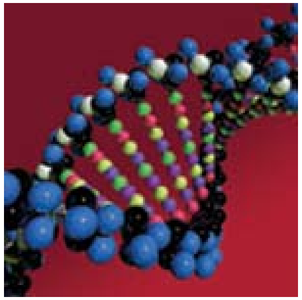
Nutritional and Toxicological Aspects of Manganese Intake

Annette Santamaria, PhD, MPH, DABT

ENVIRON International Corporation

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Overview

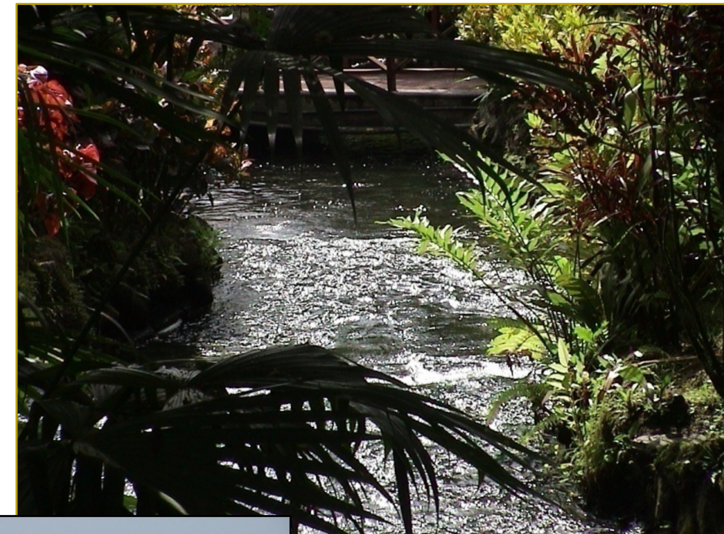
- Sources of Manganese Exposure
- Essentiality and Toxicity of Manganese
- Research Update
- Risk Assessment Issues

Manganese

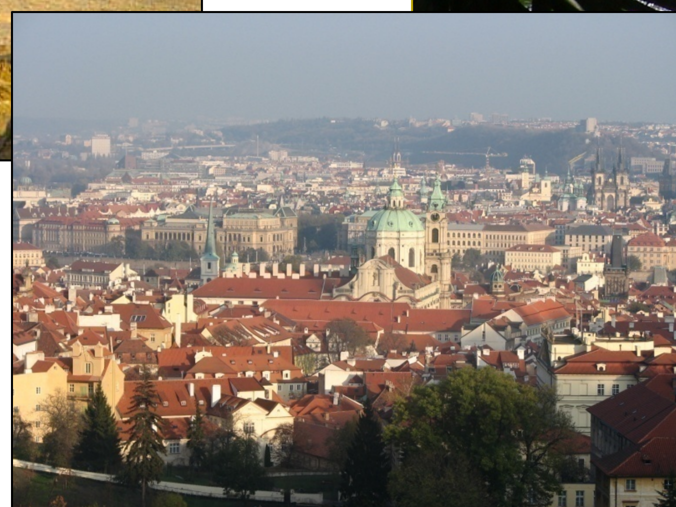
- Manganese is the 12th most-abundant element in the earth's crust; 4th most commonly used metal
- Manganese is naturally present in soil, water, air, and food
- Manganese is an essential trace element and is necessary for maintaining good health

Mn Occurs Naturally in the Environment

Mn natural soil concentration: 40 to 900 mg/kg



Mn natural fresh water concentration: 0.3 to 3,200 µg/L



Mn natural air concentration: 0.01 to 0.07 $\mu g/m^3$

Mn is in Food and Drinking Water

99.8 % of daily Mn intake is from food and water

Cup of tea
1.2 mg Mn

Slice bread
600 µg of Mn

One banana -
225 µg of Mn

Drinking water
WHO – 0.4 mg/L

Supplements -
1-20 mg/d

Sweet Potato
500 µg Mn ½ cup

Man-made Sources of Mn

Metal alloy production (steel) – ~90% of Mn Use

Dry-cell batteries

Welding rods

MMT® fuel additive

Maneb (fungicide)

Homeostatic Regulation of Essential Elements

- Essential trace elements such as Mn are subject to homeostatic control mechanisms that may include regulation of absorption, excretion, and/or tissue retention.
- Toxicity can occur when the exposure is above or below the range which can be accommodated by homeostatic mechanisms.

