State Water Resources Control Board

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SUBJECT: RECOMMENDATION FOR REVISED NOTIFICATION AND RESPONSE LEVELS FOR MANGANESE

Request

Based on the potential risk for manganese-induced neurotoxicogical effects to bottle-fed infants, the Division of Drinking Water (DDW) scientific staff recommends revising the notification and response levels for manganese, which are currently set at 500 µg/L and 5,000 µg/L, respectively. For comparison purposes, the secondary maximum contaminant level for manganese is 50 µg/L.

DDW requests for the Office of Environmental Health Hazard Assessment (OEHHA) to review and comment on the following derivation of a manganese health protective concentration (HPC) of 20 µg/L. The health protective concentration would serve as the basis for future recommended revisions to the current notification and response levels.

Background

Manganese is the 12th most abundant element and composes approximately 0.1% of the earth's crust, which makes it ubiquitous in the environment (Martinez-Finley et al., 2012). It can naturally occur in both surface water and groundwater sources.

Manganese is an essential nutrient and enzyme cofactor that is naturally present in many foods and available as a dietary supplement, but despite its nutritional benefits, adverse health effects can be caused by over-exposure. There is substantial evidence that demonstrates that exposure to manganese at high levels can pose a neurotoxic risk (ATSDR, 2012; US EPA, 2004; WHO, 2004). Occupational manganese exposure has

been shown to cause a distinct neurologic condition known as manganism, a clinical syndrome of cognitive dysfunction that resembles Parkinson disease (Andruska et al., 2015).

The main route of manganese absorption is through the gastrointestinal tract, but absorption also occurs in the lungs following inhalation exposure (O'Neal, 2015). Clinically significant cases due to inhalation are mainly associated with occupational exposures (O'Neal, 2015). There is little evidence that dermal contact with manganese results in significant absorption through the skin and dermal contact is not generally viewed as an important source of exposure (ATSDR, 2012).

Children are considered to be particularly susceptible to possible effects of high levels of manganese exposure because they absorb and/or retain more manganese than adults (ATSDR, 2012). Overexposure to manganese can adversely affect child neurodevelopment (Collipp et al.,1983; Tran et al., 2002; Wasserman et al., 2006; Claus Henn et al., 2010, Bouchard et al., 2011).

Recognizing the vulnerability of children to manganese, some regulating agencies have developed more restrictive guidance or standards to address the potential health risk for infants who may be exposed to elevated levels of manganese in drinking water. For example, Minnesota's Department of Health has a 100 µg/L guidance level, based on the study of Kern, et al., (2010) and Health Canada has a maximum allowable concentration of 120 µg/L.

In view of research findings that show the susceptibility of the developing nervous system to elevated levels of manganese, it is clear that the current notification level of 500 µg/L and response level of 5,000 µg/L should be revised downward, in order to provide a more protective health-based guidance. Such a change is further supported by recent revisions of drinking water advisories and standards for manganese by other regulating agencies outside of California.

Summary of Pertinent Research

Animal Data

In 2006, OEHHA developed a technical document recommending a child-specific reference dose (chRD) for manganese for its school site risk assessment. OEHHA reviewed both human data (see below) and animal data. OEHHA evaluated two neurotoxicological studies on neonatal rats:

- Dorman et al. (2000) evaluated the relative sensitivity of neonatal rats after the administration of 0, 25, or 50 milligrams (mg) manganese chloride/kilogram (kg)-day (0, 11, or 22 mg manganese/kg-day derived by OEHHA) over 21 postnatal days. The study concluded from startle response data that neonates may be at greater risk for manganese-induced neurotoxicity from a dose of 11 mg manganese/kg-day.

- Tran et al. (2002) analyzed the potential neurological effect of manganese supplements on neonatal rats after the administration of 0, 50, 250, or 500 mg manganese chloride/kg-day (0, 1.6, 8.3, or 16.7 mg manganese/kg-day derived by OEHHA) over 21 postnatal days. The study concluded that at 8.3 mg manganese/kg-day, adverse effects were seen in the homing test, and at 1.6 mg manganese /kg-day, adverse effects were seen in the passive avoidance test.

