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Manganese Health Research Program

The Manganese Health Research Program (MHRP) is funded by the United States Department of Defense. The MHRP Steering Committee is made up of independent scientists, occupational health experts from Mn producer and end-user companies and is chaired by the Secretary General of the International Manganese Institute. Dr. Michael Aschner of Vanderbilt University Medical Center is the Principal Investigator (PI) and the overall administrative oversight is carried out by his university.

Request for Proposals for Phase III

The Manganese Health Research Program (MHRP) invites preliminary research applications to investigate the relationship between manganese exposure and human health concerns, and to explore mechanisms by which manganese contributes to the development, progression, or exacerbation of human disease. The major purposes of this initiative are to:

- support innovative, multidisciplinary research in humans and animal models on the specific cellular, molecular and physiologic mechanisms by which manganese mediates adverse effects;
- identify and investigate factors, such as age, pre-existing disease, and genetics that make individuals more susceptible to the effects of manganese.

Objectives

To protect the health of U. S. military personnel and others who may be exposed to manganese through their work or in the environment through developing an improved understanding of the relationship between exposure and health effects by:

- Consideration of the relevant health issues.
- Characterization (assessment) of exposures in occupational and environmental scenarios.
- Development of appropriate biomarkers of exposure.
- Quantifying the relationships between exposure and ill health including the role of confounders.
- Understanding the mechanisms of Mn transport, damage and repair.

Research Needs

Although much is known concerning the essentiality and toxicity of Mn there remains a number of pressing research needs that are focused on (a) human exposure assessments; (b) elucidation of mechanisms determining Mn disposition in the body including identification of biomarkers of exposure; (c) mechanisms of damage or repair; and (d) evaluation of carcinogenicity, mutagenicity and reproductive toxicity of manganese compounds. In accordance with these research needs, timely and topical issues specific to each of these categories are identified below.

1. Exposure Assessments

A. There are few estimates of occupational exposure to Mn and/or comprehensive studies of exposure in the general population.

Better estimates of exposure will improve dose-response analyses that have implications for regulatory purposes. Exposure assessments should include methods (e.g., questionnaires) to estimate and take account of Mn exposure arising from the diet. In addition to determination of exposure levels, these studies should evaluate biomarkers of exposure, and be relevant to identification of no adverse effect levels (NOAELs) or other toxicological indicators (NOAEL). (Note: a biomarker study attempting to derive a NOAEL should be linked with a study measuring a defined adverse effect.) Most likely population choices for the above studies include workers from battery, ferroalloy plants, Mn mines, steel production or welders. Consideration should also be directed at the population at large in the vicinity of point sources of high Mn emissions.

The studies should involve Mn compounds with different physical and/or chemical characteristics in order to compare the effect of differences in valence, solubility, particle size, etc.

B. Mn and Fe homeostasis appear to share common pathways. Therefore, Fe deficiency has consequences regarding Mn homeostasis, e.g., increased absorption of Mn across the gastrointestinal tract. It is noteworthy that Fe deficiency (ID), defined as an insufficient supply of Fe to the cells of the body after Fe reserves have been exhausted, is the most prevalent single nutritional deficiency, affecting over 2 billion people, mostly in the developing world. Infants, small children, adolescents and pregnant and fertile-age women are most vulnerable.

Studies of Mn in humans should include a thorough assessment of the diet, assessing the nutritional adequacy of Mn exposed populations, including the assessment of nutritional and environmental factors that might attenuate or exacerbate the effect of Mn on the health points measured. Studies with humans and animals should examine changes in the dose-response characteristics of Mn effects associated with nutritional factors.

C. There is a need to evaluate the amount of variability that occurs in brain Mn concentrations during different life-stages.

Studies with human cadaver samples should examine normal variability in brain Mn levels at different life stages. Development of histochemical approaches to assess tissue Mn content would greatly advance this area of research.

2. Mechanisms determining Mn disposition in the body and identification of biomarkers of exposure

A. Certain brain substructures demonstrate a particular affinity for Mn, and as a consequence absorb a disproportionate percentage of available Mn. Incorporation of Mn into mitochondria proteins results in a long half-life and thus slow clearance from brain tissue. Other pools of Mn are governed by different kinetics, where accumulation and clearance occur more quickly. Research is needed to clarify Mn retention and clearance issues and to investigate any health consequences of long-term retention.

Studies should be carried out to delineate the mechanism/s of Mn uptake, distribution and retention in brain. Research in animals is needed to better define the immediate and long-term effect of early chronic low-level Mn exposure on Mn metabolism and retention in the brain.

