## Applicant Information

<table>
<thead>
<tr>
<th>Applicant Name</th>
<th>Michael Georgieff, MD and Pat McGovern PhD; <a href="mailto:georg001@umn.edu">georg001@umn.edu</a> &amp; <a href="mailto:pmcg@umn.edu">pmcg@umn.edu</a></th>
</tr>
</thead>
<tbody>
<tr>
<td>Project Title</td>
<td>Creating Evidence Based Public Health Guidance for Manganese Levels in Drinking Water</td>
</tr>
<tr>
<td>Depart./Center</td>
<td>The Center for Neurobehavioral Development and the Center for Environment and Health Policy</td>
</tr>
<tr>
<td>Dept./Center Head’s Name</td>
<td>Center for Neurobehavioral Development, Michael Georgieff, MD Center for Environment and Health Policy, Interim Director, Bill Toscano, PhD</td>
</tr>
<tr>
<td>Dept./Center Head’s email</td>
<td><a href="mailto:georg001@umn.edu">georg001@umn.edu</a> <a href="mailto:tosca001@umn.edu">tosca001@umn.edu</a></td>
</tr>
<tr>
<td>Dean’s Name</td>
<td>Medical School, Aaron Friedman School of Public Health, John Finnegan</td>
</tr>
<tr>
<td>Dean’s email</td>
<td><a href="mailto:alfried@umn.edu">alfried@umn.edu</a> <a href="mailto:finne001@umn.edu">finne001@umn.edu</a></td>
</tr>
<tr>
<td>How did you hear about this funding opportunity?</td>
<td>Consortium Website</td>
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</table>

## Funding

**Amount of funding requested:** **$31,870**

Explain how these funds will help the Consortium member or JDP partner program further their work on the societal implications of the life sciences. **Indicate if more than one Consortium/JDP partner program is involved.**

This pilot study will facilitate development of a proposal to the National Institutes of Health investigating levels of manganese in drinking water, creating novel biomarkers to measure body burden of manganese and assessing adverse infant neurobehavioral outcomes in association with excessive manganese levels, an emerging scientific and public health policy issue salient across Minnesota. An essential micronutrient, low levels of dietary manganese are beneficial for health. However, an emerging literature suggests low levels of environmental exposure to manganese may also adversely affect child neurodevelopment; evidence-based policy specific to infants is lacking. Our pilot study aims to: 1) Assess determinants of manganese exposure levels in prenatal women 2) Evaluate manganese levels in drinking water at the household tap; 3) Estimate the association of drinking water manganese with prenatal biomarkers of manganese from women’s toenail clippings; 4) Estimate the association of manganese exposure in infants’ toenail clippings with effects on infants’ neurobehavioral development; 5) Obtain metrics of feasibility and participation. Findings will facilitate a new research partnership between the Center for Neurobehavioral Development, the Center for Environment and Health Policy, and the Minnesota Department of Health’s Risk Assessment and Water Protection Units, extending the Consortium’s reach to new stakeholders keenly interested in the cross-section of public policy, health and the environment.

## Approvals

Check all appropriate approvals required for your proposal. **Approvals must be obtained prior to receipt of funding.** **If you have applied for approval but have not yet received it, indicate that approval is pending.**

<table>
<thead>
<tr>
<th>IRB</th>
<th>Yes [ ] No [ ] NA [ ] Application pending</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other</td>
<td>Yes [ ] No [ ] NA [ ] Application pending</td>
</tr>
</tbody>
</table>

IRB approval is contingent on the protocol and questionnaires being developed. These are some of products of the proposed work scope but we will meet with the IRB to discuss a preliminary approval.

Specify: Subsequent to UMN IRB approval, we will seek approval from the relevant health care institution

## Checklist

- [ ] The proposal is approximately 2000 words excluding budget, biographies, references & citations.
- [ ] The proposal includes a work plan, timeline to identify work to be done & completion dates.
- [ ] The budget form is complete including the funds sought for this project, other pending applications for this project, and the amount/source of matching or other funds.
- [ ] Faculty descriptions and roles on the project are included.
- [ ] A biographical sketch for each investigator or project leader (1-2 paragraphs) is included.
- [ ] Approval (email) from the administrator/fiscal responsibility for the department or center is included.
- [ ] All necessary approvals are pending or received.
Creating Evidence Based Public Health Guidance for Manganese Levels in Drinking Water, proposal submitted by M. Georgieff and P. McGovern

Overview: The University’s Center for Neurobehavioral Development (CNBD) and the Center for Environment and Health Policy are collaborating on this funding request to launch a new line of interdisciplinary research that will inform public policy on safe levels of manganese in drinking water. 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.

