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Creating a Safer and Healthier World
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PROGRAM

49th Annual Meeting and ToxExpo™

SALT LAKE CITY, UTAH

March 7–11, 2010

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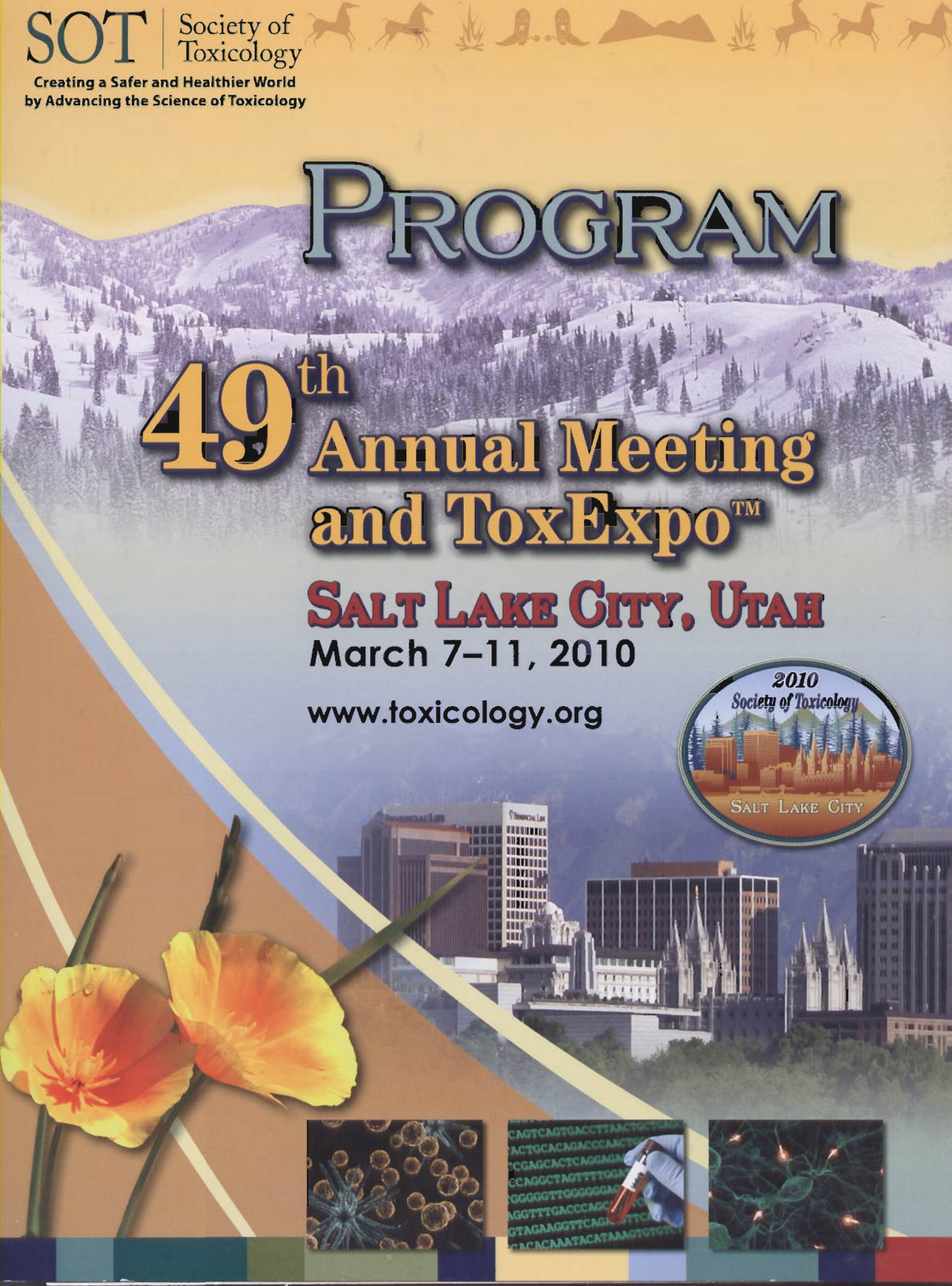

