 (or 0.00005) mg/m^3, based on impaired neurobehavioral function in adults (www.epa.gov/iris/subst/0373.htm, I.B.1) (35). Last Workgroup Verification Date 9/23/93.

U.S. ATSDR Minimal Risk Level (MRL): 0.00004 mg/m^3 (chronic inhalation), based on neurological effects (http://www.atsdr.cdc.gov/mrls/index.html) (89). Last revised 9/00.

VII. U.S. FEDERAL REGULATORY INFORMATION

- In the Clean Air Act of 1977, the U.S. EPA banned the use of the gasoline additive methylcyclopentadienyl manganese tricarbonyl (MMT) in gasoline. However, a 1995 federal court ruling overturned this ban. The U.S. EPA concluded that further research was needed to assess health risks following exposures to manganese from the use of MMT, and such research is currently in process (90). Currently the Section 211k(2)(D) of the Clean Air Act bans MMT in Reformulated Gasoline (RFG); MMT is still used in limited amounts in the gasoline pool, but limited information is available, and the extent of use is unclear (90).
- Manganese compounds, as a group, are listed as hazardous air pollutants (HAPs) under section 112(b) of the 1990 Clean Air Act Amendments, and are regulated from more than 170 industrial source categories; there are 188 pollutants on this list (91).
- The manganese-containing pesticides maneb (81) and mancozeb (82) each are regulated by the U.S. EPA, and a Reregistration Eligibility Decision (RED) document is available for each pesticide (81, 82). The RED summarizes human health risk assessment conclusions and outlines any risk reductions necessary for continued registered use of the pesticide in the United States.
- The U.S. EPA requires reporting of quantities of certain chemicals that exceed a defined reportable quantity, and that quantity varies for different chemicals (92). Under the Emergency Planning and Community Right-to-Know Act (EPCRA) Section 313 “Toxic Chemicals,” quantities of manganese greater than 25,000 pounds manufactured or processed, or greater than 10,000 pounds otherwise used, is required (92).

VIII. BACKGROUND ON CHEMICAL

A. CAS Number: 7439-96-5

B. Physicochemical Properties: Manganese in pure form is a silver metal, but is most often found in a compound with oxygen, sulfur, or chlorine. Manganese compounds are most often in white powder form, or dissolved in water (1). For more information, go to the National Library of Medicine ChemID Web site (*http://chem.sis.nlm.nih.gov/chemidplus/*) and search for manganese, MMT, maneb, or mancozeb.

C. Production: Manganese is an elemental metal that is most commonly found and used as a compound (manganese combined with sulfur, carbon, or oxygen). It can be released from mining and smelting operations, during welding, and from coal- or oil-burning factories or power plants (1, 93). In the U.S., over 19 million pounds of manganese, and over 189 million pounds of manganese compounds were reported in disposals and releases in 2004 (94).

D. Uses: Manganese and manganese compounds are used to make steel, used in some pesticides (e.g., maneb or mancozeb), and used as anti-knock agents in gasoline (MMT) (1, 93). Mancozeb was ranked as number 20 for most commonly-used active ingredients in pesticides in the U.S., with 6-8 million pounds estimated use in 2001 (95). Manganese is also found in generally small amounts in some foods (e.g., cereal, soy formulas, vegetables, fruits, and tea) and in nutritional supplements.

E. Environmental Fate: Manganese can be released into air from various industrial operations (e.g., mines, coke ovens). Manganese can be directly released or deposited from airborne releases into water or soil (1, 93). Manganese is also a naturally occurring metal that can be found in rivers and lakes. Plants can absorb and bioconcentrate manganese from contaminated water (93).

F. Synonyms and Trade Names: Colloidal manganese, magnacat, mangan, manganese, Mangan nitridovany, tronamang.

Additional information on manganese is available in the TEACH Database for Manganese and at the following Web sites:

http://minerals.er.usgs.gov/minerals/pubs/commodity/manganese/index.html
http://www.epa.gov/ttn/atw/hlthef/manganes.html
http://www.epa.gov/waterscience/library/wqcriteria/manganese.pdf

