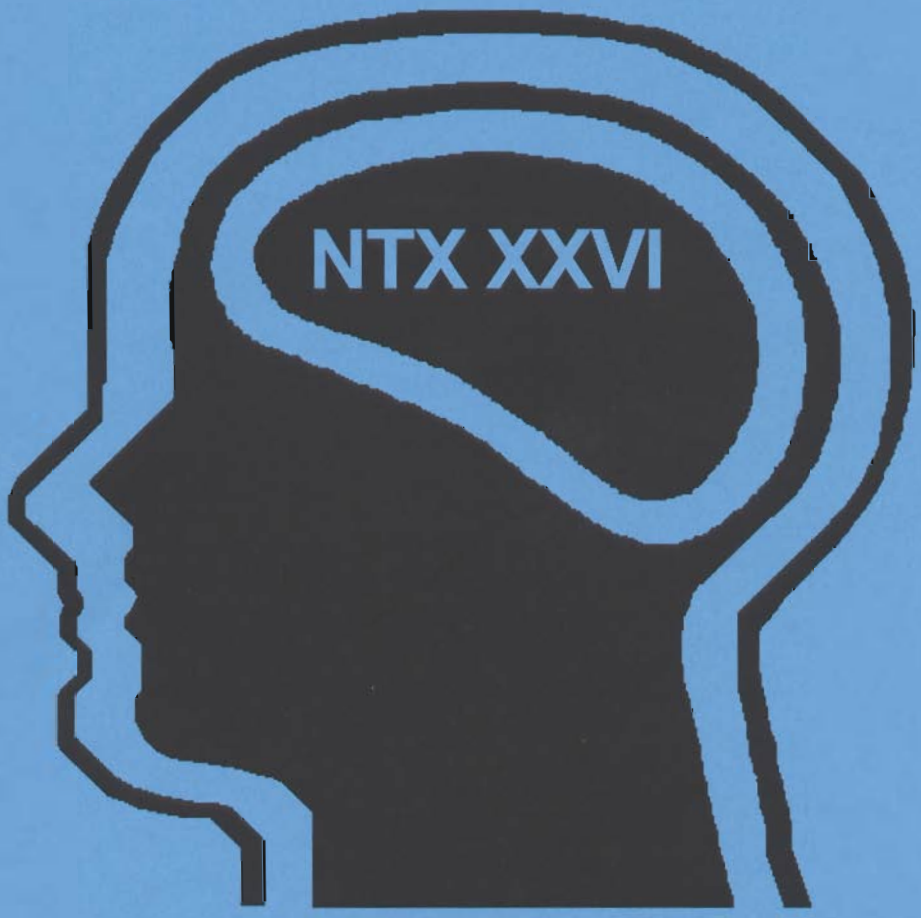
TWENTY-SIXTH INTERNATIONAL NEUROTOXICOLOGY CONFERENCE

Theme:

Unifying Mechanisms of Neurological Disorders:

Scientific, Translational, and Clinical Implications



Abstracts

DAVID reveals that there is a five-fold enrichment in the GO category "Disease mutations" containing 49 genes, such as genes involved in retinoblastoma (RB1), breast cancer (BRCA1), and Wilm's tumors (WT1). This data supports the Barker Hypothesis that early life exposures to lead can affect the development of later diseases. In addition to the 423 genes with significant ($P < 0.05$) positive correlations between Pb and DNA methylation, there are also 728 genes with significant negative correlations. The two most significantly negatively correlated CpG methylations were near the genes Cdkn1c ($P = 0.00024$) and Ptprm ($P = 0.000015$). Cdkn1c is a cyclin-dependent kinase inhibitor that is imprinted (OFF on the paternal chromosome and ON on the maternal chromosome). Ptprm encodes a protein tyrosine phosphatase that down-regulates growth factor signaling. The Preliminary identification of Cdkn1c and Ptprm is especially exciting because of similar findings from another laboratory. Le-Niculescu and colleagues recently found that gene expression levels in human blood can be used to identify useful biomarkers for neuropsychiatric disorders, including Ptprm..

Panel Discussion/Brainstorming

Moderators:

- M. Daniele Fallin
- Jason Richardson

Symposium

SESSION IX: NEUROTOXIC EFFECTS OF ENVIRONMENTAL EXPOSURE TO MANGANESE IN CHILDREN AND ADULTS

Session Chair: **Donna Mergler**
Co-Chair: **Roberto Lucchini**

Theme and Rationale: *Since Couper first identified manganese intoxication in 1837, there have been hundreds of reports of neurologic disorders and neurobehavioral deficits due to high levels of occupational exposure to manganese. Since manganese is an essential element and subject to homeostatic control, there has been little concern about possible neurotoxic effects of environmental exposure through air and water. Recent studies with children and adults living in the vicinity of manganese mines and processing plants and with children exposed to manganese through drinking water, suggest that environmental manganese exposure is associated with loss of nervous system function. This is an emerging field and many questions still need to be answered: What are the effects throughout the lifespan? What is the contribution of in utero exposure? What is the most adequate biomarker of exposure? Are current guidelines protective for health? In this session, researchers from several countries present their studies on environmental exposure to manganese.*

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NEUROBEHAVIORAL EFFECTS OF INHALED MANGANESE IN ITALIAN ADOLESCENTS. Roberto Lucchini, *University of Brescia, Occupational Health, Brescia, Italy*