Kern et al. (2010) studied the relationship between early manganese exposure and neurobehavioral deficits. The authors administered oral doses of manganese to neonatal rats at levels of 0, 25, or 50 mg/kg/day over 21 postnatal days. Kern then evaluated the rats' performance in behavioral tests, and measured levels of chemicals in areas of the rat brains. Specifically, the behavioral tests were open arena, elevated plus maze, and 8-arm radial maze. The chemicals evaluated were levels of dopamine D1 and D2 receptor proteins, as well as the dopamine transporter (DAT), which were measured in the prefrontal cortex, nucleus accumbens, and dorsal striatum. For the neonates receiving the 50 mg/kg/day dose, the authors observed altered locomotor activity and behavioral disinhibition in the open area test, altered learning and increased number of errors in the radial maze, and impaired learning/memory in the 8-arm radial test. For the neonates receiving the 25 mg/kg/day dose, Kern observed impaired learning/memory in the 8-arm radial test and reported a reduced level of D1 receptor levels in the dorsal striatum.

Beaudin et al. (2017) studied whether early postnatal oral manganese exposure causes lasting attentional and impulse control deficits in adulthoods and whether lifelong exposure could exacerbate those effects. Neonatal rats were exposed to manganese orally with 0, 25, or 50 mg/kg/day over 21 postnatal days, and then were subjected to a series of learning and attention tasks, using the five-choice serial reaction time task. The study demonstrated that early postnatal manganese exposure caused lasting attentional dysfunction due to impairments in attentional preparedness, selective attention, and arousal regulation. Specifically, manganese exposure impaired performance in the focused attention task, but the dysfunction was limited to the early postnatal (postnatal days 1-21) 25 mg/kg/day group and lifelong 50 mg/kg/day group.

Human Data

In 2006, OEHHA recommended a chRD of 0.03 mg/kg-day for manganese for its school site risk assessment. This recommendation was based on human data, specifically the daily manganese intake upper limit (UL) of 11 mg/L for which there were no observed adverse effects in adults (Food and Nutrition Board, 2002). OEHHA derived the chRD by adjusting for background source contributions of manganese and applied an uncertainty factor of 3 to account for differences between children and adults in GI absorption, biliary excretion, blood-brain barrier, and transferrin receptors (OEHHA, 2006).

Additional Data Conclusions

OEHHA's chRD of 0.03 mg/kg-day for manganese was considered in the development of the notification level but was determined to provide less health protection for infants than

the health protective concentration (HPC) calculated by DDW staff. Given the potential increased sensitivity of the developing infant to neurological toxicity, DDW staff would have used an uncertainty factor of 10 rather than a value of 3 [which was used in the OEHHA (2006) document for school site risk assessments]. This change accounts for differences in infants versus adults, in order to provide more appropriate public health protection for the very young. Thus, because of the difference in uncertainty factors, the chRD was not considered further.

OEHHA (2006) noted that its calculated values were in a narrow range, and that its child reference dose of 0.03 mg/kg-day based on humans was comparable to the value of 0.035 mg/kg-day, a value derived from averaging all the calculated values from the animal data. In addition, the reasoning behind calculating an equivalent manganese content from manganese chloride was not discussed. Nevertheless, OEHHA did not use the cited animal data to develop the chRD. DDW staff considered using these data in developing the notification level, but ultimately decided to use the more recent study by Kern et al., (2010) in this process.

Calculation of Health Protective Concentration for the Notification Level

To derive the HPC for manganese, DDW staff made use of HPC calculations that OEHHA uses in its recommendations for notification levels in drinking water and for its established public health goals.