Essentiality of Manganese

- Essential nutrient necessary for a variety of functions:
  - Skeletal development
  - Immune system function
  - Energy metabolism
  - Activation of enzymes
  - Nervous system function
  - Reproductive hormone function
  - Blood clotting
  - Bone and connective tissue growth

Essentiality of Manganese

- Necessary for amino acid, lipid, protein, carbohydrate metabolism and neurotransmitter synthesis
- Serves as a cofactor for several classes of enzymes:
  - hydrolases, kinases, decarboxylases and transferases
- Component of several metalloenzymes:
  - Arginase, pyruvate carboxylase, superoxide dismutase

Dietary Manganese

- The existence of well-known homeostatic mechanisms has led regulatory authorities to conclude that the body is able to handle substantial variations in dietary Mn on a daily basis without adverse consequences.
- EPA RfD is 0.14 mg/kg/day (10 mg/d adult)
- Based on average intakes of adults eating Western-type and vegetarian diets in various surveys ranging from 0.7 to 10.9 mg Mn/d

Manganese Dietary Requirements

Age Group	AI (mg/day)	UL (mg/day)
0-6 mos	0.003	Not established
7-12 mos	0.6	Not established
1-3 yrs	1.2	2
4-8 yrs	1.5	3
9-13 yrs	1.6 – 1.9	6
14-18	1.6 – 2.2	9
$\geq$19	1.8 – 2.3	11
Pregnant/lactating	2.0 – 2.6	9 – 11

IOM 2004

Manganese Deficiency

- Animal Models
  - Effects on growth and maintenance of connective tissue, cartilage, and bone; reduced fertility
  - Altered carbohydrate metabolism, reduced glucose metabolism, abnormal lipid metabolism, and impaired insulin synthesis and action
- Human Subjects
  - Dermatitis, slow growth of nails and hair, decreased serum cholesterol levels, decreased clotting proteins, weight loss
  - Low levels serum Mn – epilepsy, osteoporosis, cataracts, multiple sclerosis, maple syrup urine disease

Toxicity of Excess Intake

- Manganism
  - Parkinson’s-like movement disorder
  - Manganese accumulation and toxicity in mid-brain structures (striatum and globus pallidus)
  - Mechanism of toxicity under investigation

Toxicity of Excess Intake

- Manganism observed in workers in certain occupations where workers were exposed to high concentrations of manganese-containing dust
- MRIs confirm excess Mn accumulation in the brain
- Clinical neurotoxicity observed in cohorts with exposures typically greater than 1,000 $\mu g/m^3$ for prolonged periods of time

Toxicity of Excess Intake

- Clinical neurotoxicity observed in patients with liver disease or liver failure -- cannot adequately excrete Mn.
- Neurotoxicity in patients administered TPN with Mn (Fell et al. 1996; Devenyi et al. 1994; Dickerson et al. 2001; Hardy et al. 2008).
- Patients on long-term TPN can develop biliary stasis or obstructive jaundice resulting in excess Mn tissue accumulation.

Toxicity of Excess Intake

- A few studies raise concerns about adverse neurological effects from exposure to elevated concentrations of Mn in drinking water (Kawamura et al. 1941; Kondakis et al. 1989; Wasserman et al. 2006; Bouchard et al. 2007).
- Studies have reported potential neurological effects in residents living close to industrial sources of Mn (Mergler et al. 1999; Lucchini et al. 2007; Finkelstein and Jerrett 2007).

Manganese Exposure in Infants and Children

- Concerns have been raised about infants and children being more susceptible to the neurotoxic effects of excessive Mn exposure:
  - Potential for increased absorption (Dorner et al. 1989), increased retention (Lonnerdal et al. 1994), increased bioavailability (brain, lung)
- Potential for increased Mn exposure levels:
  - High Mn cord blood levels (Rossipal et al. 2000; Takser et al. 2003, 2004)
  - Mn in infant formulas (Hozyasz and Ruszczynska 2004)

High Oral Intake of Manganese

- Dietary studies have demonstrated that relatively high doses of Mn can be safely tolerated by healthy adults
- Female subjects:
  - 15 mg/d for 124 d – elevated serum Mn and SOD activity (Davis & Greger 1992)
  - 20 mg/d for 60 d – no neurological or metabolic effects, shorter half-life than low dose group (Finley et al. 2003)