Abstract #

Monday Morning, March 8
9:15 AM to 12:00 NOON
Ballroom A

S

Symposium Session: Mechanistic Role of Reactive Intermediate Protein Covalent Binding in Target Organ Toxicity: Past, Present, and Future

Chairperson(s): *Jose E. Manautou, University of Connecticut, Storrs, CT, and George B. Corcoran, Wayne State University, Detroit, MI.*

Sponsor:
Mechanisms Specialty Section

Endorsed by:
Drug Discovery Toxicology Specialty Section
Molecular Biology Specialty Section

The pioneering work of Brodie and co-workers in the early 1970's demonstrated that protein covalent binding of a reactive metabolite of acetaminophen, N-acetyl-p-benzoquinoneimine, was strongly associated with hepatotoxicity. Over the last three decades, immunological, biochemical, molecular biological, and proteomic approaches have been used to identify specific proteins adducted by reactive electrophilic metabolites. Although the identity of a number of protein targets, and the effects of covalent adduction on protein structure and function are known, the precise role of protein covalent binding in chemical-induced toxicities remains a subject of contention. Indeed, the importance of reactive intermediate protein binding has been challenged by multiple studies employing experimental manipulations that reduce toxicity in the absence of an effect on protein binding. To adequately address these findings state-of-the-knowledge of reactive intermediate protein binding and its toxicological consequences will be presented. The specific topics to be discussed include current views on the importance of protein covalent binding, latest *in vivo* and *in vitro* approaches to study covalent binding, the pharmaceutical industry's perspective on the role of reactive intermediate binding in toxicity and the current safety assessment guidelines for drug candidates with covalent binding liability. Finally, current and future tools and technologies for studying reactive intermediate biology will be highlighted.

#14 9:15 MECHANISTIC ROLE OF REACTIVE INTERMEDIATE PROTEIN COVALENT BINDING IN TARGET ORGAN TOXICITY: PAST, PRESENT, AND FUTURE. *J. E. Manautou*[1] and *G. B. Corcoran*[2]. [1]Pharmaceutical Sciences, University of Connecticut, Storrs, CT and [2]Pharmaceutical Sciences, Wayne State University, Detroit, MI.

#15 9:20 REACTIVE INTERMEDIATES AND THEIR INTERACTION WITH CELLULAR PROTEINS: HISTORICAL PERSPECTIVE. *P. Moldeus.* Safety Assessment, AstraZeneca, Södertälje, Sweden.

#16 10:00 THE ENIGMA OF REACTIVE METABOLITES. *J. Uetrecht.* Faculty of Pharmacy, University of Toronto, Toronto, ON, Canada.

#17 10:40 BIOACTIVATION AND COVALENT BINDING APPLIED IN A DRUG RESEARCH SETTING. R. Obach. Pfizer Inc., Groton, CT. Sponsor: *J. Manatou.*

#18 11:20 KNOWNS AND KNOWN UNKNOWNS IN PROTEIN COVALENT BINDING AND TOXICITY. *R. P. Hanzlik.* Department of Medicinal Chemistry, University of Kansas, Lawrence, KS.

Abstract #

#18A 11:28 Drug Hypersensitivity: Molecular Aspects from Molecule to Man. K. Park, MRC Centre for Drug Safety Science, University of Liverpool, United Kingdom. Sponsor: *J. Manatou.*

Monday Morning, March 8
9:15 AM to 12:00 NOON
Room 150

S

Symposium Session: Neurological Responses after Exposure to Inhaled Metal Particles

Chairperson(s): *James Antonini, CDC-NIOSH, Morgantown, WV, and Lung-Chi Chen, New York University School of Medicine, Tuxedo Park, NY.*