Background and Objective: Increased parkinsonism was observed in Valcamonica, a valley in the province of Brescia, Italy. Prevalence data were higher in the vicinities of ferroalloy plants and associated to the concentration of manganese in deposited dust. The aim of the present study was to assess motor, cognitive and neurosensory functions in adolescents in the exposed area and in a reference area. Methods: Metals were measured in airborne particles collected with 24-hours personal samplers, and in various environmental media. Soil was analyzed at surface and 10cm depth. Adolescents were recruited through the local school system for neurobehavioral examination and assessment of dietary intake of metals. Blood and urine samples were collected for metal analysis. Results: A total of 303 children residing in an exposed area and a reference area participated in the study. Airborne manganese was 84.38±89.65 ng/m3 in the exposed area and 22.79±23.82 ng/m3 in the reference area. Lead, iron, zinc and chromium also showed significantly higher levels. Manganese results were significantly higher also at the surface and at 10 cm depth of soil and in salad. Exposure biomarkers were not significantly different between the two areas. Children in the exposed area showed impairment of motor coordination and odour identification associated with airborne manganese at multivariate analysis. Blood lead was inversely associated with IQ. Conclusion: Environmental exposure to manganese in adolescents is related to deficit in motor and olfactory functions whereas concomitant lead exposure is related to decrease of IQ. Acknowledgement: This work was partially supported by the EU through its Sixth Framework Programme for RTD (contract no FOOD-CT-

2006- 016253). It reflects only the authors' views. The European Community is not liable for any use that may be made of the information contained therein.

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ELEVATED MANGANESE AFFECTS MOTHERS' AND CHILDREN'S COGNITION. José A. Menezes-Filho, Cristiane de O. Novaes, Ciro R. Paes, Josino C. Moreira, Paula N. Sarcinelli & Donna Mergler. *Laboratory of Toxicology, College of Pharmacy, Federal University of Bahia, Salvador, Bahia, Brazil.*

There is growing evidence that excess manganese (Mn) in children is associated to neurobehavioral impairments. In Brazil, hair Mn concentrations among children living in the vicinity of a ferro-manganese alloy production plant, are highest nearest and downwind from the plant. Little is known about the effects of airborne Mn on children's and their parents' cognitive functions. This study sought to investigate the relations between biomarkers of Mn exposure (hair and blood) and children's neurobehavioral performance and to examine the relation between mothers' hair Mn concentrations and their performance on a test of intelligence. In a cross-sectional study, we assessed Mn blood and hair levels, blood lead (PbB) and cognitive performance, using the WISC-III, for 83 children aged 6 to 11 years and 11 months. The Raven Progressive Matrix was administered to the mothers and their hair Mn was determined. An interview administered questionnaire served to collect socio-demographics. Mean blood and hair Mn were 8.2 µg/L (range: 2.7 - 23.4) and 5.83 µg/g (range: 0.1 - 86.68 µg/g), respectively. Mean PbB was 1.43 µg/dL (range: 0.2 - 10.35 µg/dL). Mean maternal MnH was 3.50 µg/g (range = 0.10 - 77.45), and was significantly correlated (rho=0.29, p=0.01) with children's MnH levels. Children's MnH concentrations were significantly and negatively, related to Full-Scale (FS) and Verbal IQ. After adjusting for maternal education, nutritional status the coefficients for Mn were β=-5.78, p=0.03 and β=-6.72, p=0.02 for FS and Verbal IQ, respectively. MnH levels explained 5.6% and 6.8 % of the variance of the respective IQ scores. Maternal MnH was negatively associated with performances on the Raven's score (β=-2.689, p=0.055), after adjusting for education years, family income and age (partial r^2 for Mn=5.6%). The present study confirms that high MnH levels in children are associated with cognitive deficits, especially in the verbal domain. Mother's IQ is likewise associated to Mn exposure, suggesting that, in this situation of environmental airborne exposure to Mn, children's cognition may be doubly affected by exposure to airborne Mn.

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EFFECTS OF ENVIRONMENTAL EXPOSURE TO MANGANESE ON MOTOR FUNCTION OF CHILDREN IN MEXICO. Riojas Rodríguez Horacio, Ph.D. Hernández Bonilla David, Npsic. Schillman Astrid, McSc. *Instituto Nacional de Salud Publica, Mexico.*

Objective: The Molango mining district located in the state of Hidalgo has important manganese (Mn) deposits. An ecosystem health approach has been used to study the factors that determine the population exposure using the interaction between social, environmental and health sciences. The objective of this study is to evaluate the effect of Mn exposure on motor skills in school-aged children. Materials and methods: School-aged children between 7 and 11 years old were selected from two communities in the Molango mining district (100 children) and 95 children from non-exposed communities with similar socioeconomic conditions. The Luria motor scale was applied. The exposure to Mn was measured as blood Mn (MnB) and hair Mn (MnH). Multivariate lineal regression was performed to assess the effect of Mn on the global index of motor function adjusting by relevant covariates. Results: Median MnH and MnB were significantly different in exposed (12.6 mcg/g and 9.5 mcg/L) and not exposed (0.6 mcg/g and 8.0 mcg/L) children. After adjusting for haemoglobin, maternal education, gender, age and blood lead levels, MnB, was associated with a worse performance in the global Luria's test (coefficient 3.2, p=0.022). In a gender stratified analysis the boys execution is was worse compared with the girls. A significant interaction term between MnB and age was found. Conclusions: The younger boys were more susceptible to the adverse effect. The environmental exposure to Mn has an adverse effect on some aspects of motor function in school-aged children.

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METHODOLOGICAL ASPECTS OF AN EPIDEMIOLOGIC STUDY OF ADULTS LIVING NEAR A MN POINT SOURCE*

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