Manganese: An Overlooked Drinking Water Contaminant and the Potential for Child Development Risks

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October 4, 2018

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SCHOOL OF PUBLIC HEALTH, UNIVERSITY OF MINNESOTA

Talking points

- Background/Regulatory history
- Minnesota activities
- Biomarkers of Exposure and & Infant Brain Development
- Minnesota activities (outreach)
- Challenges
- Recommendations

Background & Reg History

Essential nutrient
(we get enough from food)

and

OSHA.gov

At high levels: a neurotoxin
"Manganism"

Common in U.S. drinking water sources

Food intake >> than water intake (mg/day vs. µg/day)

Background & Reg History

1998: Mn on EPA's first Contaminant Candidate List (CCL)

2003: EPA "Health Effects Support Document"

Children's Exposure/PK Considerations

- Infant formula: 72 to 726 µg/L vs. breastmilk: 7 to 15 µg/L
- Higher absorption in water compared to food
- Animal studies show:
  - Young animals absorb significantly more Mn in gut
  - Mn crosses blood-brain barrier in neonates at rate 4x higher than in adults
  - Biliary excretion system (primary route) not completely developed in neonates

Background & Reg History

2003: Health Effects Support Document: HRL=300 µg/L

- RfD based on upper end of intake from adult Western diet
- Adult BW (70 kg) and DW consumption rate (2L/day)

3x "modifying factor" applied "as precautionary measure" based on:

- Increased bioavailability from DW
- Epi studies (neurological deficits in residents in areas with high vs. low DW exposures)
- Evidence of higher absorption/lower excretion in neonates
- Potential for children's increased susceptibility to neurotoxic effects
- Formula reconstituted with DW represents additional source for sensitive population

Background & Reg History

2003: CCL Regulatory Determination Support Document

Regulating manganese does not present a meaningful opportunity to reduce health risk.

2004: Drinking Water Health Advisory for Manganese

"The lifetime HA value of 300 µg/L will protect against concerns of potential neurological effects. However, it is advised that for infants younger than 6 months, the lifetime HA of 300 µg/L be used even for an acute exposure of 10 days."

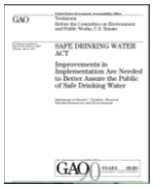
What level is safe for infants to consume for >10 days?

Background & Reg History

2011: GAO comments on EPA's regulatory determination:

- States there are 'no data to indicate children are more sensitive to Mn than adults' which is contrary to Health Effects Support document.
- Did not consider that high levels of Mn in formula can be magnified when reconstituted with Mn-contaminated water
- Used health reference level that was not based on, and not protective of, children

2016: Mn is back on the CCL; process takes several years


GAO

SAFE DRINKING WATER ACT

Improvements in Implementation Are Needed to Better Assure the Public of Safe Drinking Water

Background & Reg History

Secondary Maximum Contaminant Level (SMCL)=50 µg/L

Assumption

People won't drink water much above the SMCL because water will taste bad and Mn will stain laundry and fixtures

Minnesota Activities

MDH Health-based Value (2012)

100 µg/L

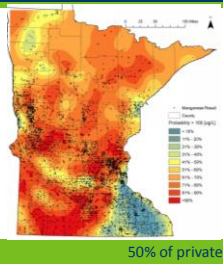
http://www.health.state.mn.us/divs/eh/risk/guidance/gw/manganese.pdf

Based on:

- Neurodev. effects in rats
- Formula-fed infant

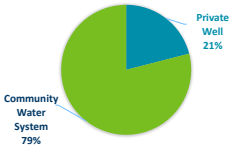
300 µg/L protective for all other populations (including infants not drinking water and pregnant women)

Minnesota Activities



What are the concentrations in MN groundwater?

Drinking Water Sources in Minnesota



50% of private wells in the state >100 µg/L

Minnesota Activities

What are the concentrations in CWS?

# of CWS by mean Mn concentration category

Mean concentration (µg/L)	Frequency	Percent
0 to 100	675	70%
>100 to 300	158	16%
>300	97	10%
Missing	36	4%

*20 systems with source water results >100 µg/L have treatment type that may reduce Mn

~26% of CWS >100 µg/L

Minnesota Activities

Do people **drink water** with manganese > MDH's guidance value?

Wells & Increased Infant Sensitivity & Exposure (**WIISE**) Study 2015-16

Do **treatment devices** commonly used by private well owners reduce manganese?

274 households enrolled

Phase I: Outdoor spigot sampled & online survey

Phase II: Indoor tap sampled if Mn >100 µg/L in Phase I

http://www.health.state.mn.us/divs/eh/risk/studies/wiisereport.pdf

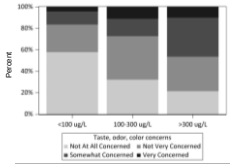
Minnesota Activities

Do people drink water with elevated Mn?