Sponsor:
Inhalation and Respiratory Specialty Section

Endorsed by:
Immunotoxicology Specialty Section
Metals Specialty Section

Most studies examining the toxicology of inhaled metal particles have focused on responses in the target organ, the respiratory system. Less information exists regarding the effects associated with the inhalation of metals in extrapulmonary organs, specifically the central nervous system. There is increasing interest in the health effects of airborne incidental and manufactured metal nanoparticles (particles with one dimension <100 nm) in the environment and workplace. These smaller particles may translocate more easily from deposited sites in the respiratory tract to brain structures after inhalation. Mechanisms of particle translocation include uptake and transport along olfactory and sensory neurons, transcellular transport across respiratory epithelium to the circulation, and lymphatic clearance. Chemical composition, oxidation state, and solubility all may affect metal transport and biological responses to inhaled metals. Both animal and human studies have demonstrated that inhaled metals can translocate to the central nervous system, as well as, induce neurofunctional changes. Alterations in markers of neuroinflammation and cellular toxicity have been observed in specific brain regions using animal models after exposure to a variety of occupational particles and ambient air pollution. Cognitive deficits, brain abnormalities, and neurodevelopmental effects have been associated with exposure to metals in healthy children in Europe and North America. Our panel of experts from the fields of inhalation, neurological, metal, and occupational toxicology will highlight neurological findings of animal and human studies after occupational and environmental lung exposures. All aspects of the topic, such as metal chemistry, inhalation exposure of metal particles, metal translocation from the respiratory system to the central nervous system, and neurological responses, will be examined. An increase in the understanding of metal particle inhalation and neurotoxicity may allow for the development of prevention strategies to better protect susceptible populations in the workplace and environment.

#19 9:15 NEUROLOGICAL RESPONSES AFTER EXPOSURE TO INHALED METAL PARTICLES. *J. M. Antonini*[1] and *L. Chen*[2]. [1]NIOSH, Morgantown, WV and [2]New York University, Tuxedo Park, NY.

#20 9:20 OLFACTORY TRANSPORT OF INHALED PARTICLES AND METALS. *D. C. Dorman.* College of Veterinary Medicine, North Carolina State University, Raleigh, NC.

#21 9:52 DOPAMINERGIC NEUROTOXICITY FOLLOWING EXPOSURE TO MANGANESE-CONTAINING WELDING FUMES. *K. Sriram.* CDC-NIOSH, Morgantown, WV.

#22 10:24 CENTRAL NERVOUS SYSTEM EFFECTS AFTER EXPOSURES TO NANO-SIZED PARTICLES. *P. Gillespie, G. Kang* and *L. Chen.* New York University School of Medicine, Tuxedo, NY.

PROGRAM DESCRIPTION (CONTINUED)

Abstract #

#23 **10:56** **NEUROBEHAVIORAL EFFECTS IN ADOLESCENTS EXPOSED TO METALS.** *R. Lucchini*[1], N. J. Zimmerman[3], E. Albini[1], S. Micheletti[1], S. Zoni[1], F. Tagliani[1], C. Nardoni[1], G. Parrinello[4], F. Donna[1], R. Ferri[1], Z. Annalisa[2], B. Laura[2] and E. Bontempi[2]. [1]Occupational Health, University of Brescia, Italy, Brescia, Italy, [2]Chemistry Laboratory for Technologies, University of Brescia, Brescia, Italy, [3]School of Health Sciences, Purdue University, West Lafayette, IN and [4]Statistics and Biometry, University of Brescia, Brescia, Italy.

#24 **11:28** **NEUROINFLAMMATION, SEVERE AIR POLLUTION AND CHILDREN.** L. Calderon-Garciduenas[1,3], L. Gonzalez-Gonzalez[3], A. D'Angiulli[2] and H. Medina-Cortina[3]. [1]The University of Montana, Missoula, MT, [2]Psychology Carleton University, Ottawa, ON, Canada and [3]Instituto Nacional de Pediatria, Mexico City, Mexico. Sponsor: *J. Antonini.*

Monday Morning, March 8
9:15 AM to 12:00 NOON
Ballroom B

S

Symposium Session: Ovarian Toxicity: Current Concepts in Toxicology, Pathology, and Mechanisms

