Manganese

Potential Designated Chemical

November 2, 2010 Meeting of Scientific Guidance Panel (SGP)
Biomonitoring California[1]

Manganese (Mn) is an element that occurs in nature most commonly as manganese dioxide, manganese carbonate and manganese silicate. If manganese is added to the list of designated chemicals for the California Environmental Contaminant Biomonitoring Program (also known as Biomonitoring California), this listing would cover any form of manganese. The Program would determine the most appropriate methods for biomonitoring manganese.

There is an extensive body of literature on manganese. The Office of Environmental Health Hazard Assessment (OEHHA) has developed reference exposure levels (OEHHA, 2008) and a child-specific reference dose for manganese (OEHHA, 2006). The current document provides a brief overview of information relevant to the Scientific Guidance Panel's consideration of manganese as a potential designated chemical.

Exposure or potential exposure to the public or specific subgroups:

For the general population, exposure to manganese occurs mainly through food intake (ATSDR, 2008; WHO, 1999). However, manganese in drinking water or air has been shown in some circumstances to result in significant exposure. Occupational exposures to manganese are most likely to occur via inhalation.

Nuts and grains are naturally rich in manganese (ATSDR, 2008; WHO, 1999). Other dietary sources of manganese include tea, beans, and leafy green vegetables (ATSDR, 2008; Drake, 2010). Infant formulas contain higher manganese concentrations than breast milk, with levels in soy formula found to be the highest. Manganese intakes in formula-fed infants can be 10 to 50 times higher than breast-fed infants (Lönnerdal, 1997).

Manganese and manganese compounds are used in a wide variety of industrial processes and applications. Certain metal alloys, such as steel, include manganese to increase hardness. Welding rods may contain manganese and can be a significant source of exposure to welders (OEHHA, 2008). Manganese compounds are used in

[1] California Environmental Contaminant Biomonitoring Program, codified at Health and Safety Code section 105440 et seq.

the manufacture of dry-cell batteries, fireworks and matches, and in fertilizers, ceramics, varnishes and glazes (ACGIH, 2001).

Maneb and mancozeb are manganese-containing fungicides that are extensively used in California. In 2008, approximately 830,000 pounds of maneb and 333,000 pounds of mancozeb were applied statewide (CDPR, 2008).

Manganese has also been used as a gasoline additive, in the form of methylcyclopentadienyl manganese tricarbonyl (MMT). MMT was used to replace or reduce the lead content of gasoline. MMT was formally banned from unleaded gasoline in California effective in 1977 and this ban is still in effect for gasoline in current use (Sierra Research, 2008; Title 13, California Code of Regulations, Section 2254).

Steel dust from erosion of subway rails has been identified as a source of manganese exposure (Crump, 2000; Chillrud et al., 2005).

The US Geological Survey (2010) reported imports of manganese as manganese ore, ferromanganese and silicomanganese totaling more than 500 thousand tons. Manganese ore has not been produced in the US in any significant quantity since 1970.

The California Toxics Inventory reported annual statewide manganese emissions of 1,055 tons in 2004 and 1,023 tons in 2008 (available at: http://www.arb.ca.gov/toxics/cti/cti.htm). The California statewide average ambient air concentration of manganese was 31.5 ng/m^3 in 2002 and 24.0 ng/m^3 in 2008 (see: http://www.arb.ca.gov/adam/toxics/statepages/mnstate.html). The chronic reference exposure level for manganese is 90 ng/m^3, based on impairment of neurobehavioral function in humans (OEHHA, 2008).

The US Environmental Protection Agency (US EPA, 2004) set a drinking water health advisory value of 0.3 mg/L for manganese based on potential for neurological effects. The California health-based notification level in drinking water is 0.5 mg/L. From 2001-2004, detections above the notification level were reported for 276 drinking water sources from 199 drinking water systems (of approximately 12,000 drinking water sources in 4,400 drinking water systems) (CDPH, 2005). Detections above 0.5 mg/L occurred in 42 of California's 58 counties.

Known or suspected health effects:

Manganese is an essential nutrient, but it is also a neurotoxicant. Reports in the 19th and early 20th century identified a distinctive neurological syndrome, "manganism", in

workers exposed to high levels of manganese, primarily by inhalation (Inoue and Makita, 1996). More recently, lower levels of occupational exposure have been associated with effects on motor and neurobehavioral function (Roels et al., 1992; Lucchini et al., 1997; Bouchard et al., 2007a),

Studies in rodents and nonhuman primates have confirmed the neurotoxic potential of manganese and further characterized the basis of this neurotoxic disorder in the brain (Aschner et al., 2007; Gwiazda et al., 2007). These studies highlight biological actions of manganese such as generation of reactive oxygen species, interaction with iron metabolism, impact on cellular processes, and accumulation in specific brain areas (Finkelstein et al., 2007; Fitsanakis et al., 2007; Erikson et al., 2004). Manganese biological actions and toxicity have been reviewed in connection with establishing recommended daily intakes of this essential nutrient (NAS, 2001).