Occupational Groups Potentially Exposed to Manganese by Inhalation

- Clinical neurotoxicity has been reported in certain occupations where workers were exposed to high concentrations of manganese-containing dust.
- Subclinical neurobehavioral and neurological effects measured in cohorts exposed to lower levels of Mn.
- ACGIH TWA-TLV is 200 $\mu g/m^3$

Neurofunctional Effects Reported in Manganese Exposed Occupational Cohorts

- Altered motor functions
  - Sequential alternating movements
  - Finger tapping
- Reduced hand steadiness
- Decreased response speed
- Decrease in cognitive functions
- Greater self-reporting levels of fatigue, tension, anger, and confusion

Occupational Groups Potentially Exposed to Manganese by Inhalation

Study	Respirable Mn (mg/m^3)	Industry
Roels et al. 1992	0.15 (Effects)	Alkaline Battery
Iregren 1990	0.25 (Effects)	Foundry
Järvisalo et al. 1992	1.37 (Effects)	Welders
Mergler et al. 1994	0.12 (Effects)	Mn Alloy
Gibbs et al. 1999	0.066 (No effects)	Mn Alloy
Deschamps et al. 2001	0.057 (No effects)	Enamels
Young et al. 2005	0.058 (No effects)	Smelter

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Benchmark Doses for Mn

Study	Ave. Duration	$BMDL_{10}$ mg/m^3	Mean mg/m^3
Roels et al. (1992)	5.7	0.10 – 0.26	0.19
Gibbs et al. (1999)	14.1	0.09 – 0.27	0.19

Clewell et al. 2003

Benchmark Doses for Mn

Agency	Study	BMDL mg/m^3	Reference Level $\mu g/m^3$
EPA 1994	Roels et al. 1992	$BMDL_{10}$ 0.072 – 0.118 $BMDL_5$ 0.031 – 0.056	0.09 – 0.2 (not implemented)
ATSDR 2000	Roels et al. 1992	$BMDL_{10}$ 0.074	0.04
WHO 2001	Roels et al. 1992	$BMDL_5$ 0.030	0.15

Inhalation Exposure

- Only a very small amount of Mn is normally taken into the body by inhalation (>1 μg/d).
- Large amounts can be absorbed in the cases of high air concentrations such as in occupational exposures (>1000 μg/d).

Oral vs. Inhalation Exposure

- Mn is absorbed more efficiently following Inhalation than oral exposure.
- Historically there have been uncertainties regarding homeostatic control of low-level chronic Mn inhalation exposure.
- These uncertainties have been reflected in the risk assessments and reference concentrations for manganese over the years.

Exposure and Risk

- To estimate risk, the measured exposure level of Mn in the environment can be compared to the exposure level that is considered to be safe for continuous exposure
- Exposure guidelines are established by regulatory agencies such as OSHA, WHO, USEPA, or the Environmental Health organizations within specific countries or states (e.g., Health Canada, California)
- Environmental regulations for Mn are very protective values with very large safety factors, to protect all members of the population

Environmental Manganese Guidelines

Agency	Current Guideline	Proposed Guideline
WHO	0.15 $\mu g/m^3$ (2001)	N/A
U.S. EPA	0.05 $\mu g/m^3$ (1994)	0.09 – 0.2 $\mu g/m^3$ (1998) Current IRIS Review
Health Canada	0.11 $\mu g/m^3$ (1994)	0.05 $\mu g/m^3$ (2008)*
Cal EPA (OEHHA)	0.2 $\mu g/m^3$ (1999)	0.11 $\mu g/m^3$ (2008)
ATSDR	0.04 $\mu g/m^3$ (2000)	TBD – Nominated for Review

* Currently open for public comment

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Risk Assessment Considerations

- Direct nose-to-brain transport along olfactory nerve
  - Efficient delivery to olfactory bulb
  - Limited impact on other brain tissues
- Concerns for fetuses and neonates
  - High demand for Mn during early brain development
  - Little to no excretion

Recent Research

- Toxicokinetics of *dietary versus inhaled Mn*
- The effect of *different forms* of Mn *on* uptake and distribution;
- The effects on *potentially sensitive subgroups* within the population;
- Whether *duration of exposure* impacts Mn homeostasis.