REFERENCES

1. U.S. Centers for Disease Control (ATSDR). 2000. "Toxicological Profile for Manganese." http://www.atsdr.cdc.gov/toxprofiles/tp151.html.
2. Lonnerdal, B., et al. 1983. "Iron, zinc, copper, and manganese in infant formulas." Am.J.Dis.Child 137(5):433-437.
3. Stastny, D., et al. 1984. "Manganese intake and serum manganese concentration of human milk-fed and formula-fed infants." Am.J.Clin.Nutr. 39(6):872-878.
4. Krachler, M., et al. 1999. "Trace element transfer from the mother to the newborn--investigations on triplets of colostrum, maternal and umbilical cord sera." Eur.J.Clin.Nutr. 53(6):486-494.
5. Collipp, P.J., et al. 1983. "Manganese in infant formulas and learning disability." Ann.Nutr.Metab 27(6):488-494.
6. Dorner, K., et al. 1989. "Longitudinal manganese and copper balances in young infants and preterm infants fed on breast-milk and adapted cow's milk formulas." Br.J.Nutr. 61(3):559-572.
7. Krachler, M., et al. 2000. "Concentrations of selected trace elements in human milk and in infant formulas determined by magnetic sector field inductively coupled plasma-mass spectrometry." Biol.Trace Elem.Res. 76(2):97-112.
8. Cockell, K.A., et al. 2004. "Manganese content of soy or rice beverages is high in comparison to infant formulas." J.Am.Coll.Nutr. 23(2):124-130.
9. Sharma, R., and S.P. Pervez. 2005. "Toxic metals status in human blood and breast milk samples in an integrated steel plant environment in central India." Environ.Geochem.Health 27:39-45.
10. Yamawaki, N., et al. 2005. "Macronutrient, mineral and trace element composition of breast milk from Japanese women." J.Trace Elem.Med.Biol. 19(2-3):171-181.
11. Alarcon, O.M., et al. 1996. "Manganese levels in serum of healthy Venezuelan infants living in Merida." J.Trace Elem.Med.Biol. 10(4):210-213.
12. Arnaud, J., and A. Favier. 1995. "Copper, iron, manganese and zinc contents in human colostrum and transitory milk of French women." Sci.Total Environ. 159(1):9-15.
13. Imam, Z., and S.V. Chandra. 1975. "Histochemical alterations in rabbit testis produced by manganese chloride." Toxicol.Appl.Pharmacol. 32(3):534-544.
14. Laskey, J.W., et al. 1982. "Effects of chronic manganese (Mn3O4) exposure on selected reproductive parameters in rats." J.Toxicol.Environ.Health 9(4):677-687.
15. Elbetieha, A., et al. 2001. "Effects of long-term exposure to manganese chloride on fertility of male and female mice." Toxicol.Lett. 119(3):193-201.
16. Colomina, M.T., et al. 1996. "Effect of day of exposure on the developmental toxicity of manganese in mice." Vet.Hum.Toxicol. 38(1):7-9.
17. Sanchez, D.J., et al. 1993. "Maternal and developmental toxicity of manganese in the mouse." Toxicol.Lett. 69(1):45-52.
18. Lown, B.A., et al. 1984. "Effects on the postnatal development of the mouse of preconception, postconception and/or suckling exposure to manganese via maternal inhalation exposure to MnO2 dust." Neurotoxicology 5(1):119-129.
19. Webster, W.S., and A.A. Valois. 1987. "Reproductive toxicology of manganese in rodents, including exposure during the postnatal period." Neurotoxicology 8(3):437-444.
20. Zhang, B.Y., et al. 2002. "Effect of manganese on heat stress protein synthesis of new-born rats." World J.Gastroenterol. 8(1):114-118.

