CONSORTIUM ON LAW AND VALUES AWARD REPORT

Creating Evidence Based Public Health Guidance for Manganese Levels in Drinking Water

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Project Summary

The University’s Center for Neurobehavioral Development (CNBD) and the Center for Environment and Health Policy collaborated on a pilot study to launch a new line of interdisciplinary research to inform public policy on safe levels of manganese in drinking water. Manganese is an essential micronutrient; low levels of dietary manganese are beneficial for health. However, an emerging literature suggests environmental exposure to manganese may also adversely affect child neurodevelopment. While most metropolitan public drinking water supplies are treated (e.g., filtered) for manganese, some are not; moreover, many ex-urban and rural communities are not treated. Since the median manganese concentration in Minnesota’s ground water is equivalent to the highest safe level allowable by the Environmental Protection Agency (EPA) and Minnesota lacks consistent treatment systems, concerns exist about potential health implications for fetuses and infants as they have the most rapidly growing brains, thus are most likely to take up manganese from water and food and be at risk for toxicity. Research is needed to assess the neurodevelopmental effects of manganese exposure for infants. Our long-term goal is to assess fetal and infant exposure to manganese in drinking water, measure the body burden of manganese with novel biomarkers, assess infant neurobehavioral outcomes and provide the evidence base needed for policy on safe levels of manganese in water.

Our pilot study was designed to 1) develop novel biomarkers of manganese (Mn), 2) Evaluate the association of exposure to water-manganese using biomarkers, 3) Evaluate the association of the biomarkers and water with infant neurobehavioral development, and 4) Assess the feasibility and success of conducting the study.

We recruited volunteer women from two cities that have naturally occurring high levels of manganese in the ground water and similar population demographics. However, one city did not filter their municipal water supply for manganese while the other city had negligible levels of manganese in their drinking water supply due to a municipal filtration system. Some women were recruited into the study during pregnancy through a midwifery clinic and others were recruited postnatally through the Infant Participant Pool at the Institute for Child Development. Mothers were provided with gift cards to local stores and books for their infants in appreciation for their contribution to the study. We collected data via questionnaires, water samples, and biospecimens including maternal blood, hair and toenails pre- and postnatally and infant hair and toenails at 7 months of age, and conducted neurodevelopmental and behavioral assessments at the Center for Neurobehavioral Development (CNBD) at approximately 10 months of age. Descriptive and nonparametric statistics were used to analyze the data.

Our sample included 28 women of whom 7 were exposed to higher concentrations of Mn in tap water. Maternal-infant pairs from the two communities (Mn-exposed and not exposed) were similar in demographic and socioeconomic characteristics (maternal age, education, marital status, parity, and household income), overall maternal health status, duration of infant gestation, birthweight and whether or not the infant was ever breastfed. The only statistically significant difference between the two groups was the intermittent use of bottled or filtered water with tap water for reconstituting infant formula which was reported more frequently among women from the Mn-exposed community.

Among 15 (54%) women providing tap water samples, higher concentrations of water-Mn were positively associated with postnatal concentrations of Mn in maternal hair (Rho=0.65; p=0.008) and slightly less so for maternal toenails (Rho=0.45; p=0.069) and infant hair (Rho=0.46; p=0.082). While the test statistic between water and infant toenails was nonsignificant (Rho=0.21; p=0.413), where the tap water concentrations of Mn were elevated above 100 µg/L the maternal toenail-Mn concentrations were also elevated.
Among the 20 (71.4%) women whose 10 - 11 month old infants were tested at the Center for Neurobehavioral Development and also submitted some biospecimens, test results indicated differences for infants in their response to novel stimuli detected with an “oddball” electrophysiological (ERP) task that is dependent on normal dopaminergic brain activity. Results showed differences between the infants by residential location which may indicate reductions in brain dopaminergic activity associated with exposure to higher levels of Mn. Additionally, infants who showed a diminished electrophysiological response to novel stimuli (an oddball versus a standard tone) had mothers with increased concentrations of postnatal hair-Mn (Rho=-0.47, p=0.040), and postnatal toenail-Mn (Rho=-0.42; p=0.052). Higher levels of tap water Mn were also significantly and inversely associated with infants’ far (Rho= -0.61; p=0.015) and near (Rho= - 0.54; p= 0.038) deviant response on the oddball test. In contrast to the findings for maternal biomarkers and water samples, the infants’ biomarkers of hair and toenails were not significantly associated with the ERP data.