Key Determinant of Toxicity

- The key determinant of toxicity appears to be ***dose to target tissue*** across:
  - Route and duration of exposure
    - Oral, inhaled, i.v.
  - Form of Mn
- PBPK models are a tool to examine those issues

PBPK Models Can Improve Risk Assessments

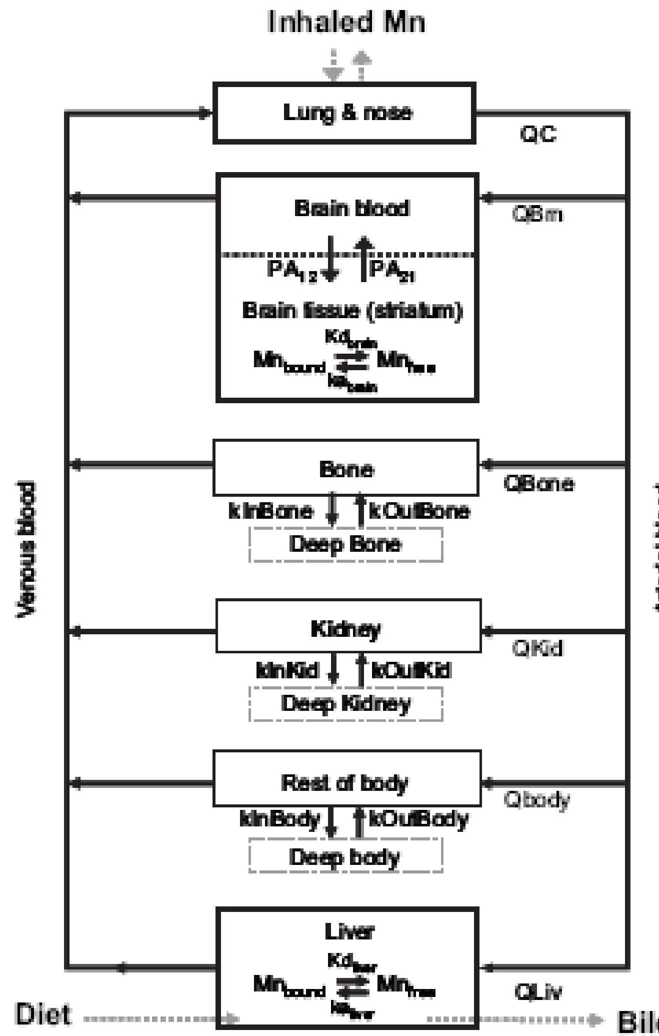
- Pharmacokinetic data may be used to address questions about how the body handles a chemical and to support the application of chemical-specific adjustment factors (CSAF) instead of UFs to the risk assessment of the chemical (EPA 2006).
- OEHHA recommends expanding the use of techniques such as the benchmark dose method and physiologically based pharmacokinetic (PBPK) modeling wherever possible in order to improve the protection of public health with acute, eight-hour and chronic RELs for all members of the population, and for infants and children in particular.

U.S. Environmental Protection Agency (EPA). (2006) Approaches for the Application of Physiologically Based Pharmacokinetic (PBPK) Models and Supporting Data in Risk Assessment. National Center for Environmental Assessment, Washington, DC; EPA/600/R-05/043F.

OEHHA 2007. Risk Assessment Guidelines. Technical Support Document for the Derivation of Noncancer Reference Exposure Levels.

Physiologically Based Pharmacokinetic (PBPK) Modeling

- PBPK modeling
  - Mathematical representation of absorption, distribution, metabolism, and excretion
  - Built with and validated by extensive pharmacokinetic literature for Mn
  - Can be used to predict tissue levels at exposure ranges outside of those used to create the model
  - Models for manganese being published by the Hamner Institutes for Health Sciences



Nong et al. 2007

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How Can PBPK Models Help Refine Mn Risk Assessments?

- Determine the relative contribution of inhaled and ingested Mn to tissue levels in target organs
- Evaluate the movement of Mn: 1) throughout the body, including the brain; 2) along the olfactory nerve to the olfactory bulb in rats and non-human primates
- Quantify differences regarding tissue delivery due to differences in form and solubility
- Provide a quantitative explanation for varying Mn levels during development, both in normal conditions and conditions of increased airborne Mn exposure

Conclusions

- Dose to target tissue is likely a key determinant in Mn toxicity, regardless of route
- Dose to target tissue by all dose routes can be examined by PBPK modeling
- Risk assessments considering background tissue concentrations and potentially toxic increases by overexposure can therefore be greatly aided by the use of PBPK models

Thank you!

asantamaria@environcorp.com

713-436-5878