Chairperson(s): *William J. Brock, Brock Scientific Consulting, LLC, Montgomery Village, MD, and Ali Faqi, MPI Research, Mattawan, MI.*

Sponsor:
Reproductive and Developmental Toxicology Specialty Section

Endorsed by:
Regulatory and Safety Evaluation Specialty Section
Reproductive and Developmental Toxicology Specialty Section
Women in Toxicology Special Interest Group

The ovary is responsible for the differentiation and release of a mature oocyte for fertilization and for synthesizing and secreting hormones that are essential for follicle development, estrous cyclicity, and maintenance of the reproductive tract and its function. Reproductive toxicity studies are important components of the regulatory approval of drugs and chemicals. The identification of ovarian toxicity and determination of its cause requires familiarity with ovarian anatomy, physiology, relationships with other components of the female reproductive tract, and the neuroendocrine regulation of the estrous cycle. A mechanistic approach at the morphologic, biochemical, and molecular level demonstrate that various factors are involved in ovarian toxicity. Therefore, our focus will be on the basic concepts of ovarian anatomy, histopathology, and potential mechanisms of toxicity. We will begin by discussing the importance of assessing fertility that utilizes a combination of methods including evaluation of estrous cycle length, fertility endpoints, and ovarian weights. Recent collaborative work suggests a 2-week rodent study may be sufficient to elucidate the effect of pharmaceuticals on ovarian function and its impact on the revised ICH M3 will be presented. Better interpretation of drug induced ovarian toxicity will be highlighted as fertility effects in rodents, especially when both sexes are treated do not often distinguish between male or female mediated effects. A mechanistic model of ovarian toxicity of 4-vinylcyclohexene diepoxide provides an understanding of the potential risk of human exposure to environmental ovarian toxicants and greater insight of toxicants on reproductive health in women will also be discussed.

#25 **9:15** **OVARIAN TOXICITY: CURRENT CONCEPTS IN TOXICOLOGY, PATHOLOGY, AND MECHANISMS.** *W. J. Brock*[1], *A. Faqi*[2], M. Mirsky[3], *P. Hoyer*[4] and A. Sanbuissho[5]. [1]Brock Scientific Consulting, Montgomery Village, MD, [2]MPI Research, Mattawan, MI, [3]Pfizer, Groton, CT, [4]University of Arizona, Tucson, AZ and [5]Daiichi-Sankyo, Fukuroi Shizuoka, Japan.

Abstract #

#26 **9:20** **OVARIAN TOXICITY—ANATOMY, PATHOPHYSIOLOGY, AND THE ILLUSION OF SIMPLICITY.** *M. Mirsky.* Pfizer, Groton, CT.

#27 **10:00** **OVARIAN TOXICITY INDUCED BY PHARMACEUTICALS AND CHEMICALS.** *A. S. Faqi.* Toxicology, MPI Research, Mattawan, MI.

#28 **10:40** **OVOTOXICITY CAUSED BY 4-VINYLCYCLOHEXENE DIEPOXIDE: MECHANISTIC INSIGHTS.** *P. Hoyer.* University of Arizona, Tucson, AZ.

#29 **11:20** **COLLABORATIVE WORK ON EVALUATION OF OVARIAN TOXICITY BY REPEATED-DOSE AND FERTILITY STUDIES IN FEMALE RATS.** A. Sambuissho. DAIICHI SANKYO CO., LTD., Fukuroi, Shizuoka, Japan. Sponsor: *W. Brock.*

Monday Morning, March 8
9:15 AM to 12:00 NOON
Ballroom G

S

Symposium Session: Silica and Asbestos Immunotoxicity: Mechanisms to Fibrosis, Autoimmunity, and Modified Tumor Resistance

Chairperson(s): *Andrij Holian, University of Montana, Missoula, MT, and Takemi Otsuki, Kawasaki Medical School, Kurashiki, Japan.*

Sponsor:
Immunotoxicology Specialty Section

Endorsed by:
Inhalation and Respiratory Specialty Section
Mechanisms Specialty Section
Occupational and Public Health Specialty Section