Manganese toxicity is currently one of the most active areas of metal toxicology research in human populations. Studies have recently examined links between manganese in environmental media (soil and airborne particulates) and the incidence of Parkinson's disease (Lucchini et al., 2007; Finkelstein and Jerrett, 2007). Recent studies have also shown that manganese is associated with developmental neurotoxicity. Risk of manganese neurotoxicity is potentially higher prior to maturation of blood brain barrier and manganese homeostasis (Winder, 2010). Manganese concentrations in drinking water and hair were found to be related to children's IQ (Bouchard et al., 2010; Wasserman et al., 2006) and manganese in hair was associated with ratings of oppositional and hyperactive behavior (Bouchard et al., 2007b). Manganese concentrations in serum were associated with attention deficit/hyperactivity disorder (ADHD) diagnosis and methylphenidate (Ritalin) therapy (Farias et al., 2010). Developmental neurotoxicity has been demonstrated in rodents (Kern et al., 2010; Torrente et al., 2002; Tran et al., 2002a; Tran et al., 2002b) and a relevant study in rhesus monkey infants is available (Golub et al., 2005). Alterations in dopamine system are implicated in the origin of developmental manganese toxicity (Kern et al., 2010).

Developmental neurotoxicity due to exposure during pregnancy has also been studied. Associations have been identified between tooth manganese profiles reflecting prenatal exposure and indications of behavioral disinhibition such as ratings of attention, disruptive, and externalizing behavior, and errors in tests requiring inhibition of responding (Ericson et al., 2007). Additionally, elevated blood manganese was associated with lower scores on infant neurobehavioral development scales (Claus Henn et al., 2010; Takser et al., 2003). One of these studies (Ericson et al., 2007) involved children in California.

Lung inflammatory disorders have been associated with industrial manganese exposures but a unique role of manganese has not been established (ATSDR, 2008; Dorman et al., 2005). Two animal studies have shown lung inflammation in response to acute manganese inhalation (OEHHA, 2008).

Male reproductive dysfunction was also reported in occupational exposures (Robbins, 2006) and supporting evidence is provided by rodent dietary studies that showed effects of manganese on fertility, sperm production and testes histopathology (Golub, 2010; ATSDR, 2008). Some information is available in the literature on aspects of female reproduction and effects of manganese on pregnancy outcome in animal models (Golub, 2010), and there is very limited information indicating increased early infant mortality in human populations exposed to excess manganese (Hafeman et al., 2007). In recent studies that sampled maternal and cord blood at birth, associations have been found with birthweights (Zota et al., 2009; Vigeh et al., 2008). While little has been done to evaluate endocrine effects, a series of recent studies has shown effects on gonadotrophic hormones and accelerated puberty onset in rodents (Prestifilippo et al., 2008; Lee et al., 2007; Prestifilippo et al., 2007; Lee et al., 2006; Pine et al., 2005).

The National Toxicology Program (1993) conducted animal cancer bioassays of manganese sulfate monohydrate, finding equivocal evidence of carcinogenicity in male and female mice based on marginally increased incidences of thyroid gland follicular cell adenoma and significantly increased incidences of follicular cell hyperplasia. Other organ systems are impacted primarily at near lethal doses in chronic toxicity studies in rodents (ATSDR, 2008). One organ system that has received some attention in the literature is the cardiovascular system (ATSDR, 2008). Manganese toxicity to the cardiovascular system has been described in animal studies, primarily under conditions of magnesium deficiency (ATSDR, 2008).

Potential to biomonitor:

Bioaccumulation: Lower aquatic organisms can significantly bioconcentrate manganese. Bioconcentration factors (BCFs) of 10,000 to 20,000 were reported for marine and freshwater plants, 10,000 to 40,000 for aquatic invertebrates, and 140,000 to 300,000 for aquatic worms living near hydrothermal vents (ATSDR, 2008; WHO, 2004). For fish, estimated BCFs ranged from 35 to 930. The World Health Organization (WHO, 1999) postulated that “the high reported BCFs probably reflect the essentiality of manganese for a wide variety of organisms; specific uptake mechanisms exist for essential elements.”

