lower respiratory tract (LRT) viral infection. Respiratory syncytial virus (RSV) is a major etiological agent for LRT infections in infants, the elderly, and the immunocompromised, and may lead to chronic wheezing and the development of asthma in children. In this study we examined the effects of ultrafine particle exposure on RSV-induced pulmonary inflammation, chemokine and cytokine expression, and airway hyperresponsiveness in a mouse model of RSV. Female BALB/c mice were instilled *via* the trachea (i.t.) with 1x106 pfu RSV or with uninfected culture media. On day 3 of infection, mice were i.t. instilled with either 40 μg ultrafine carbon black (CB) particles or with saline vehicle. Endpoints were examined on days 4, 5, 7, and 14 of RSV infection. Viral titer and clearance in the lung were unaffected by CB exposure. Neutrophil numbers were elevated on days 4 and 7, and lymphocyte numbers were higher on days 4 and 14 of infection in CB-exposed, RSV-infected mice. CB exposure also enhanced RSV-induced airway hyperresponsiveness to methacholine, BAL total protein, and virus-associated chemokines MCP-1, MIP-1α, and RANTES. Immunohistochemistry and laser capture microdissection revealed that MIP-1α expression was localized to the alveolar epithelium, where ultrafine particles deposit in the lung. These data demonstrate a synergistic effect of particles on RSV infection, and suggest a mechanism for increased pneumonia in human populations after PM exposure.

1824 VARIED EXPOSURE REGIMES TO METHYL MERCURY (MEHG) DURING POSTNATAL DEVELOPMENT LEADS TO DIFFERENT IMMUNE RESPONSES.

M. M. Peden-Adams[1], C. Adams[1], K. Meyers[1], A. EuDaly[1], J. Smythe[1], J. EuDaly[1] and D. E. Keil[2,1]. [1]*Department of Health Professions, Medical University of South Carolina, Charleston, SC and* [2]*NIOSH, Morgantown, WV.*

Infantile autism (IA) is a neurodevelopmental syndrome with 1-5 cases found in every 10, 000 children. The spectrum of autism disorders includes a range of impaired communication and language development. Also reported are diverse immunological effects including decreased T-cell proliferative function and activation, increased serum IL-2 levels, decreased CD8+ cells, decreased NK cell function, and development of anti-neural autoantibodies. Several studies indicate that the etiology of IA is multi-factorial and includes exposure to environmental chemicals. In particular, Thimerosal, an adjuvant in vaccines that contains ethyl mercury, has been implicated in IA. This association has been criticized due to a lack of supportive experimental dose-response data. Consequently, this project was designed to compare dose-responsive immunological effects between Thimerosal and methyl mercury, a known immunotoxicant. In this phase of the study, B6C3F1 pups were exposed to MeHg (10 or 50 ug/kg) and two different exposure regimes were examined during postnatal development. Pups were exposed either on postnatal days (PND) 7, 10, and 12 or weekly on PND 7, 14, and 21. On PND 22, T-cell proliferation and the IgM plaque forming cell response were enhanced after exposure on PND 7, 14, and 21, but not affected after exposure on PND 7, 10, and 12. Weekly exposure to 50 ug MeHg/kg prior to weaning resulted in selective increases in CD8+ thymic T cells, whereas 10 ug MeHg/kg exposure on PND 7, 10, and 12 increased splenic CD4+ T-cell subpopulations. The exposure regime utilized during developmental periods must be considered when assessing mercury exposure, as this affects responses in immune parameters. This understanding may be useful when evaluating vulnerable periods of mercury exposure in children. Future studies will compare effects of Thimerosal with MeHg, and include assessment of cytokine levels, autoantibody production, serotonin levels and cognitive function.

1825 MERCURY (Hg) ACCELERATES AUTOIMMUNE DISEASE IN MICE.

E. K. Silbergeld[1], I. Silva[1], C. S. Via[3], M. Afanasyeva[2], J. Nyland[2], P. Nguyen[3] and N. R. Rose[2]. [1]*Environmental Health Sciences, Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD,* [2]*Johns Hopkins School of Medicine, Baltimore, MD and* [3]*Medicine, University of Maryland School of Medicine, Baltimore, MD.*

Inorganic mercury (iHg) has a range of immunotoxic effects, including induction of autoimmunity in certain inbred strains of rats and mice. However, no associations between Hg and autoimmune disease have been shown in humans. We hypothesize that expression of frank disease may require interactions between Hg and other susceptibility factors, genetic or acquired. To test this hypothesis, we examined the effects of iHg pretreatment on the pathophysiology of experimental autoimmune disease in two well characterized models, the graft versus host disease (GVHD) model of chronic systemic lupus erythmatosis (SLE) and the cardiac myosin peptide (CMP) model of autoimmune myocarditis (AIM). We induced SLE by transfer of maternal splenocytes into C57Bl/6xDBA/2-F_1 hybrid offspring; and we induced AIM by immunization of A/J mice with purified murine CMP. In GVHD, both donors (female DBA/2) and hosts (female B6D2-F_1) were exposed to 20 or 200 mcg/kg $HgCl_2$ by s.c. injection every other day for 15 days; on day 20, GVHD was initiated by splenocyte transfer and disease was evaluated over 4 months. In the AIM model, male A/J mice were pretreated similarly with $HgCl_2$ at 10 or 100 mcg/kg; on day 20, mice were administered 100 nmol CMP s.c. and pertussis toxin i.p. Disease was monitored by observation, interim analyses of serum autoantibodies, and histopathological evaluation of the heart at sacrifice. The results are consistent with the hypothesis that Hg can interact with other risk factors to induce frank autoimmune disease, at low doses of Hg and in strains of mice (DBA/2, C57Bl/6) that are not susceptible to Hg immunotoxicity. *Research supported by the Arthritis Foundation and NIH (NIEHS, NHLBI).*