Effects of silica/asbestos on local and systemic immune system components are very important in the cascade of events in a host that evolve over the course of time from the point of initial exposure to the ultimate onset of lung fibrosis (i.e., silicosis, asbestosis), malignant tumors (i.e., lung cancer, mesothelioma), or autoimmune disorders (e.g., systemic sclerosis, rheumatoid arthritis—Caplan syndrome). In particular, mechanisms used by immune competent cells to process the entrained silica or asbestos may affect induction of these pathologies. With regard to asbestos specifically, there may also be a reduction in local/general anti-tumor immune responses that serves to amplify its own carcinogenic potential *in situ*. We will begin with an up-to-date overview of emerging topics in the field of silica/asbestos toxicology that can, in turn, serve as a basis to understand mechanistic interpretations that link development of pneumoconioses to fibrotic diseases, autoimmunity, and cancer. To better understand these issues the latest findings on the roles that particle recognition, inflammasome formation, cytokine-driven inflammation, or immune dysfunction have in eventual induction of fibrosis, altered autoimmunity, and/or modified tumor resistance *in silica*/asbestos-exposed hosts. It is anticipated that with an enhanced understanding of the molecular pathological mechanisms underlying the immunotoxicologic effects of silica/asbestos, researchers in many fields (including immunology, immunotoxicology, pulmonary biology and medicine, occupational medicine) will be better able to develop therapeutic tools for the prevention, mitigation, or treatment of debilitating diseases induced by these agents.

#30 **9:15** **SILICA AND ASBESTOS IMMUNOTOXICITY: MECHANISMS TO FIBROSIS, AUTOIMMUNITY, AND MODIFIED TUMOR RESISTANCE.** *A. Holian.* University of Montana, Missoula, MT.

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Submitted

on August 05, 10:42 PM

for sot2010

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CONTACT (NAME ONLY): Roberto Lucchini

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KEYWORDS: children, neurobehavioral chenges, manganese and lead.

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DATE/TIME SUBMITTED: August 5, 2009, 10:42 PM

Abstract

TITLE: NEUROBEHAVIORAL EFFECTS IN ADOLESCENTS EXPOSED TO METALS

AUTHORS (LAST NAME, FIRST NAME): Lucchini, Roberto[1]; Zimmerman, Neil J.[3]; Albini, Elisa [1]; Micheletti, Serena[1]; Zoni, Silvia[1]; Tagliani, Fiorella[1]; Nardoni, Chiara[1]; Parrinello, Giovanni[4]; Donna, Filippo[1]; Ferri, Roberta[1]; Annalisa, Zacco[2]; Laura, Borgese[2]; Bontempi, Elza[2]

SPONSOR NAME: James Antonini

INSTITUTIONS (ALL): 1. Occupational Health, University of Brescia, Italy, Brescia, Italy.
2. Chemistry Laboratory for Technologies, University of Brescia, Brescia, Italy.
3. School of Health Sciences, Purdue University, West Lafayette, IN, USA.
4. Statistics and Biometry, University of Brescia, Brescia, Italy.

ABSTRACT BODY: Background: Increased parkinsonism was observed in Valcamonica, a valley in the Italian Alps. Prevalence was higher in the vicinities of ferroalloy plants and associated to the manganese level in deposited dust. The aim of this study was to assess motor and cognitive functions in adolescents in the exposed area.
Methods: Metals were measured in PM10 airborne particles collected with 24-hours personal samplers. Samples were analyzed with Total Reflection X-Ray Fluorescence. Soil was analyzed at surface and 10cm depth. Adolescents of 11-13 years old were recruited through the local school system for neurobehavioral examination. Various biomarkers were collected for metal analysis.
Results: A total of 303 children residing in the exposed area and a reference area participated in the study. Average airborne manganese was 57.79 ng/m3 (n.86, range 1.24-516.70) in Valcamonica and 22.45 ng/m3 (n.11, range 5.30-36.59) 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. 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, but only in the metal exposed area of Valcamonica.
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.