Nature and Importance: Manganese is an essential micronutrient; low levels of dietary manganese are beneficial for health. However, an emerging literature suggests low levels of environmental exposure to manganese may also adversely affect child neurodevelopment. Research is needed to assess the effects of manganese exposure for infants. MDH published a Health-Based Guidance: 1)100 µg/L. for infants <1 year to protect infants that drink untreated tap water or formula prepared with tap water, and 2) 300 µg/L. for children one year and older and adults. The higher threshold also applies to infants less than one year who are exclusively breastfeed. The guidance addresses a concern that when drinking water containing manganese is used to prepare infant formula (which also contains manganese), the formula fed infant may be exposed to manganese at unsafe levels. Infants at greater than average risk are those with low iron status, born prematurely (< 32 weeks gestation), or whose mothers had prenatal diabetes or hypertension.

While most metropolitan public drinking water supplies are treated 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 EPA (see below), and MN 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.

Few studies address child health outcomes and no prospective studies have investigated exposures and outcomes for pregnant women and infants, but animal models strongly suggest a toxic effect on the brain, particularly its rapidly developing learning/memory and social-affective systems.
Creating Evidence Based Public Health Guidance for Manganese Levels in Drinking Water, proposal submitted by M. Georgieff and P. McGovern

Pilot Study Aims:

1. Assess determinants of manganese exposure levels in pregnant women, including diet, water supply and filtration, and individual risk factors
2. Evaluate manganese levels in water at the household tap
3. Estimate the association of water-manganese with prenatal biomarkers of manganese (toenail clippings)
4. Estimate the association of manganese in infants’ toenail clippings with neurobehavioral development
5. Obtain metrics of feasibility and participation.

Innovative Contribution

Policies vary. The WHO discontinued their health-based drinking water guideline for manganese of 400 µg /L for adults in 2011 reporting their health based value is well above concentrations of manganese normally found in drinking water so there was no need to derive a formal guideline. Conversely, EPA issued a Lifetime Health Advisory of 300 µg/L. Given inconsistent policies and emerging science, the MDH’s literature review led to the Health-Based Guidance, but research is needed to create evidence-based policy.

Workplan

The Co-PIs have assembled an interdisciplinary team that has met regularly since June 2012 to discuss the science.

1st quarter
- MDH will classify Minnesota communities by levels of water manganese in relation to the presence of treatment systems
- GIS consultant will map distribution of births by hospitals in communities with high water-manganese to identify a clinic to recruit 10 prenatal women
- Develop recruitment materials, surveys, protocols
- Submit IRB applications.

2nd quarter
- Recruit pregnant women, collect survey data, tap water samples and toenail clippings
- MDH will measure manganese levels in drinking water samples
- Recruit a maximum of 40 mothers from the Institute for Child Development’s (ICD’s) Infant Participant Pool to assess infant neurodevelopment in association with water-manganese levels identifying potential participants by zip codes. Neurodevelopment will be assessed using tests associated with mechanisms of dopamine transport and function of the prefrontal cortex hypothesized to be influenced by excessive manganese. Tests will include an odd-ball task which measures the neural reactions to unpredictable, but recognizable events and is reflective of prefrontal cortex activity, and the “A not B” or delayed response task which measures the ability to integrate information across a temporal delay, and is reflective of both memory and inhibitory control. Both tasks have been shown in animal models to be modulated by dopamine levels, which are perturbed by manganese toxicity and are essential for learning/memory and social-affective competence in the developing child.
Creating Evidence Based Public Health Guidance for Manganese Levels in Drinking Water, proposal submitted by M. Georgieff and P. McGovern

3rd quarter
- Analyze manganese levels from prenatal women’s toenail clippings and infant toenail clippings
- Estimate associations between manganese in:
  - Maternal toenail clippings and tap water
  - Infants’ toenail clippings and neurobehavioral assessments.

4th quarter
- Write final narrative and financial report and submit 7/31/14
- Prepare proposal (PA12-153)
Creating Evidence Based Public Health Guidance for Manganese Levels in Drinking Water, proposal submitted by M. Georgieff and P. McGovern

References


xii (PA12-153) *Research to Action: Assessing and addressing Community Exposures to Environmental Contaminants*) cosponsored by NIEHS and NINR.
Investigator Biographies

Co-Principal Investigators

Dr. Michael K. Georgieff is the Martin Lenz Harrison Land Grant Professor of Pediatrics and Child Psychology at the University of Minnesota School of Medicine and the University of Minnesota Amplatz Children’s Hospital in Minneapolis, Minnesota. He received his medical training at Washington University in St. Louis, and his pediatric and neonatology training at the Children’s Hospital of Philadelphia at the University of Pennsylvania. He has been on faculty at the University of Minnesota since 1985. He is currently the vice-chair of Pediatrics, the section head for Neonatology and the Director of the Center for Neurobehavioral Development.