Household survey

At higher levels of Mn, there was increase in…

- Concern about "taste, odor or color of their water"
- Concern about "iron and other minerals"
- Drinking treated or bottled water (modest increase)



Some evidence of greater awareness of cosmetic issues & increased mitigation

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Minnesota Activities

Do people drink water with elevated Mn?

Inside tap samples

- 78% of those with Mn level between 100-300 µg/L regularly drink the water.
- 85% of those with Mn level >300 µg/L regularly drink the water.

Elevated manganese in tap water does not always deter someone from drinking it

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Minnesota Activities

Do **treatment devices** commonly used by private well owners reduce Mn?

✓ **Water softeners:** very effective

✓ **Carbon filters** may reduce manganese but often not to below 100 µg/L

✓ **Reverse osmosis** (shown in other studies)

X **Sediment** and **iron filters**: no effect

Softened water not recommended for bottle feeding due to sodium added by softener

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Minnesota Activities

Mn concentrations in infant formula (2018):

"Most infant formulas contain ~100-fold higher Mn concentrations compared with breast milk, excluding any Mn in water" (Ljung and Vahter 2007).

MDH tested 27 different formulas (*preliminary results*):

- Mn level higher than what was calculated based on label info (mean ratio=2.4)
- Concentrations ranged from 72 to 726 µg/L
- Some provided higher dose than MDH's current RfD (without water contribution)
- Amino acid-based and soy-based formula > cow's milk-based formula

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Minnesota Activities

MDH Human Biomonitoring Study (2018)

- Chemicals that can harm development; includes Mn
- Urine from preschoolers in
  - urban area in proximity to known Mn industrial air emissions
  - rural area with private wells

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Creating Evidence Based Public Health Guidance Manganese Levels in Drinking Water

October 4, 2018

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Residents and students: Kriti Choudary, MD, MPH, Donna Coetzee, MPH , Donna Coetzee, MPH & Shannon Sullivan, MPH

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"How Much Does the Loss of a Few IQ Points Among Our Children Really Matter?"

www.huffingtonpost.com/2014/11/20/toxins-children-brain-little-things-matter_n_6189726.html

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Literature Review

Coetzee et al. Environmental Health (2016) 15:91
DOI 10.1186/s12940-016-0174-4

Environmental Health

REVIEW Open Access

Measuring the impact of manganese exposure on children's neurodevelopment: advances and research gaps in biomarker-based approaches

Donna J. Coetzee[1], Patricia M. McGovern[2*], Raghavendra Rao[3], Lisa J. Harnack[4], Michael K. Georgieff[5] and Irina Stepanov[6]

Data on Childhood Toxicity

- Most of this evidence comes from studies of elevated exposures to Mn through drinking water in school-aged children.
- Canada: higher levels of Mn in drinking water were associated with hyperactive and oppositional behaviors and lower IQ scores. (Bouchard, 2007, 2011)
- Bangladesh: higher Mn level in water was significantly associated with lower IQ scores and with reduced mathematics achievement test scores. (Khan, 2012)
- Other: high Mn levels in children's blood and hair were associated with poor memory, low cognitive scores, and impaired motor function. (Coetzee, 2016)
- Only 2 recent studies in the US:
  - An association between Mn levels in tooth enamel and behavioral disinhibition in children (externalizing behaviors and attention problems). (Ericson, 2007)
  - An association of high blood and hair Mn with lower IQ scores in children living near a ferromanganese refinery in Ohio. (Haynes, 2015)

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Studies of Infants & Toddlers

- Few studies investigated Mn exposures with biomarkers & neurodevelopment outcomes in infants
- Studies using prospective designs provided compelling evidence of the adverse effect of Mn.
- Biomarkers of Mn using cord blood or serum provided a temporal association between fetal Mn exposures and later outcomes including:
  - Cognitive and language development scores in 2 year olds [Lin et al, 2013]
  - Attention and nonverbal memory and hand skills in 3 year olds [Tasker et al, 2003]
  - Behavioral neurological development in newborns [Yang et al, 2014].

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Pilot Study Aims

- Develop novel biomarkers of manganese for infants
- Evaluate the association of environmental exposure to dietary and water-manganese using biomarkers
- Evaluate the association of the biomarkers and water-manganese with infant neurobehavioral development
- Assess the feasibility and success of conducting the pilot study

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Toenail Mn as a Potential Biomarker of *In Utero* and Early Childhood Exposure

- Toenail biomarker levels indicate cumulative exposure over 6-12 months.
- In utero: nail starts forming in fingers of embryos 9 weeks old and at 17 weeks the nail almost covers the entire nail bed; the changes of the nail from 17 weeks to newborn are mainly those of growth.
- Compared to hair: always present in relatively similar amounts in newborns and infants; unlikely to encounter resistance to sample collection; do not contain melanin ; less likely to be externally contaminated.
- A study of arsenic exposure in US mother-infant pairs: infant toenail arsenic levels were strongly correlated with maternal toenail concentrations and with maternal arsenic intake from water and diet.
- A study in Bangladesh used toenail biomarkers. Infants' toenail Mn levels correlated with those in maternal toenails at one month postpartum.

