models. Experimental approaches and animal models used to verify that direct olfactory transport occurred have varied. Most studies examining direct "nose-to-brain" transport of a variety of materials have relied on intranasal instillation of the material with subsequent verification of the presence of the particle of interest in the olfactory bulb of animals. Other investigators have relied on the mechanical occlusion of one nostril prior to inhalation exposure. This procedure restricts olfactory transport to the side of the brain ipsilateral to the patent nostril. Other approaches have included direct visualization of translocated particles using analytical chemical or imaging modalities and surgical transection of olfactory nerve fibers prior to particle administration. Certain metals (e.g., cadmium, manganese, iron, and thallium), drugs, and some solvents have been shown by these methods to undergo olfactory transport to the brain, where they may achieve tissue concentrations sufficient to initiate their toxic or pharmacologic effects. There is growing evidence that ultrafine particles can be taken up by the nerve endings and subsequently delivered to the brain via these retrograde transport processes. A pharmacokinetic model describing the olfactory transport of manganese following acute inhalation exposures has been developed for the rat. The parameterized model was used to estimate the relative contribution of blood delivery versus olfactory transport in the rat. Several studies have also begun to explore the pharmacokinetic mechanisms involved in olfactory transport. For example, the organic anion transporters and divalent metal transporters likely play a role in the olfactory transport of manganese.

20036571

S 21 DOPAMINERGIC NEUROTOXICITY FOLLOWING EXPOSURE TO MANGANESE-CONTAINING WELDING FUMES.

K. Sriram. *CDC-NIOSH, Morgantown, WV.*

The potential for development of Parkinson's disease (PD)-like neurological dysfunction following occupational exposure to welding fumes (WF) is an area of emerging concern. Welding generates a complex aerosol of fine and ultrafine metal particles that can potentially translocate from olfactory or pulmonary targets and accumulate in the brain. Manganese (Mn) in welding consumables is thought to be the causative factor for development of neurological deficits seen in welders. However, lack of definitive epidemiological evidence for such a causal association warrants further experimental investigation. To address this, Sprague-Dawley rats were exposed by whole-body inhalation or intra-tracheal instillation to a variety of WFs that differ in elemental composition and solubility. Short-term inhalation exposure (40mg/m^3; 3h/d x 10d) to gas metal arc-mild steel (GMA-MS; low Mn, less soluble) resulted in deposition of Mn in the olfactory bulb and striatum, altered the expression of divalent metal transporter 1 (Dmt1), dopamine D1 (Drd1) and D2 (Drd2) receptors, and induced a subtle neuroinflammatory response in the striatum and midbrain. On the other hand, a similar exposure to gas metal arc-stainless steel (GMA-SS; high chromium, less soluble) did not affect any of the indices described above. Repeated intratracheal instillations (0.5mg/rat, 1/week x 7 weeks) of GMA-MS or manual metal arc-hard surfacing (MMA-HS; high Mn, more soluble) also led to deposition of Mn in the brain. By 1d post-exposure, both fumes caused loss of tyrosine hydroxylase (TH) protein and altered the expression of various synaptic proteins in the striatum and midbrain. While loss of TH following GMA-MS was transient, a sustained loss was observed in the midbrain even after cessation of MMA-HS exposure. In addition, both fumes down-regulated Drd1, Drd2 and Vmat2 mRNAs in the midbrain. Whether such effects will persist and cause neurodegeneration remains to be elucidated. Current research aims at addressing these concerns, which may help support or refute findings that suggest an association between WF exposure and PD-like neurological disorder.

S 22 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.*

The respiratory tract is the primary target for inhaled nano-sized particles (NSP), but there is evidence of adverse effects in secondary organs like the brain. In general, the toxic potential of NSP has been attributed to two major characteristics: chemical composition and particle morphology with little attention given to the former. The aim of this study was to demonstrate the role of chemical composition in inducing neurotoxic responses. We exposed, by inhalation, C57BL/6J mice to either ~550 μg/m3 of laboratory generated metals (Ni, Mn, and Cu) or non-metal (C, graphite) NSP of similar shape and sizes; or filtered air for 4 h. Three brain regions (olfactory bulb, midbrain, and cerebellum) were harvested and used for dosimetry and biological assays (oxidative stress (OS) and inflammation) 24 h post exposure. Of these three brain regions, a significant difference was only detected in the olfactory bulb (n=8/group, $P<0.05$) followed by detectable amounts in the midbrain and, to a lesser extent, the cerebellum. Brain region-specific toxicological profiles were noted for each tested material but with nickel inducing the most significant response. These distinct profiles demonstrate chemical specific neurotoxic effects with Ni NSP appearing to be the most toxic. Long term studies were also conducted with Ni NSP in which C57BL/6 mice inhaled 100 μg/m3 for 5h/d, 5d/w, for up to 5m. The three brain regions were collected 1w, 3m, and 5m, 24 h after the last day of exposure for gene expression analyses (n=4/group). PCR profiling systems for OS and inflammatory pathways were used to evaluate change in expressions of 168 genes (confirmed by individual RT-PCR for genes with 2x or high change). Collectively the following rank for altered gene expression was observed: olfactory bulb > midbrain>> cerebellum. In summary, acute and chronic studies suggest that all three regions are affected by exposures of inhaled Ni NPs via oxidative stress- inflammatory mediated pathways; but, the olfactory bulb may be a more sensitive target to adverse effects.

S 23 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.*

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.

S 24 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.

Exposure to air pollution is associated with systemic inflammation in healthy children in Mexico City (MC). Children are at risk since childhood and adolescence are crucial periods of brain development associated with dynamic behavioral, cognitive and emotional changes. Children living in MC exhibit evidence of chronic inflammation of the upper and lower respiratory tracts, alterations in circulating inflammatory mediators, breakdown of the nasal respiratory epithelial barrier and the blood-brain-barrier (BBB), ultrafine particulate matter (UFPM) in frontal endothelial cells, and elevated levels of plasma endothelin-1. Fifty-six % of Mexico City children show prefrontal white matter hyperintense lesions by MRI compared to controls in low pollution areas.

Autopsy studies measuring mRNA COX2, IL-1β, and CD14 in target brain regions from low or highly exposed residents 25.1 ± 1.5y, have shown upregulation of COX2, IL-1β, and CD14 in olfactory bulb, frontal cortex, substantia nigrae and vagus nerves, disruption of the BBB, endothelial activation, oxidative stress, and inflammatory cell trafficking in highly exposed subjects. Amyloid beta 42 immunoreactivity was observed in 58.8% of APOE 3/3 <25y, and 100% of the APOE 4 subjects. Brainstem accumulation of amyloid beta 42 and alpha synuclein and microglia activation are present in exposed children in keeping with the infra-tentorial inflammation. Alterations in measures of fluid intelligence and cognitive control along with alterations in auditory brainstem pathways predict school performance, complex learning, reasoning and the ability to block impulsive anti-social