21. Pappas, B.A., et al. 1997. "Perinatal manganese exposure: behavioral, neurochemical, and histopathological effects in the rat." Neurotoxicol.Teratol. 19(1):17-25.
22. Brenneman, K.A., et al. 1999. "Manganese-induced developmental neurotoxicity in the CD rat: is oxidative damage a mechanism of action?" Neurotoxicology 20(2-3):477-487.
23. Dorman, D.C., et al. 2000. "Neurotoxicity of manganese chloride in neonatal and adult CD rats following subchronic (21-day) high-dose oral exposure." J.Appl.Toxicol. 20(3):179-187.
24. Lai, J.C., et al. 1991. "Effects of chronic manganese treatment on rat brain regional sodium-potassium-activated and magnesium-activated adenosine triphosphatase activities during development." Metab.Brain Dis. 6(3):165-174.
25. Deskin, R., et al. 1981. "Neurochemical alterations induced by manganese chloride in neonatal rats." Neurotoxicology 2(1):65-73.
26. Deskin, R., et al. 1981. "The effect of chronic manganese administration on some neurochemical and physiological variables in neonatal rats." Gen.Pharmacol. 12(4):279-280.
27. Golub, M.S., et al. 2005. "Neurobehavioral evaluation of rhesus monkey infants fed cow's milk formula, soy formula, or soy formula with added manganese." Neurotoxicol.Teratol. 27(4):615-627.
28. Tran, T.T., et al. 2002. "Effects of neonatal dietary manganese exposure on brain dopamine levels and neurocognitive functions." Neurotoxicology 23(4-5):645-651.
29. Tran, T.T., et al. 2002. "Effect of high dietary manganese intake of neonatal rats on tissue mineral accumulation, striatal dopamine levels, and neurodevelopmental status." Neurotoxicology 23(4-5):635-643.
30. Weber, S., et al. 2002. "Effects of manganese (Mn) on the developing rat brain: oxidative-stress related endpoints." Neurotoxicology 23(2):169-175.
31. Lai, J.C., et al. 1982. "The effects of chronic manganese chloride treatment expressed as age-dependent, transient changes in rat brain synaptosomal uptake of amines." J.Neurochem. 38(3):844-847.
32. Erikson, K.M., et al. 2005. "Persistent alterations in biomarkers of oxidative stress resulting from combined *in utero* and neonatal manganese inhalation." Biol.Trace Elem.Res. 104(2):151-163.
33. Kontur, P.J., and L.D. Fechter. 1988. "Brain regional manganese levels and monoamine metabolism in manganese-treated neonatal rats." Neurotoxicol.Teratol. 10(4):295-303.
34. Mergler, D., et al. 1999. "Manganese neurotoxicity, a continuum of dysfunction: results from a community based study." Neurotoxicology 20(2-3):327-342.
35. U.S. Environmental Protection Agency. 1988. "Integrated Risk Information System (IRIS): Manganese (CASRN 7439-96-5)." http://www.epa.gov/iris/subst/0373.htm.
36. Weiss, B. 2006. "Economic implications of manganese neurotoxicity." Neurotoxicology 27(3):362-368.
37. Pihl, R.O., and M. Parkes. 1977. "Hair element content in learning disabled children." Science 198(4313):204-206.
38. Devenyi, A.G., et al. 1994. "Dystonia, hyperintense basal ganglia, and high whole blood manganese levels in Alagille's syndrome." Gastroenterology 106(4):1068-1071.
39. Fell, J.M., et al. 1996. "Manganese toxicity in children receiving long-term parenteral nutrition." Lancet 347(9010):1218-1221.
40. Ono, K., et al. 2002. "Myoclonic involuntary movement associated with chronic manganese poisoning." J.Neurol.Sci. 199(1-2):93-96.