While study findings are limited by the small sample size which necessitated use of bivariate (not multivariate) analyses, the findings revealed tap water levels of Mn varied significantly by residential location and maternal biomarkers of hair and toenails showed greater evidence of exposure to Mn than infant biomarkers. Infants of mothers exposed to Mn had test scores that were different than those of infants whose mothers were not exposed to Mn which may indicate possible reductions in brain dopaminergic activity associated with maternal prenatal exposure to higher levels of Mn. Additional research with a larger sample of mother-infant pairs is needed to validate these findings.

Study findings also provided insight on the feasibility, strengths and weaknesses of the various data collection protocols. A comprehensive study enrolling a larger sample of mother-infant pairs that would be focused on postnatal data collection and Mn biomarkers of hair and toenail (not blood), samples of tap water and other water sources (bottled or filtered) and self-report data on infant feeding practices is urgently needed. Participant incentives and a supportive, continuing relationship between the mother and study personnel would be critical to successful participant retention.

Financial summary
(See attachment).

Funding was primarily used for salary support (e.g., public health nurse who made home visits to collect participant data, lab technician to draw participant bloods, student research assistants to conduct literature review and analyze manganese in biospecimens, study coordinator at CNBD who enrolled and tested infants), participant incentives, and lab supplies for biospecimens.

We augmented grant funding with other sources. The Minnesota Department of Health awarded funds to Dr. McGovern to pay for the supplies and testing of manganese in water samples. Dr. Stepanov used her start-up funds to pay for the manganese analyses in hair, toenails and blood. Dr. McGovern also used nonsponsored funds to collect water samples from participants’ homes.

Products

Publications, planned, in press, or published


1 MPH student, Division of Environmental Health Sciences, School of Public Health, University of Minnesota
2 Associate Professor of Pediatrics (Neonatology Division), at University of Minnesota School of Medicine
3 Professor and Director for the Nutrition Coordinating Center in the Division of Epidemiology and Community Health, School of Public Health, University of Minnesota
4 Associate Professor, Division of Environmental Sciences, School of Public Health and the Masonic Cancer Center at the University of Minnesota.
Ms. Coetzee was also a Master in Public Health (MPH) student and pilot study research assistant. She successfully defended her MPH plan B research paper, “Neurodevelopmental Effects of Manganese on Children: A Literature Review,” March 27, 2015 and was accepted into Medical School, University of Minnesota, September 2015. Her plan B paper served as the basis for the manuscript cited above.

Presentations (planned or completed). Students’ names are underscored.

Georgieff, M. Invited seminar, Nutrition and Early Brain Development: Effects of Timing, Dose and Duration. Division of Environmental Health Sciences, School of Public Health, University of Minnesota, April 25, 2016. (See attached flyer).

Sullivan, S., McGovern, P., Miller, N., Choudhary, K., Rao, R., Georgieff, M., Stepanov, I. Biomarkers to Assess Neurodevelopmental Toxicity of Manganese: A Pilot Study. Poster Presentation, Women’s Health Research Conference, Powell Center for Women’s Health, April 4, 2016 and School of Public Health Research Day, April 7, 2016, University of Minnesota. [This poster was recognized by the School of Public Health with a Public Health Impact Award, 2016]

McGovern, P., Scher, D., Eshnaur, T. co-taught a two hour class for PubH 6105, Environmental and Occupational Health Policy,” Environmental Risk Communication: a Case Study of Manganese in Drinking Water & Infant Neurodevelopment.” The class involved lectures and a service learning project where graduate student teams redesigned Minnesota Department of Health communication materials for pregnant women and new parents on well water protection for Manganese and other contaminants, February 24 and March 3, 2015.