B. The role of genetic factors in Mn-induced neurotoxicity has not been evaluated.

Studies with humans and animals should examine changes in the dose-response characteristics of Mn effects associated with genetic factors.

C. Additional research should be directed towards the identification of Mn transport proteins.

Studies with animals should evaluate whether the divalent metal transporter (DMT1) plays a critical role in Mn metabolism or delivery to brain and other target organs. Specifically, studies should be directed at the mechanisms of Mn transport across the blood-brain barrier.

D. There are no reliable biomarkers of Mn exposure.

Data are needed that reliably measure biomarkers of Mn exposure.



E. The potential health effects of metal fumes on exposed workers represent a growing concern with respect to occupational environments.

Prospective studies with exposed workers should collect data on Mn blood concentrations (and other biological media potentially relevant to exposure, such as saliva) along with brain imaging studies, to assess its potential effect to alter brain chemistry (neurotransmitter levels, receptor function). Brain imaging studies of exposed populations should be considered a high priority. (It should be noted that exposed workers are exposed to a wide range of inhaled substances, Mn being only one of many, and these will need to be taken into account.)

3. Mechanisms of damage or repair

A. High dose chronic exposure to Mn is associated with adverse neurological, reproductive, and respiratory effects. Considerably less is known regarding health effects associated with chronic low-dose exposure especially in potentially sensitive subpopulations.

Research is needed to determine the long-term effects of low-level Mn exposure, specifically increased risk for neurological disease.

B. Potential mechanisms for Mn-induced neurotoxicity have been identified (a decrease in the content of “protective” enzymes (peroxidase and catalase), and production of free radicals, which “attack” dopamine, dopaminergic cells). Recent studies also suggest that Mn might play a causative role in prion disease. It was found that Mn could be incorporated into prion protein (PrP) and that this PrP was partially proteinase resistant. It was suggested that it is possible to generate proteinase-resistant PrP, a possible mechanism for the formation of the scrapie isoform of the PrP as generated in sporadic prion disease.

Studies should characterize the mechanisms of Mn neurotoxicity, including effects on signaling pathways and the conformation of enzymes and structural proteins should be studied especially during brain development, because the development and function of the brain would be particularly sensitive to such effects. Studies on the mechanisms of Mn neurotoxicity should also be carried out in non-human primates at dose levels that have some relevance to human exposure levels.

C. Mn toxicity has been associated with male reproductive dysfunction, often manifesting in symptoms such as loss of libido, impotence, and similar complaints. *Research is needed to assess the effects of Mn on reproduction, including the effects on fertility indicators, such as sperm production, conception rates, and pregnancy outcomes.. Animal studies should determine the multigenerational reproductive effects of Mn in rodents.*

D. Mn preferentially accumulates in mitochondria, a critical target organelle mediating its toxicity.

Research is needed to address the mechanisms of transport of Mn into mitochondria and the consequences of its accumulation in this organelle. The studies should include mechanisms of Mn-induced changes in mitochondrial enzyme function, as well as the potential for Mn-induced cell death by apoptotic means.

4. Neurobehavioral Tests Mechanisms

A. Mn exposed workers exhibit significant differences in performance on tests of visual reaction time, eye-hand coordination, and hand tremor, as well as a plethora of other effects, both in humans and various animal models.

Research is needed to address the mechanisms associated with these effects, correlating behavioral endpoints with changes in brain neurochemistry. Studies should also assess the validity of neurobehavioral tests to accurately distinguish effects of Mn from other neurotoxicants

5. Genetic Toxicology and Cancer

A. There is some suggestive evidence to show that manganese may have effects upon genetic material although many of these studies have not been carried out to OECD or other guidelines and thus it is not easy to evaluate the potential of manganese to act as a genetic toxicant.

In order to establish whether or not experimental studies are required to clarify this issue, it would be helpful to have an in-depth critical review and evaluation of all the existing data in this area and from this, to propose where, if any, efforts are required.

Proposal Submissions

Interested researchers should submit brief expressions of interest (2-3 pages) providing objectives, a description of the plan of work, a timeline, outline costs and brief CVs of those involved by August 1, 2007. These materials will be reviewed by the MHRP Steering Committee in September. Researchers will be notified of the Committee's decision, and where appropriate full proposals will be requested by November 1, 2007. Funding is subject to review and final approval by the Department of Defense.

Please send proposals to Alycia Buford-Penn, via e-mail to alycia.buford@vanderbilt.edu