MANGANESE AS A NEURODEVELOPMENTAL TOXICANT

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Avoid deficiency and toxicity

- Complicated dynamics based on complex kinetics
Mn adult neurotoxicity

- **Occupational:** mines, ferroalloy, welders, etc
  - fine motor impairment, gait deficits, dystonia
  - Mood changes towards aggressivity

- **Globus pallidus as critical target**

T(1)-Weighted MRI hyperintensity
Target Globus pallidus

- GP: dopaminergic and GABAergic control of motor functions and mood
Mn adult neurotoxicity

Environmental:
- Increased frequency of parkinsonism from
  - Mexican mines (Rodriguez-Agudelo et al., 2006)
  - Italian ferroalloy plants (Lucchini et al., 2007)
  - Canadian industrial sites and car traffic MMT (Finkelstein and Jerrett, 2007)

  OR for PD = 1.034 (1.00-1.07) per 10 ng/m³ increase of Mn in TSP
Prenatal exposure: animals

- Drinking water exposure to dams:
  - increased brain Mn levels in pups and adolescent (Seth 1977, Chandra and Shukla 1979, 1980, 1981)
  - increased activity at PND 17 (Pappas 1996)
- Inhalation study to dams:
  - aberrations in offspring behavior (Lown 1984)
- Maternal dietary intake increases fetal Mn levels (Jarvinen 1975, Kirchgessnes 1981)
- Placenta partially sequesters inhaled manganese, limiting fetus exposure (Dorman et al 2005)
Pre/post-natal: humans

- Learning disabilities in Chinese children 11-13 yrs associated with MnW 241- 346 μg/L (300 EPA lifetime health advisory level) 
  
  *(He et al 1994)*

- Mn tooth enamel (which develops 20 gestational wk - 7 mo postnatal) associated to behavioral outcomes 
  
  *(Ericson et al 2007)*
Manganese levels in mother's and cord blood, mother's and newborn hair, and placental tissue in initial population and the sample followed up to 6 years

<table>
<thead>
<tr>
<th>Manganese levels</th>
<th>Initial population</th>
<th>Follow-up sample at 6 years of age</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mother</td>
<td>Cord/newborn</td>
</tr>
<tr>
<td>Blood manganese (µg/l)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>n</em></td>
<td>222</td>
<td>222</td>
</tr>
<tr>
<td>Geometric mean</td>
<td>20.4</td>
<td>38.5</td>
</tr>
<tr>
<td>5th–95th percentiles</td>
<td>11.1–40.4</td>
<td>19.1–71.2</td>
</tr>
<tr>
<td>Range</td>
<td>6.3–151.2</td>
<td>14.9–92.9</td>
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<tr>
<td>Hair manganese (µg/g)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>n</em></td>
<td>173</td>
<td>173</td>
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<tr>
<td>Geometric mean</td>
<td>0.36</td>
<td>0.75</td>
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<tr>
<td>5th–95th percentiles</td>
<td>0.16–0.87</td>
<td>0.22–4.25</td>
</tr>
<tr>
<td>Range</td>
<td>0.10–3.24</td>
<td>0.05–13.33</td>
</tr>
<tr>
<td>Placental manganese (µg/g)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>n</em></td>
<td>200</td>
<td></td>
</tr>
<tr>
<td>Geometric mean</td>
<td>0.10</td>
<td></td>
</tr>
<tr>
<td>5th–95th percentiles</td>
<td>0.06–0.16</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>0.01–0.49</td>
<td></td>
</tr>
</tbody>
</table>

No significant differences were observed between initial and follow-up populations (*t*-test was used).

**Takser et al., 2004**
Mn at birth associated with psychomotor sub-tests at 3 yrs not 9 mo not 6 yrs

No association with cognitive tests

Takser et al., 2004
MnW: High MnW and low AsW in Bangladesh

- Wasserman et al., 2006
Interaction Hair Mn/As on IQ from Tar-Creek, OK

- Wright et al., 2006
MnH from high MnW associated with hyperactive behavior

- Bouchard et al., 2007
Mn essentiality

- For metalloenzymes: arginase, glutamine synthetase (nitrogen metabolism), pyruvate carboxylase (carbohydrates synthesis)
- In tissues with high metabolic rate (brain for glutamine in astrocytes)
- Free radical defense (MnSOD)

*developing brain needs Mn*
Very efficient in regulating absorption and excretion rates in adults.
Adult vs Infant homeostasis

- **Dietary Mn Intake**
  - Adult ~ 10mg/ kg/ day
  - Breast-fed infants ~ 0.0005mg/ kg/ day
  - 20,000-times less than adults!

- **GI Mn Absorption**
  - Adults – 3-4% of ingested Mn
  - Infants ~ 80%

- **Mn Excretion / Retention**
  - Adults – significant hepato-biliary excretion
  - Infants – little hepato-biliary excretion

- **Brain Mn Uptake**
  - Adults – BBB regulates Mn uptake
  - Infants – immature BBB – Mn uptake poorly regulated
Therefore, there is a delicate balance between a great need for Mn and a possible overload, especially in infants.
Mn in Infant Formula

Human milk: 4ug/ L Mn (ppb)
Cow milk:
Formulas

Cow based: Similac 73ug/ L
Soy based: Isomil: 436ug/ L
ProsoBee: 749ug/ L
Enfamil: 1,289ug/ L

(Stastny, 1984)

*In the U.S. 20% of infants are fed soy formula, with 750,000 infants receiving soy formula every year (Mercola, 2001).
**Outcomes:**

- **Activity** - motor activity and behavior (SMART)
  - Analysis of Zones within arenas
  - Time spent and distance traveled
- **Learning / Memory** - 8-arm radial maze

**Oral Mn Exposoure**

- Vehicle (Sucrose sol’n)
- 25mgMn/kg/day
- 50mgMn/kg/day *(MIMICKS HIGH LEVEL IN FORMULA)*
- N=14 – 18 /treatment/outcome
Blood and Brain Mn increased by the end of Treatment on PND 21

Blood Mn Levels, PND 24

Brain Mn Levels, PND 24
Total Activity Males PND 23: 5-30 min, ANOVA p=0.0241

Mn increased activity
Increased activity in the center

Example of video motor track

Ratio Perimeter Distance: Center Distance 5-30 Minutes

Rodents usually prefer periphery of arena—favor thigmotaxis

Open arena is a measure of gross motor activity and reaction to a stressful event; not on exploration

Increase time in center indicates decrease response to stressful event
Mn decreases ability to learn

Percent of animals per treatment who reached the maze criteria

Mn Neonate: Maze: Males % success in learning criteria
(4 or less working errors 3 days in a row)

Control          25mg/kg            50mg/kg
Mn Treatment

Mn increases time needed to learn

No of days to reach learning criteria

Control          25mg/kg            50mg/kg
Mn Treatment

*
In summary

- Pre- and post-natal exposure increase Mn levels and cause motor and cognitive impairment
- Pre- and post-natal exposure + adult environmental and occupational ⇒
- Neurodegeneration as cumulative long term effect ?