Grants Proposals Submitted

Three proposals were developed to extend the work of the pilot study and submitted as noted below in addition to a fourth related proposal; unfortunately, none were funded. A proposal, Creating Evidence-Based Public Health Policy for Safe Levels of Manganese in Minnesota’s Drinking Water: Protecting Infant Neurodevelopment, designed to expand this pilot study was submitted to the state-funded MnDRIVE Transdisciplinary Research Program, April 2014. A proposal was also developed as a component of a larger, interdisciplinary center application, “Midwest Center for Studies on Community Health Impacts of Environmental and Life Course Disparities Center” and submitted to the National Institute for

5 PhD student, Division of Environmental Health Sciences, School of Public Health, University of Minnesota
6 MPH student, Division of Epidemiology and Community Health Education, School of Public Health, and Study Coordinator, Center for Neurobehavioral Development, University of Minnesota
7 Medical Resident, Medical School, University of Minnesota
8 Exposure Assessment Unit, Division of Environmental Health, Minnesota Department of Health.
9 Planning Director, Water Protection Unit, Minnesota Department of Health.
Environmental Health Sciences (NIEHS), January 2015. An R-21 application, *Determining the Feasibility, Reliability and Sensitivity of Toenails as a Biomarker of In-Utero and Early Life Exposure to Manganese*, was submitted to the National Institute for Environmental Health Sciences (NIEHS) for an extension of our pilot work, February 2016. The peer review process was conducted 7/29/16 and our application was not funded. However, as noted below, we will revise our R-21 application to address the peer review comments and resubmit it. An additional, related proposal was submitted to the NIH by one of our co-investigators on the pilot study, Professor Tim Church, “Environmental Influences on Child Health Outcomes (ECHO) Program-Data Analysis Center.

**Future project plans**

We are planning to engage students with faculty on manuscripts from the pilot data specific to biomarker and neurobehavioral findings. Additionally, we hope to revise and resubmit our R-21 to the NIH.

Submitted 8.24.16
Brain Development in the Fetus and Infant
A seminar by Dr. Michael Georgieff
Co-sponsored by the Brookdale Clinic Midwives and the University of Minnesota

Please join us for this exciting seminar by Dr. Michael Georgieff, an international expert in child development and nutrition.

An informal reception with light refreshments will precede the seminar.

Tuesday, October 28, 2014
7:30 pm - 9:00 pm
Methodist Hospital, Women’s Center

Michael K. Georgieff, M.D., is a Professor of Pediatrics and Child Psychology and Director of the Division of Neonatology. He received his M.D. from Washington University in St. Louis, Missouri. He served his internship and residency at The Children’s Hospital of Philadelphia. He followed with a residency in neonatology at the University of Pennsylvania and at the University of Minnesota. In addition to attending on the Neonatal Intensive Care Unit, Dr. Georgieff is director of the NICU Follow-up Clinic, director of Neonatal Nutrition Support Service and director of the Center for Neurobehavioral Development.

Dr. Georgieff’s research focuses on fetal/neonatal nutrition, specifically, the effect of fetal/neonatal iron nutrition on brain development and neurocognitive function. He has published in numerous journals, including American Journal of Physiology, Pediatric Research, Journal of Nutrition and Journal of Pediatrics. He was recently awarded the Samuel J. Fomon Nutrition Award from the American Academy of Pediatrics (AAP) in recognition for his outstanding research achievement relating to the nutrition of infants and children.
ABSTRACT

The cognitive, social and emotional parts of the brain continue to develop across the lifespan. However, the brain's growth and development trajectory is heterogenous across time. A great deal of the brain's ultimate structure and capacity is shaped early in life before the age of 3 years. The identification and definition of this particularly sensitive time period has sharpened the approach public policies are taking related to promoting healthy brain development. The ramifications are large because failure to optimize brain development early in life appears to have long-term consequences with respect to education, job potential and adult mental health. These long-term consequences are the “ultimate cost to society” of early life adversity.

Among the factors that influence early brain development, three stand out has having particularly profound effects; reduction of toxic stress and inflammation, presence of strong social support and secure attachment, and provision of optimal nutrition. This talk focuses on the latter by first describing the important features of brain development in late fetal and early postnatal life, discussing basic principles by which nutrients regulate brain development during that time period, and presenting the human and pre-clinical evidence that underscores the importance of sufficiency of several key nutrients early in life in ensuring optimal brain development.