Manganese

Pharmacokinetics:

Absorption of ingested manganese is variable. Adults have been reported to generally absorb approximately 3 to 5% (ATSDR, 2008; WHO, 1999). The major route of excretion of manganese is via bile, with a lesser amount of manganese excreted via urine (Davis et al., 1993). Adults exposed to dietary levels of manganese tend to maintain manganese homeostasis (Aschner and Aschner, 2005; US EPA, 1984).

Davidsson et al. (1989) found wide interindividual variation in whole body manganese retention at 10 days post-exposure in 14 adult subjects administered radiolabeled manganese in infant formula. Retention at 10 days averaged 2.9%, with a range of 0.6 to 9.2%.

Neonates and infants have been reported to have poorly developed biliary excretion (Aschner and Aschner, 2005). Ballatori et al. (1987) examined this question in suckling rats. Manganese was retained to a larger degree when exposures were very low. However, when manganese exposure was increased, neonatal rats were efficient at eliminating relatively large amounts of manganese. Biliary excretion was still less than in adults. Fourteen-day old neonatal rats excreted about 30 to 60% less manganese (measured as a percentage of administered dose) compared to adults.

Dorner et al. (1989) studied retention of manganese for breast-fed and formula-fed infants. They calculated that breast-fed infants had a relative retention (as percent of intake) of approximately 40% and formula-fed infants 20%. They noted that absolute retention from formula was higher, because of the more than 10 times higher intake of manganese from formula.

Manganese in blood is nearly all bound to plasma proteins, predominantly β1-globulin (Foradori et al., 1967). A smaller fraction of manganese is bound to transferrin. Manganese bound to transferrin can enter the brain via transferrin receptors in cerebral capillary beds. Other mechanisms involved in uptake of manganese by the brain have been identified, and it is likely that several transport processes are involved (see discussion in Erikson et al., 2007). In the fetus and neonate, an incompletely formed blood-brain barrier results in a greater permeability to manganese (Erikson et al., 2007).

The highest concentrations of manganese are found in tissues with high energy demand, such as the brain, and high pigment content, such as the retina (Aschner and Aschner, 2005). Other tissues observed to have high manganese concentrations are bone, liver, pancreas, and kidney.

Inhaled manganese deposited in the lung can be absorbed directly into the blood stream, or can migrate (by mucociliary transport) into the upper respiratory tract and then be swallowed for possible absorption in the gastrointestinal tract (OEHHA, 2008). In experimental animals, inhaled manganese is transported via olfactory nerves directly to the brain following absorption from nasal passages (Brenneman et al., 2000; Dorman et al., 2002).

Manganese levels in blood increase in pregnant women, with levels at full term measured to be at least twice as high as in non-pregnant women (Smargiassi et al. 2002; Takser et al., 2004). Several studies have found cord blood levels to be approximately twice as high as maternal levels (Zota et al., 2009; Smargiassi et al. 2002; Takser et al., 2004).

Iron deficiency causes an increase in manganese absorption (Davis et al., 1992). Women have been shown to have higher manganese levels than men, likely reflecting differences in iron status (Baldwin et al., 1999; Aschner and Aschner, 2005). In experiments in animals, an iron deficient diet was shown to result in increased levels of manganese in the brain (Erikson et al., 2002).

Subpopulations that may be at greater risk for excessive manganese exposures include neonates, iron-deficient individuals, and others with certain medical conditions such as cholestatic liver disease (OEHHA, 2008; ATDSR, 2008).

Past biomonitoring studies:

OEHHA identified numerous studies that measured manganese levels in various populations, including the general population, pregnant women, children and workers. Some of these studies were conducted to investigate potential health effects of manganese, which are reviewed in the above section on “Known or suspected health effects.” In the current section, the biomonitoring results from selected studies are outlined.

In a study by the Centers for Disease Control & Prevention (CDC), levels of trace metals were analyzed in urine (Paschal et al.,1998). Manganese was detected in 73% of the 496 participants, with a geometric mean urinary concentration of 0.53 µg/L (0.48 µg/g creatinine) and an arithmetic mean concentration of 1.19 µg/L.

Manganese was measured in the blood and urine of 5,309 individuals in the Canadian Health Measures Survey Cycle 1 (2007-2009). A geometric mean manganese

concentration of 9.22 µg/L was found in blood, and 0.08 µg/L in urine (Health Canada, 2010). The arithmetic mean values were 9.68 µg/L in blood and 0.15 µg/L in urine.