1826 EFFECT OF INORGANIC MERCURY ON PRIMARY MOUSE AND HUMAN MONOCYTE FUNCTION.

J. Koropatnick[1], W. Kennette[1] and R. K. Zalups[2]. [1]*Oncology, University of Western Ontario, London, Ontario, ON, Canada and* [2]*Division of Basic Medical Sciences, Mercer University School of Medicine, Macon, GA.*

Transition metal ions are toxic to human tissues and organs. Although they can be toxic to immune cells, they can also induce gene expression (including metallothioneins [MTs]) in the absence of toxic events. The consequences of non-toxic metal exposure on immune function are largely unexplored. Innate immune activation involves the acute phase response and respiratory burst of mononuclear cells (including monocytes) in response to extracellular signals. We have reported that *in vitro* treatment of immortalized human monocytes with zinc, cadmium, or mercury, at levels at least tenfold lower than that required to exert detectable cellular injury, significantly inhibits monocyte activation potential. We now report that that *in vitro* pre-treatment of primary human and mouse monocytes, isolated from peripheral blood, with low, non-cytotoxic levels of zinc (40 μM) or mercury (2 μM) have significantly decreased activation potential (assessed by reactive oxygen production and interleukin-1β [IL-1β] mRNA expression in response to phorbol myristate acetate [PMA]). In addition, pre-treatment of mice with low, non-toxic levels of inorganic mercury (0.2 - 1 μmole Hg/kg body weight, i.p.) had no effect on monocyte viability, but significantly inhibited the ability of primary peripheral blood monocytes to undergo LPS- or PMA-induced respiratory burst and differentiation into adherent macrophages. These data indicate that low level exposure to inorganic zinc or mercury inhibits primary monocyte activation potential (and, therefore, innate immune function) in the absence of cytotoxicity. The connection between low, non-toxic metal ion exposure and innate immune function, combined with the critical role of innate immunity in resistance to infection and tumour formation, highlight the potential importance of environmental metals in these pathological events.*Supported by grants from the NIEHS (ES11288) and CIHR*

1827 *IN VITRO* EXPOSURE TO SODIUM ARSENITE INCREASED INTRACELLULAR CA^{2+} LEVELS IN PHYTOHAEMAGGLUTININE STIMULATED HUMAN T LYMPHOCYTES.

R. C. Goytia-Acevedo[2,1], L. C. Acosta-Saavedra[1], M. E. Cebrián[1] and E. S. Calderón-Aranda[1]. [1]*Sección de Toxicología, CINVESTAV, México, D F, Mexico and* [2]*Facultad de Medicina, UJED, Gómez Palacio, Dgo, Mexico.*

Arsenic exposure inhibits murine and human T lymphocyte proliferation. Free intracellular ($[Ca^{2+}]i$) levels have been implicated as a regulatory signal for proliferation and death cell processes. This prompted us to investigate whether sodium arsenite ($NaAsO_2$)induced changes in $[Ca^{2+}]i$ of human stimulated human T lymphocytes and if this alteration was associated with the inhibitory effects of arsenic on T cell proliferation. We used mononuclear cells from healthy human subjects to measure free $[Ca^{2+}]i$ levels by spectrophotofluorometry using Fluo-3AM label. Proliferation was determined by [methyl-^{3}H]-thymidine incorporation. *In vitro* exposure to $NaAsO_2$ (1.0 to 7.5 μM) dose-dependently increased free $[Ca^{2+}]i$ in both PHA-stimulated lymphocytes and non-stimulated cells. However the effect was more pronounced in mitogen-activated cells simultaneously treated with $NaAsO_2$ at concentrations producing inhibition of T cell proliferation. In cells pretreated with a calcium ionophore (A23187) at concentrations able to increase $[Ca^{2+}]i$ to levels comparable to those induced by $NaAsO_2$, PHA-induced proliferation was similarly inhibited. These results suggest that increased free $[Ca^{2+}]i$ levels play an important role in the inhibitory effect of arsenic on human T cell proliferative response. Partially supported by CONACYT 34508-M to ESCA.

1828 ARSENIC-INDUCED ALTERATIONS IN CONTACT HYPERSENSITIVITY.

R. M. Patterson[1], L. Vega-Lloyo[2], K. J. Trouba[1], J. A. Teague[1] and D. R. Germolec[1]. [1]*LMT, NIEHS, Research Triangle Park, NC and* [2]*Cinvestav, National Polytechnical Institute, Mexico City, Mexico.*

Chronic exposure to arsenic contaminated drinking water has been associated with neoplasias in multiple organ systems, including the skin, liver, bladder and lung. Previous studies in our laboratory indicate that arsenic alters the levels of growth