Calculations of HPCs involve determination of the point of departure (POD) from the dose-response data, and an estimation of an acceptable daily dose (ADD), as described below:

- POD is a dose of a chemical from a study in animals or humans that is used as a starting point for calculation of the ADD. It is a statistical determination that identifies a point at which exposure levels that result in no toxicological response among test subjects deviate to exposures that do result in a toxicological response. With adequate data, statistical benchmark dose (BMD) modelling can be used. When data are not amenable to BMD modeling, a no observed adverse effect level (NOAEL) or a lowest observed adverse effect level (LOAEL) may serve as the POD. Kern et al. (2010) reported a reduced level of D1 receptor levels in the dorsal striatum and impaired learning/memory for neonate rats at the LOAEL of 25 mg/kg-day.
- ADD is an estimated maximum daily dose (expressed as mg/kg-day) of a chemical that can be consumed by humans for an entire lifetime without toxic effects. To determine the ADD, the POD is adjusted by uncertainty factors (UFs).
- UFs are used in noncancer risk assessments to account for uncertainties in data that provide the basis for the risk estimate. These include the availability of data (LOAEL vs. NOAEL), differences between animals and humans (interspecies extrapolation), and differences among humans (intraspecies variation, including sensitive subgroups) in response to a chemical exposure. OEHHA (2008) has

established possible default uncertainty factors for reference exposure levels. DDW has applied a combined UF of 1,000:10 for the use of a LOAEL in the absence of a NOAEL; 10 for interspecies extrapolation, consisting of √10 for pharmacodynamics and √10 for pharmacokinetics; and 10 for intraspecies variability, consisting of √10 for pharmacodynamics and √10 for pharmacokinetics, which accounts for variability within the human population, e.g., for children vs. adults.

ADD = POD ÷ UF

ADD = 25 mg/kg-day ÷ 1000

ADD = 0.025 mg/kg-day

According to the current dietary guidelines for infants (American Academy of Pediatrics, 2020), infants are expected to be exclusively fed human milk or iron-fortified infant formula. At approximately six months of age nutrient-dense complementary foods are introduced to the infant diet. Therefore, DDW used this guidance to justify both the relative source contribution (RSC) and the daily water intake (DWI) of the affected population.

- RSC is the proportion of exposures to a chemical attributed to drinking water. and typically ranges from 20 to 80 percent (expressed as 0.20 to 0.80). In the absence of complete data, the estimated RSC involves a large component of "professional judgment." (OEHHA, 2004).

  There are several factors that were considered for the selection of an appropriate RSC. Since infants have been identified as the susceptible population, the amount of manganese expected to come from infant formula was considered. Frisbie, et al. (2019) measured manganese levels in 25 infant formula products from the United States, and found an average of 650 µg/L and median value of 400 µg/L. In addition, California has an enforceable drinking water standard, secondary maximum contaminant level (SMCL) of 50 µg/L. Lastly, the required daily intake for infants under the age of 6 months was considered. According to the Institute of Medicine (US) Panel on Micronutrients (2001), the recommended adequate intake of manganese for children under the age of 6 months is 3 µg/L and reflects the observed mean manganese intake of infants principally fed human milk. Based on the manganese fortification in the infant formulas, intake was determined to be in excess from each source contribution.

  It is expected that infants under the age of 6 months are almost exclusively fed with liquid versus solid food, and formulas are typically mixed at a 1:1 ratio. Therefore, for such infants, ingestion of manganese in drinking water (say, at concentrations below the 50 µg/L SMCL) is considerably lower than that coming from infant formula on the average, as mentioned above, by at least a couple of orders of magnitude. Given the dietary contribution of manganese from sources other drinking water, DDW staff used an RSC of 0.2.

- DWI is expressed in units of liters per kilogram of body weight per day (L/kg-day). OEHHA's derivation of drinking water public health goals (PHGs) uses age-specific and normalized-to-body-weight water ingestion estimates (OEHHA, 2012). DDW selected the 95th percentile consumer-only water intake rate of 0.237 L/kg-day for infants 0-6 months of age for the notification level derivation. Use of the 0- to 6-month infant drinking water intake rate is consistent with OEHHA's approach for two other drinking water toxicants, namely, perchlorate (OEHHA, 2015) and perfluorobutane sulfonic acid (OEHHA, 2021).

- HPC is derived by multiplying the ADD by the relative source contribution (RSC) and dividing by the daily water intake (DWI) of the affected population.

  HPC = ADD X RSC ÷ DWI

  HPC = 0.025 mg/kg-day X 0.2 ÷ 0.237 L/kg-day

  HPC = 0.021 mg/L (or 21 µg/L, rounded to 20 µg/L)

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