Baldwin et al. (1999) analyzed blood samples from 297 residents between the ages of 20 and 69 in Southwest Quebec to investigate indications of neurotoxicity in a population with only environmental exposure to manganese. The geometric mean for the entire study population was 7.14 µg/L. Levels in women were higher than in men (7.50 µg/L versus 6.75 µg/L). For women, manganese blood levels correlated with serum iron, and decreased as age increased. Baldwin et al. also found that higher airborne concentrations of manganese and consumption of leafy vegetables and cereals were correlated with higher manganese blood levels.

Ohashi et al. (2006) analyzed stored samples from 1,000 Japanese women, finding a geometric mean manganese concentration of 0.14 µg/L in urine. Ikeda et al. (2010) reported a geometric mean manganese blood level of 13.2 µg/L in samples from 1,420 Japanese women.

Many studies have evaluated manganese levels in pregnant women, with cord blood also measured in a number of these studies (Alberta Biomonitoring Program, 2008; Creason et al., 1976; Hambidge and Droegemueller, 1974; Krachler et al., 1999; Ljung et al., 2009; Smargiassi et al., 2002; Spencer and Diet, 1999; Takser et al., 2003; Takser et al., 2004; Tsuchiya et al. 1984; Vigeh et al., 2008; Yazbeck et al., 2006; Zota et al., 2009). Several are summarized below.

Zota et al. (2009) measured manganese in maternal and cord blood to examine the relationship with infant birth weight. The study included 470 mother-infant pairs who lived near a Superfund site in Oklahoma. Mean maternal blood levels were 24 µg/L, and mean cord blood levels were 42 µg/L. The approximately two-fold higher level of manganese in cord blood compared to maternal blood has been observed in a number of studies.

The Alberta Biomonitoring Program (2008) measured a range of organic compounds, metals and mineral micronutrients in blood of pregnant women. Serum samples were randomly drawn from more than 50,000 samples collected in 2005. Pooled samples were developed that were representative of geographic region (Northern, Central, Southern Alberta) and age (≤ 25 years, 26-30 years, and 31+). Mean concentrations of manganese ranged from 2 µg/L to 21 µg/L. No differences were found with region or age. In Southern Alberta, seasonal variation was also investigated, but no differences were observed.

Smargiassi et al. (2002) studied mother-infant pairs in Montreal and Paris to compare the effects of different gasoline additives. MMT was used in Quebec, while lead was still used in Paris during the sampling period. The same mean blood level of manganese was found in pregnant women in both cities (23 µg/L). Smargiassi et al. noted that this level was more than twice as high as manganese blood levels measured in non-pregnant women of child-bearing age by Baldwin et al. (1999) in Southwest Quebec (mean of 8.3 µg/L). Mean cord blood levels were very similar in Paris (42 µg/L) and Montreal (45 µg/L) and approximately twice as high as the maternal levels. The authors found that prevalence of high manganese levels in umbilical cord blood was higher in Montreal compared to Paris, but indicated that further study would be needed to determine if this difference could be linked to use of MMT.

Takser et al. (2004) studied pregnant women in Southwest Quebec, showing that mean manganese blood levels increased during pregnancy (9.0 µg/L [first trimester] versus 16.3 µg/L [delivery]). Mean cord blood levels (34.3 µg/L) were more than double maternal levels. Manganese blood levels were significantly higher for residents of urban and agricultural areas compared to residents of small villages. Takser et al. also found higher manganese levels in individuals who reported pesticide spraying less than 1 km from their house. They speculated that higher manganese blood levels in agricultural areas and near pesticide spraying could be due to the use of mancozeb on apple orchards, however they did not gather specific data on pesticide use in the area. The authors suggested that higher blood levels in urban residents could have been due to the use of MMT and/or industrial sources.

A number of studies have measured manganese levels in infants and children (Alarcon et al., 1996; Bouchard et al., 2007b; Burguera et al., 1992; Claus Henn et al., 2010; Farias et al., 2010; Ericson et al., 2007; Rice et al., 2010; Rollin et al., 2005; Spencer and Diet, 1999; Rukgauer et al., 1997; Stastny et al., 1984; Wasserman et al., 2006). Several are summarized below.

Rice et al. (2010) studied exposure to metals, including manganese, in children aged 1-6 years residing in Maine. Private wells are used by approximately half of Maine households for drinking water and elevated manganese levels have been routinely reported. For the entire study population, the 50^{th} percentile blood level of manganese was 30 µg/L and the 95^{th} percentile was 44 µg/L. The blood level of manganese did not vary by age or region, but was significantly higher in summer. The authors suggested this could be due to greater consumption of fresh produce.