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Study Design

- Recruit women were from two neighboring MN cities with naturally occurring high levels of Mn in groundwater
- Only one location filtered Mn out of its public water supply
- Three phases (mother-infant pairs)
  - Pre-pilot pre/post-natal collection (longitudinal single pair)
  - Pre/post-natal collection (9 pairs recruited)
- Postnatal set (20 pairs recruited)
- Data collection included surveys, tap water samples, biospecimens & Evoked Response Potentials (ERPs)
- Analyses were descriptive

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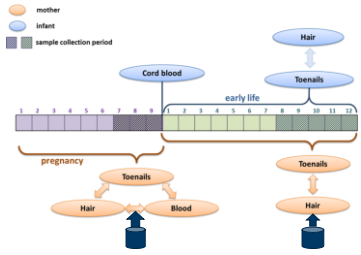
Recruitment and Sample Collection Diagram



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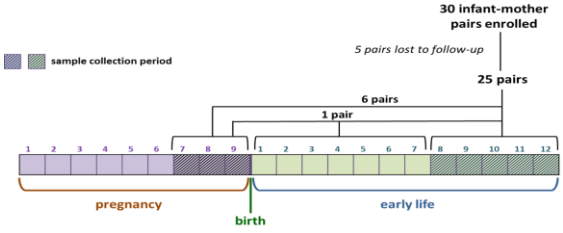
Study Enrollment and Retention



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Manganese Analysis in Biological Samples

Sample Collection
*Hair and toenails: non-invasive, easy handling & room temperature storage
*Blood: invasive

Washing
*Removes external contamination
*Used for hair & toenails (impossible for blood)

Digestion
- Mixture of 75% nitric acid & 25% hydrochloric acid (trace-metals grade)
- Independent of sample type

Analysis
- Inductively coupled plasma-mass spectrometry
- Prepared samples analyzed by MDH Lab

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Results

Sample type		*Infants*	*Mothers*
Toenails (µg/g)	N (samples)	23	24
	Mean (SD)	0.73 (1.12)	1.96 (4.15)
	Range, min – max	ND (1) – 4.59	0.19 – 20.98
Hair (µg/g)	N (samples)	23	23
	Mean (SD)	0.94 (1.40)	2.90 (3.76)
	Range, min – max	ND (4) – 6.08	0.09 – 13.35

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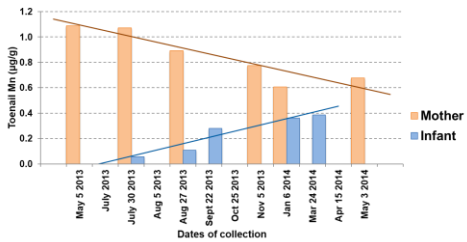
Longitudinal Mother Infant Pair



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Summary
Biomarker Measurements

- Collection of toenails from infants for Mn analysis is feasible and may have advantages over hair analysis
- There is substantial variation of toenail Mn levels among infants in this study, suggesting differences in exposures
- Results suggest that Mn levels in maternal and infant toenails and hair may be changing during the first year of the infant's life
- Future studies should focus on identifying specific time-windows for sample collection in order to obtain meaningful data on Mn exposures in infants

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Association of Tap Water Samples with Biomarkers

- Drinking water Mn levels ranged from <10 to 290 µg/L
  - No correlation between drinking water Mn levels with either infant or maternal toenail Mn levels
- Infant hair correlated with Mn levels in drinking water
  - R=0.66; p= 0.01
- Maternal hair correlated with Mn levels in drinking water
  - R=0.62; p= 0.01

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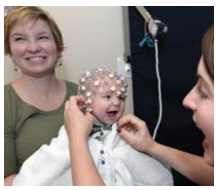
Infant Neurodevelopment

- Event-Related Potentials (ERPs)
- Are a subset of the EEG; provides information about the timing of the neurocognitive processes that occur while a person is responding to an event.
- Electrical signals spread to the scalp in response to a stimulus in response to an "odd ball" paradigm.