41. Ono, J., et al. 1995. "Manganese deposition in the brain during long-term total parenteral nutrition." JPEN J.Parenter.Enteral Nutr. 19(4):310-312.
42. Quaghebeur, G., et al. 1996. "MRI in children receiving total parenteral nutrition." Neuroradiology 38(7):680-683.
43. Kafritsa, Y., et al. 1998. "Long-term outcome of brain manganese deposition in patients on home parenteral nutrition." Arch.Dis.Child 79(3):263-265.
44. Hambidge, K.M., et al. 1989. "Plasma manganese concentrations in infants and children receiving parenteral nutrition." J.Parenter.Enteral Nutr. 13(2):168-171.
45. World Health Organization. 2006. "IARC Monographs on the Evaluation of Carcinogenic Risks to Humans: Complete List of Agents Evaluated and their Classification." http://monographs.iarc.fr/ENG/Classification/index.php.
46. World Health Organization. 1987. "IARC Monographs on the Evaluation of Carcinogenic Risks to Humans: Overall Evaluations of Carcinogenicity: An Updating of *IARC Monographs*, Volumes 1 to 42 (Supplement 7)." http://monographs.iarc.fr/ENG/Monographs/suppl7/suppl7.pdf.
47. Pennington, J.A., and D.B. Wilson. 1990. "Daily intakes of nine nutritional elements: analyzed vs. calculated values." J.Am.Diet.Assoc. 90(3):375-381.
48. Loranger, S., and J. Zayed. 1997. "Environmental contamination and human exposure to airborne total and respirable manganese in Montreal." J.Air Waste Manag.Assoc. 47(9):983-989.
49. Crump, K.S. 2000. "Manganese exposures in Toronto during use of the gasoline additive, methylcyclopentadienyl manganese tricarbonyl." J.Expo.Anal.Environ.Epidemiol. 10(3):227-239.
50. Pellizzari, E.D., et al. 2001. "Particulate matter and manganese exposures in Indianapolis, Indiana." J.Expo.Anal.Environ.Epidemiol. 11(6):423-440.
51. Smargiassi, A., et al. 2002. "A comparative study of manganese and lead levels in human umbilical cords and maternal blood from two urban centers exposed to different gasoline additives." Sci.Total Environ. 290(1-3):157-164.
52. Chillrud, S.N., et al. 2004. "Elevated airborne exposures of teenagers to manganese, chromium, and iron from steel dust and New York City's subway system." Environ.Sci.Technol. 38(3):732-737.
53. Wilson, D.C., et al. 1991. "Plasma manganese, selenium and glutathione peroxidase levels in the mother and newborn infant." Early Hum.Dev. 26(3):223-226.
54. Takser, L., et al. 2004. "Manganese levels during pregnancy and at birth: relation to environmental factors and smoking in a Southwest Quebec population." Environ.Res. 95(2):119-125.
55. Takser, L., et al. 2004. "Blood manganese content at birth and cord serum prolactin levels." Neurotoxicol.Teratol. 26(6):811-815.
56. Audrey, S., et al. 2002. "A comparative study of manganese and lead levels in human umbilical cords and maternal blood from two urban centers exposed to different gasoline additives." Sci.Total Environ. 290:157-164.
57. Vigeh, M., et al. 2006. "Lead and other trace metals in preeclampsia: a case-control study in Tehran, Iran." Environ.Res. 100(2):268-275.
58. Woolf, A., et al. 2002. "A child with chronic manganese exposure from drinking water." Environ.Health Perspect. 110(6):613-616.
59. Rukgauer, M., et al. 1997. "Reference values for the trace elements copper, manganese, selenium, and zinc in the serum/plasma of children, adolescents, and adults." J.Trace Elem.Med.Biol. 11(2):92-98.

60. Torra, M., et al. 2002. "Biological monitoring of environmental exposure to manganese in blood samples from residents of the city of Barcelona, Spain." Sci.Total Environ. 289(1-3):237-241.
61. Gulson, B., et al. 2006. "Changes in manganese and lead in the environment and young children associated with the introduction of methylcyclopentadienyl manganese tricarbonyl in gasoline--preliminary results." Environ Res 100(1):100-114.
62. Davidsson, L., et al. 1988. "Intrinsic and extrinsic labeling for studies of manganese absorption in humans." J.Nutr. 118(12):1517-1521.
63. Davidsson, L., et al. 1989. "Manganese absorption from human milk, cow's milk, and infant formulas in humans." Am.J.Dis.Child 143(7):823-827.
64. Wasserman, G.A., et al. 2006. "Water manganese exposure and children's intellectual function in Araihazar, Bangladesh." Environ.Health Perspect. 114(1):124-129.
65. Windham, G.C., et al. 2006. "Autism spectrum disorders in relation to distribution of hazardous air pollutants in the San Francisco Bay area." Environ.Health Perspect. 114(9):1438-1444.
66. Jarvinen, R., and A. Ahlstrom. 1975. "Effect of the dietary manganese level on tissue manganese, iron, copper and zinc concentrations in female rats and their fetuses." Med.Biol. 53(2):93-99.
67. Kostial, K., et al. 2005. "Regulation of manganese accumulation in perinatally exposed rat pups." J Appl.Toxicol. 25(2):89-93.
68. Dorman, D.C., et al. 2005. "Tissue manganese concentrations in lactating rats and their offspring following combined *in utero* and lactation exposure to inhaled manganese sulfate." Toxicol.Sci. 84(1):12-21.
69. Garcia, S.J., et al. 2006. "A manganese-enhanced diet alters brain metals and transporters in the developing rat." Toxicol.Sci. 92(2):516-525.
70. Kostial, K., et al. 1989. "Effect of a metal mixture in diet on the toxicokinetics and toxicity of cadmium, mercury and manganese in rats." Toxicol.Ind.Health 5(5):685-698.
71. Rehnberg, G.L., et al. 1980. "Chronic manganese oxide administration to preweanling rats: manganese accumulation and distribution." J.Toxicol.Environ.Health 6(1):217-226.
72. Ballatori, N., et al. 1987. "Homeostatic control of manganese excretion in the neonatal rat." Am.J.Physiol. 252(5 Pt 2):R842-R847.
73. Miller, S.T., et al. 1975. "Control of tissue manganese: initial absence and sudden emergence of excretion in the neonatal mouse." Am.J.Physiol. 229(4):1080-1084.
74. Bell, J.G., et al. 1989. "Higher retention of manganese in suckling than in adult rats is not due to maturational differences in manganese uptake by rat small intestine." J.Toxicol.Environ.Health 26(4):387-398.
75. Szakmary, E.et al.. 1995. "Developmental effect of manganese in rat and rabbit." Cent.Eur.J.Occup. Med.Environ.Health 1:149-159.
76. HaMai, D., et al. 2006. "Decreased expression of inflammation-related genes following inhalation exposure to manganese." Neurotoxicology 27(3):395-401.
77. Ali, M.M., et al. 1983. "Effect of low protein diet on manganese neurotoxicity: I. Developmental and biochemical changes." Neurobehav.Toxicol.Teratol. 5(3):377-383.
78. Institute of Medicine.2001. "Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc."
79. Institute of Medicine. 2001. "Dietary Reference Intakes: Elements." http://www.iom.edu/Object.File/Master/7/294/Webtableminerals.pdf.