Rukgauer et al. (1997) evaluated trace metal levels in plasma from adults and serum from infants and children (aged one month to 18 years) in Germany. The mean level in

plasma from adults was 0.79 µg/L. In the sample of infants and children, the mean level in serum was 1.4 µg/L. Rukgauer et al. detected a downward trend in the levels in infants and children, from approximately 2 µg/L in infants aged 0 to 1 year, compared to approximately 1 µg/L in children aged 14 to 18.

Alarcon et al. (1996) analyzed serum samples from 180 Venezuelan infants ranging in age from 5 days to 12 months. The average concentration of manganese decreased as age increased. The mean concentration was 0.45 µg/L in 5 day old infants and 0.29 µg/L in 12 month old infants.

Burguera et al. (1992) measured manganese levels in serum from 202 Venezuelan infants and children ranging in age from 0 to 72 months. The authors reported that mean levels did not change significantly from 0 to 11 months and that levels decreased gradually thereafter. The data included in the paper indicated a mean level of 0.40 µg/L for infants aged 0 to 1 month, 0.36 µg/L for infants aged 1 to 11 months, and 0.24 µg/L for infants aged 24 to 72 months.

Rollin et al. (2005) measured manganese blood levels in first graders in South Africa. They found that manganese blood levels of children were higher in an area where MMT was added to gasoline compared to an area where it was not (9.80 µg/L versus 6.74 µg/L).

Manganese has also been biomonitored in a wide range of worker populations, such as welders, workers involved in producing manganese compounds or alloys and workers at dry alkaline battery manufacturers (Meyer-Baron et al., 2009). Several occupational studies are summarized below.

Bowler et al. (2007) studied welders working on the San Francisco-Oakland Bay Bridge to examine the relationship between manganese levels and neurological and neuropsychological effects. The mean level in whole blood was 9.6 µg/L. Forty-three percent of the welders had a blood level exceeding 10 µg/L. Mean urinary levels were 0.28 µg/g creatinine. Welders who were still actively welding at the time of the study had significantly higher mean manganese blood levels (10.3 µg/L) than those who had stopped working at the bridge one month or more ago (8.7 µg/L).

In a study of neurotoxicity in 68 welders in China, Yuan et al. (2006) found blood manganese levels of 48.4 µg/L compared to 19.2 µg/L in controls.

Mergler et al. (1994) found that workers in a ferromanganese and silicomanganese alloy facility in Quebec had higher blood manganese levels than workers in the same region without workplace exposure (11.2 µg/L versus 7.2 µg/L).

In a small study of Italian farm workers (n = 7), Canossa et al. (1993) reported that mean urinary manganese levels increased from 0.32 µg/g creatinine to 0.53 µg/g creatinine after a three-day exposure to mancozeb.

Need to assess efficacy of public health actions:

Manganese is an essential nutrient, yet excessive exposure to manganese can cause neurotoxicity, including developmental neurotoxicity. While industrial exposures have been identified and monitored, the potential for excessive exposures to the general population and to sensitive subpopulations has not been well characterized. There is little data on exposure to manganese from the wide use of maneb and mancozeb in California. Biomonitoring manganese will help the state to assess the extent of exposure to California residents.

Availability of analytical methods:

The Environmental Health Laboratory of the California Department of Public Health is currently measuring manganese in whole blood on a trial basis in connection with its determinations of heavy metals by Inductively Coupled Plasma Mass Spectrometry (ICP-MS). The results appear reproducible and analyses of external proficiency materials have been within expected ranges. Development of urine manganese capability continues as part of the urine metals panel. ICP-MS has been used in previous biomonitoring studies to measure manganese in blood and urine.

Cowan et al. (2009) studied manganese levels in the erythrocytes, plasma, urine, hair and saliva of smelting workers. Because the manganese-exposed workers had lower blood iron levels compared to controls, Cowan et al. hypothesized that the blood manganese-iron ratio could be a useful biomarker. They analyzed the results for this ratio and found that the manganese-iron ratio in erythrocytes was a more sensitive measure of occupational exposure, compared to manganese levels alone. The manganese-iron ratio in plasma also showed promising results.

Dr. Asa Bradman (2010, pers comm.) is currently investigating measuring manganese in deciduous teeth as a biomarker of prenatal, early post-natal and cumulative manganese exposure.

Availability of adequate biospecimens: Blood and urine.

Incremental analytical cost: Analysis could be bundled with lead, cadmium, and mercury (total) determination in whole blood using ICP-MS, at a minor incremental cost.

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