Dr. Georgieff is one of the world’s experts on the role of nutrients in brain development. Specifically, he studies the effect of fetal and neonatal iron deficiency on the developing hippocampus which underlies recognition learning and memory processing. His career in this area has spanned more than 20 years and includes investigations of memory function in humans and rodent models. His team generated the first genetic models of fetal/neonatal hippocampal specific iron deficiency in order to elucidate the specific requirement of iron for brain development. He serves as an advisor to the Endocrinology, Nutrition and Growth Branch of the National Institute of Child Health and Development (NIH), was a permanent member of the Nutrition Study Section (NIH) and was on the Committee on Nutrition for the American Academy of Pediatrics. He has used his expertise in translational approaches to developmental neuroscience to propose potential brain and behavior target pathologies induced by neonatal iron deficiency. He has published over 150 peer-reviewed papers and has been continuously funded by the NIH since 1992.

Patricia McGovern, PhD, MPH, RN is the Bond Professor of Environmental and Occupational Health Policy in the Division of Environmental Health Sciences, School of Public Health, University of Minnesota—the institutional home of the Center for Environment and Health Policy. She earned a bachelor’s degree in nursing, a Master of Public Health degree focused in occupational and environmental health nursing, and a doctorate in health services research and policy. She serves as the principal investigator of the National Children’s Study (NCS) Center at the University, one of 40 centers conducting the Vanguard (or pilot) phase of a national prospective study of children’s health in relation to gene-environment interactions. She also serves as the deputy director of the Midwest Center for Occupational Health and Safety, an interdisciplinary Education and Research Center.

Over the past 15 years she has conducted studies investigating risk and protective factors for maternal and child health. Her research on women’s health in association with childbirth and use of Family and Medical Leave policies is internationally recognized. Her expertise in the NCS will contribute to her leadership role on the pilot study. Her research team enrolled a cohort of 150 pregnant women recruited through household mailings and collected panel data on health, demographics, use of health services and environmental exposures from pregnant women and mothers during the infants' first year. As part of the NCS, she also met with the leadership
of the major health systems and hospitals in the area to successfully facilitate hospital-based data collection. She serves on an advisory board for the Environmental Health Tracking and Biomonitoring program of the MDH. Dr. McGovern has published 78 papers in peer-reviewed journals. Her research has been funded by the NICHD, NIOSH, NIMH.

Additional Investigators and Key Staff

- Members of Dr. Georgieff’s research team including neonatologist, Raghu Rao, MD, Associate Professor of Pediatrics, whose research assesses early life nutritional perturbations of brain metabolism, and Neely Miller, B.S. research coordinator in the Center for Neurobehavioral Development who has ten years’ experience conducting clinical research. Her expertise is in high-density Event-Related Potential (ERP) to assess learning/memory function in pre-verbal infants and she is responsible for supervising the ERP and behavioral paradigms that will take place at the CNBD. In that capacity, she will be responsible for subject enrollment, data collection, data analysis, and will assist with manuscript preparation.
  - Dr. Georgieff has also informally engaged the efforts of Dr. Michael Aschner, Professor of Pediatrics, Gray E.B. Stahlman Chair in Neurosciences and Professor of Pharmacology, whose research focus addresses cellular and molecular mechanisms of heavy metal neurotoxicity, and Dr. Stephnie Fretham, a post-doctoral student in Dr. Aschner’s lab who completed her Ph.D. in neuroscience at the University of Minnesota where she studied iron deficiency and hippocampal development with Dr. Michael Georgieff.

- Members of Dr. McGovern’s research team include Professor Tim Church, a biostatistician and epidemiologist with expertise in research methodology, a study designer and co-investigator with the School Health Initiative: Environment, Learning and Disease (SHIELD) study in south Minneapolis children and with Professor McGovern on the National Children’s Study, Irina Stepanov, PhD, Assistant Professor and chemist with expertise in biomarker development and analysis, and Jill Cordes, BSN, clinical coordinator with over 20 years of experience managing environmental health studies in Division of Environmental Sciences, School of Public Health.