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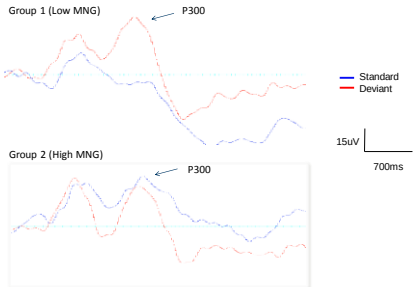
ERP Results – P300 component



Association of Biomarkers with Infant Neurobehavioral Development

- Infants who showed a diminished electrophysiological response to novel stimuli had mothers with increased concentrations of:
  - Postnatal hair-Mn (Rho=-0.47, p=0.04)
  - Postnatal toenail-Mn (Rho=-0.42; p=0.05)
- Infants consuming higher levels of tap water Mn had significant associations with deviant responses on the odd ball test.
  - Far (Rho= -0.61; p=0.02)
  - Near (Rho= - 0.54; p= 0.04)
- Infants' biomarkers of hair and toenails were not significantly associated with ERP data suggesting that prenatal exposure may be most relevant to infant outcomes.

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Limitations

- Small sample size
  - Precludes multivariate analyses
- Voluntary enrollment of study participants
  - Potential for selection bias
- Participants from two communities in the Twin Cities metropolitan area
  - Provides limited generalizability
- Study did not evaluate Mn in infant diet other than water
  - Most infants were consuming baby by six months

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Discussion

- ERP findings suggest infants with increased gestational exposure to Mn may indicate dysfunction in the prefrontal cortices
- The findings that maternal postnatal Mn levels were related to infant ERP response while infant biomarkers were not may indicate fetal exposure is driving these effects.
- Research recommendations
  - Studies with larger samples from various geographic locations are needed to facilitate more comprehensive study designs and more rigorous analyses to learn if findings generalize to other populations
  - Longer follow-up periods are needed to understand if changes in infants neurocognitive function are temporary or permanent
- Given that subclinical decrements in children's brain function are more common than diagnosed disorders and such conditions may decrease children's academic success, disturb behavior and diminish quality of life, families could benefit from learning about risk mitigation strategies
- Proactive measures such as identifying women of reproductive age with wells, to educate and encourage testing and treating their wells for water quality in association with Mn and other contaminants is advised.

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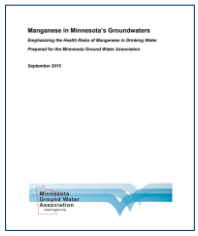
Minnesota Activities



Outreach

MGWA "White Paper" (2015)

Goal: Provide info about this issue to facilitate awareness building and a better understanding among local PH officials, public utility operators, water supply professionals, private well owners, and others.

http://www.mgwa.org/documents/whitepapers/01_manganese/Manganese_in_Minnesotas_Groundwaters.pdf

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Minnesota Activities

Outreach

- General outreach materials
- "Baby Brochure" (2018)

Goal: Inform households on private wells that have/will have a baby in the home. Discusses the importance of testing well for five contaminants before giving water to baby.

http://www.health.state.mn.us/divs/eh/wells/waterquality/safebaby.html

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Challenges for EH Practitioners

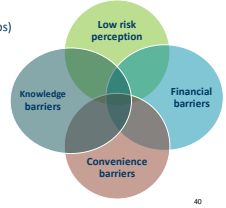
MDH guidance value is not a regulatory value

- Does not apply to public water systems
- Still widely seen as an aesthetic issue (e.g., private labs)

Difficult to conduct direct outreach to private well households

Outreach may not equal action

- Many barriers to well stewardship behaviors



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Recommendations

Disseminate brochures

- Order free "Well Water and Your Baby" and "Owners Guides to Wells" brochures from the MDH WM website
- **Maximize existing networks and develop new partnerships**

Consider hosting a well testing event in your area (contact Frieda von Qualen, MDH at Frieda.vonQualen@state.mn.us or 651-201-4547)

Incorporate private wells/drinking water in Healthy Homes programs and outreach

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Acknowledgements

WIISE Study: Supported by MDH, Dakota County, and Clean Water, Land and Legacy Amendment funds to MDH.

Additional MDH manganese activities also supported by Legacy funds.

Maternal and Infant Biomarker and ERP Pilot Study: Supported by a grant from the Consortium on Law, Values and the Health Sciences, UMN; startup funds to IS from the Masonic Cancer Center, UMN; non-sponsored funds from PM and MDH support for water –Mn analysis.

Researchers: Pat McGovern, Irina Stepanov, *Donna Coetzee, Shannon Sullivan, Kriti Choudhary, Neely Miller*, Raghavendra Rao, Lisa Harnack, Tim Church, Steve Mongin and Michael Georgieff.MDH colleagues/consultants: Pam Shubat, Rita Messing, Jim Lundy, Rich Soule and Deanna Scher. The analyses of water was conducted by the MDH Public Health Laboratory

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