

The Declaration of Brescia on Prevention of the Neurotoxicity of Metals[†]

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On 17–18 June, 2006, the Scientific Committee on Neurotoxicology and Psychophysiology and the Scientific Committee on the Toxicology of Metals of the International Commission on Occupational Health (ICOH) convened an International Workshop on *Neurotoxic Metals: Lead, Mercury, and Manganese—From Research to Prevention (NTOXMET)* at the University of Brescia. Scientists and physicians from 27 nations participated.

Data were presented for each of the three metals on environmental sources, fate and distribution; human exposure; clinical, subclinical, and developmental neurotoxicity; epidemiology; risk assessment; and prospects for prevention. Ongoing and future studies were described and discussed.

For each of the metals, initial recognition of neurotoxicity occurred in the context of high-dose exposure. For example, lead poisoning was first recognized in miners, smelters, and type setters, methylmercury poisoning in inhabitants of the fishing community of Minamata, and manganese poisoning in miners and ferroalloy workers. Subsequent development of more sensitive and sophisticated analytical instruments led to the recognition of subclinical toxicity and developmental neurotoxicity at progressively lower levels of exposure. In each case, the extent of toxicity was much greater than initially appreciated and the size of the

affected population much larger. Many decades typically elapsed between the initial recognition of neurotoxicity and the initiation of programs for prevention. Early warnings were frequently ignored and even actively resisted.

The historical observation that long delays had typically elapsed before the initiation of prevention prompted extensive discussion at the Workshop about the need to develop more effective strategies. From this discussion, a series of recommendations emerged on future directions for research and prevention of the neurotoxicity of metals.

At the closing session of the International Workshop at Brescia, the following recommendations on the prevention of the Neurotoxicity of Metals were adopted by consensus:

Intensified attention must be paid to early warnings of neurotoxicity. Clinical observations or toxicological data suggesting the existence of neurotoxicity including subclinical and developmental toxicity must be taken very seriously. Such observations should prompt consideration of prudent preventive action.

All uses of lead including recycling should be reviewed in all nations and uses contributing to environmental and human exposures, such as uses in toys, paint, water pipes, building materials, solder, electronics, medications, and cosmetics ended. The transfer of these products from one country to another should also be avoided. This approach has been adopted successfully in the EU and needs to be extended worldwide.

In particular, *tetraalkyllead must be eliminated without delay from the gasoline supplies of all nations.* The removal of organic lead from gasoline has produced declines of >90% in population mean blood lead levels in industrially developed nations, and this success is now being repeated in some of the developing nations. This action represents one of the great public health triumphs of the late 20th century and needs urgently to be extended to all nations.

Current exposure standards for lead need urgently to be reduced. Current standards were established many years ago and do not reflect recent advances in scientific knowledge about toxic effects at levels of exposure below these standards. The Brescia Workshop recommends that:

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[†]The views presented in the Declaration is the consensus reached by the participants of the workshop and do not necessarily reflect the decisions or stated policies of the affiliation organizations.

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- *For children*, the action level, which triggers community prevention efforts to reduce exposure sources, should be immediately reduced to a blood lead concentration of 50 µg/L in nations worldwide. This level is proposed as a temporary level that may need to be revised further downward in future years as new evidence accumulates on toxicity at still lower blood lead levels. This reduction of the blood lead action level will reduce the incidence of subclinical neurotoxicity in children as well as the delayed consequences of developmental toxicity.
- *For industrial workers*, the standard for lead in blood should be reduced immediately to 300 µg/L in nations worldwide. Additional consideration should be given to further reducing this standard to 200 µg/L and below in the years ahead. This reduction in exposure standard will reduce the incidence of subclinical neurotoxicity and other toxic effects during the working life and responds to new documentation presented at the Workshop that long-term lead exposure increases the risk of dementia in later life.
- *For female industrial workers of reproductive age*, the standard for lead in blood should be reduced immediately in nations worldwide to the lowest obtainable, preferably to 50 µg/L, a level consistent with the recommended blood lead standard for children. Lead passes freely across the placenta from the maternal to the fetal circulation to enter the developing brain where it causes prenatal brain injury. This recommended reduction in maternal lead exposure will reduce the incidence of fetal neurotoxicity in the offspring of women workers.