80. U.S. Environmental Protection Agency. 1992. "Integrated Risk Information System (IRIS): Maneb." http://www.epa.gov/iris/subst/0249.htm.
81. U.S. Environmental Protection Agency. 2005. "Reregistration Eligibility Decision (RED) for Maneb." http://www.epa.gov/oppsrrd1/REDs/maneb_red.pdf.
82. U.S. Environmental Protection Agency. 2005. "Reregistration Eligibility Decision for Mancozeb." http://www.epa.gov/oppsrrd1/REDs/mancozeb_red.pdf.
83. U.S. Environmental Protection Agency. 2000. "Manganese Compounds: Hazard Summary." http://www.epa.gov/ttn/atw/hlthef/manganes.html.
84. U.S. Environmental Protection Agency. 2006. "Technology Transfer Network 1999 National-Scale Air Toxics Assessment: 1999 Assessment Results." http://www.epa.gov/ttn/atw/nata1999/nsata99.html.
85. U.S. Agency for Toxic Substances and Disease Registry. 2006. "2005 CERCLA Priority List of Hazardous Substances." http://www.atsdr.cdc.gov/cercla/05list.html.
86. U.S. Environmental Protection Agency. 2002. "Child-Specific Exposure Factors Handbook (Interim Report) 2002." http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=55145.
87. U.S. Environmental Protection Agency. 2006. "Child-Specific Exposure Factors Handbook 2006 (External Review Draft)." http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=56747.
88. U.S. Environmental Protection Agency. 2006. "Drinking Water Contaminants." http://www.epa.gov/safewater/contaminants/index.html.
89. U.S. Centers for Disease Control (ATSDR). 2006. "Minimal Risk Levels (MRLs) for Hazardous Substances." http://www.atsdr.cdc.gov/mrls/index.html.
90. U.S. Environmental Protection Agency. 2003. "Comments on the Gasoline Additive MMT (methylcyclopentadienyl manganese tricarbonyl)." http://www.epa.gov/otaq/regs/fuels/additive/mmt_cmts.htm.
91. U.S. Environmental Protection Agency. 2007. "Technology Transfer Network Air Toxics Website: The Original List of Hazardous Air Pollutants." http://www.epa.gov/ttn/atw/188polls.html.
92. U.S. Environmental Protection Agency. 2001. "Lists of Lists: Consolidated List of Chemicals Subject to the Emergency Planning and Right-to-Know Act (EPCRA) and Section 112(r) of the Clean Air Act." http://www.epa.gov/ceppo/pubs/title3.pdf.
93. U.S. Agency for Toxic Substances and Disease Registry. 2000. "ToxFAQs for Manganese." http://www.atsdr.cdc.gov/tfacts151.html.
94. U.S. Environmental Protection Agency. 2007. "TRI Explorer: Chemical Report." http://www.epa.gov/triexplorer/.
95. U.S. Environmental Protection Agency. 2004. "Pesticides Industry Sales and Usage: 2000 and 2001 Market Estimates." http://www.epa.gov/oppbead1/pestsales/01pestsales/market_estimates2001.pdf.