- Brandy Toner, PhD, Assistant Professor, Department of Soil, Water & Climate, an environmental chemist whose research addresses chemical and biological processes that result in the cycling of metals in the environment and focuses on manganese and iron.

Expertise from the Minnesota Department of Health has included scientists and staff from various departments including:

- Risk Assessment Unit including, Pam Shubat, PhD, Supervisor, and toxicology/risk assessment staff, Kate Sande, MS, and David Bell, MS candidate who have provided expertise on public policy and scientific issues of manganese in drinking water.
- Drinking Water Protection/Source Water Protection Unit hydrologists, James Lundy and Rich Soule
- Drinking Water Protection, Community Water Systems-District Engineer, Hennepin and Anoka Counties, Isaac Bradlitch, MS.
## Project Title:

**Instructions:** Provide justification along with costs.

<table>
<thead>
<tr>
<th>Category</th>
<th>Description &amp; justification</th>
<th>Requested funding</th>
<th>Matching/other funding</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Your stipend</td>
<td>What is hourly wage &amp; fringe based on--departmental, community or other rate?</td>
<td>$12,427</td>
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<tr>
<td>Other personnel</td>
<td>Grad. Research Assist. to conduct literature review and develop participant questionnaires and IRB applications ($53,839 annual salary, 9-month, 25% appointment)</td>
<td></td>
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<tr>
<td>2 Other personnel</td>
<td>CNBD Research Coordinator to recruit and test of 40 infants at the Center for Neurobehavioral Development ($41,200 annual, 40 hrs setup + 4 hrs per baby)</td>
<td>$5,420</td>
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<tr>
<td>Other personnel</td>
<td>Environmental health sciences research coordinator to oversee prenatal participant recruitment and data collection ($52/hr, 5% effort for 6 months)</td>
<td>$2,704</td>
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<tr>
<td>Other personnel</td>
<td>OB Clinic Nurse to recruit pregnant women ($44.76/hr, 5% for 2 months)</td>
<td>$776</td>
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<tr>
<td>3 Other personnel</td>
<td>IT staff to set up database and conduct analysis ($63,860 annual salary, 2.26% effort 7/1/13-6/30/14)</td>
<td>$1,928</td>
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<tr>
<td>Other personnel</td>
<td>CTSI IT Professional to set up questionnire in Redcap Data Base (20 hrs @ $96.52/hr charge)</td>
<td>$1,930</td>
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<tr>
<td>4 Supplies &amp; Services</td>
<td>Identify and explain use. Participant incentives for research $25/completed protocol, N=10 prenatal women &amp; 40 new mothers; $5.00 infant toy, N =40 infants ($1,150); Stationary and office supplies for recruitment materials ($96); Copies ($54); Postage ($63)</td>
<td>$1,363</td>
<td></td>
</tr>
<tr>
<td>Other personnel</td>
<td>Analysis of 10 samples of household water for Manganese @$15.00 each; Graduate RA to analyze manganese in toenail clippings, 25% effort=$ 24,824</td>
<td>$0</td>
<td>$150; $24,824 MDH donation of analytic time in lab for water samples; Dr.</td>
</tr>
<tr>
<td>Consultants</td>
<td>GIS consultant @ $80/hr * 62 hrs to analyze birth certificate data and map hospitals with highest birthvisit volume to communities with high and low levels of manganese in water for clinic-based participant recruitment.</td>
<td>$4,960</td>
<td></td>
</tr>
<tr>
<td>6 Travel</td>
<td>Local travel to OB clinic &amp; MDH and community meetings to discuss study with stakeholders where participants will be recruited ($0.565/mile *640 miles at 32 mi. RT for UMN staff to travel to community)</td>
<td>$362</td>
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</table>

**Subtotal research expenses (2-6)** $0

**TOTAL BUDGET** $31,870

**Budget Guidelines**

1. Stipend justification. You must justify the amount of stipend you are requesting by identifying the number of hours you plan to work on the project and the hourly wage used for research assistants in your department. Include fringe benefits.

2. Identify all other personnel to be paid from this grant including interpreters, travel guides, etc. and justify their salary by identifying the number of hours they will work and the hourly wage. What is the hourly wage based on?

3. For colloquia, identify the number of speakers and the amount of honoraria you will provide.

4. Supplies and services. List out all supplies and their estimated costs. Explain in line 7 or in the body of your proposal what the supplies will be used for.

5. Travel costs must include a description of the purpose of the travel, start and stop dates of travel, transportation costs, housing costs, and allowable per diem (use University rates found at http://travel.umn.edu).