Exposures of pregnant women and women of reproductive age to methylmercury need to be reduced to prevent subclinical fetal neurotoxicity. Evidence is strong that prenatal exposure to methylmercury causes fetal neurotoxicity. Consumption of fish with high mercury concentration by pregnant women is the primary route of exposure. More than 50% of the mercury in fish may be of industrial origin.

Strategies for reducing mercury exposure recommended by the Brescia Workshop are the following:

- All industrial uses, recycling processes, and other industrial input of mercury into the environment should be reviewed in all nations, and non-essential uses should be eliminated and releases controlled. This approach has been successfully introduced in the EU and is actively promoted by the United Nations Environmental Programme.
- Mercury emissions from coal-fired power plants need to be curtailed.
- All chloralkali plants worldwide should be urgently converted to alternative technologies that are not based on mercury, and mercury stores and wastes must be safely deposited.
- Gold mining with mercury must be controlled and enforced with safety guidelines, and alternative technology should be promoted.
- Dietary advisories should be developed as effective, culturally appropriate means to limit childbearing women's consumption of fish contaminated with methylmercury. Taking into account nutrient contents and availability, healthy diets should be recommended with fish and seafood containing minimal levels of contamination.

Exposures of pregnant women and young children to manganese need to be reduced to prevent subclinical neurotoxicity. Important new data on the neurotoxicity of manganese were presented at Brescia. In adult workers, these data suggest that manganese produces subclinical neurotoxicity at levels of exposure below those that produce parkinsonism. In children, evidence from two recent epidemiological studies suggests that exposure to manganese in early life causes subclinical developmental neurotoxicity.

The addition of organic manganese compounds to gasoline should be halted immediately in all nations. The data presented at the Brescia Workshop raise grave concerns about the likelihood that addition of manganese to gasoline could cause widespread developmental toxicity similar to that caused by the worldwide addition of tetraalkyllead to gasoline. In light of this information, it would be extremely unwise to add manganese to gasoline.

Exposure standards for manganese need to be reconsidered. The drinking water standards for manganese in many countries are not based on health concerns, and those that are, do not protect against developmental neurotoxicity resulting from exposures in utero and in early postnatal life. The current occupational exposure standard may not protect workers against subclinical neurotoxicity. The value for air manganese concentration in inhalable/total dust of 100 µg/m³ should be adopted to protect the workers from prolonged exposure and consequent long-term effects.

Economic impacts of the neurotoxicity caused by metals must be considered. The costs of toxicity may be far greater than the costs of pollution control. The major contributor to these costs is damage to the developing central nervous system. Such injury can result in lifelong loss of intelligence and motor capacities, permanent psychological disturbances, and disruption of behavior. These effects can produce reduction of economic productivity, and when this reduction occurs widely across a society, the resulting economic impacts are great. The costs of pollution recur annually in each exposed birth cohort, adults, and elderly while the costs of control are one-time costs.

Need is great for continuing research into the neurotoxicity of metals. Recent studies of neurotoxicology

of each of the metals discussed at the Brescia Workshop inform us that we can anticipate harmful effects of increasingly lower levels of exposure to metals, previously considered safe as larger studies using sensitive measures of exposure and outcome, and better statistical techniques are conducted.

- a. For lead, mercury, and manganese, much remains to be learned about the delayed consequences of developmental toxicity and the prolonged exposure to low levels in the adults, as possible causes of neurodegeneration. This research is critical to guide both future research in metals as paradigms of neurotoxic pollutants and targeted programs of prevention.
- b. Prospective cohort studies from birth are needed, parallel to study on adults and elderly with a retrospective assessment of exposure.
- c. Neurotoxicological research, including research on developmental neurotoxicology, is needed on metals not considered at the Brescia Workshop—arsenic and aluminum, in particular, and on interactions with essential elements, pesticides, and persistent organic pollutants.
- d. Research is needed into genetic and other factors that contribute to susceptibility to metal toxicity.
- e. Research is needed into various determinants of the rearing environment, including the social setting, that can modify the exposure indicators to neurotoxic metals

and subsequently the magnitude of neurodevelopmental effects.

- f. Research is needed into the potential consequences of global warming for human exposures to neurotoxic metals—especially mercury.

SIGNATORIES (ORGANIZING COMMITTEE OF THE NTOXMET WORKSHOP)

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