

**1481** *IN VIVO* AND *IN VITRO* CORRELATION OF PULMONARY MAP KINASE ACTIVATION FOLLOWING METALLIC EXPOSURE.

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Residual oil fly ash (ROFA) is a particulate pollutant produced in the combustion of fuel oil. Exposure to ROFA is associated with adverse respiratory effects in humans, induces lung inflammation in animals, and induces inflammatory mediator expression in cultured human airway epithelial cells (HAEC). ROFA has a high content of transition metals, including vanadium, a potent tyrosine phosphatase inhibitor which we have previously shown to dysregulate phosphotyrosine metabolism and activate mitogen-activated protein kinase (MAPK) signaling cascades in HAEC. In order to study MAPK activation in response to *in vivo* metal exposure, we used immunohistochemical methods to detect levels of phosphorylated protein tyrosines (P-Tyr) and the MAPKs ERK 1/2, JNK, and P38, in lung sections from rats intratracheally exposed to ROFA. After a 1 h exposure to 500µg ROFA, rat lungs showed no histological changes and no significant increases in immunostaining for either P-Tyr or phospho (P)-MAPKs compared to saline-instilled controls. At 4 hs of exposure, there was mild and variable inflammation in the lung which was accompanied by an increase in specific immunostaining for P-Tyr and P-MAPKs in airway and alveolar epithelial cells and resident macrophages. By 24 hs of exposure, there was a pronounced inflammatory response to ROFA instillation and a marked increase in levels of P-Tyr and P-MAPKs present within the alveolar epithelium and in the inflammatory cells, while the airway epithelium showed a continued increase in the expression of P-ERK 1/2. By comparison, HAEC cultures exposed to 100µg/ml ROFA for 20 min resulted in marked increases in P-Tyr and P-MAPKs, which persisted after 24 hs of exposure. P-Tyr levels continued to accumulate for up to 24 h in HAEC exposed to ROFA. These results demonstrate *in vivo* activation in cell signaling pathways in response to pulmonary exposure to particulate matter, and support the relevance of *in vitro* studies in the identification of mechanisms of lung injury induced by pollutant inhalation. This abstract of a proposed presentation does not necessarily reflect EPA policy.

**1482** RESIDUAL OIL FLY ASH SLOWS THE CLEARANCE OF *LISTERIA MONOCYTOGENES* FROM RAT LUNGS.

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Inhalation of residual oil fly ash (ROFA) has been shown to increase pulmonary morbidity and impair lung defense mechanisms. The objective of this study was to evaluate the effect of ROFA exposure on the clearance of a bacterial pathogen from the lungs. Elemental analysis revealed the ROFA particles to be comprised of Al, Si, S, Ca, V, Fe, and Ni. Young adult male Sprague-Dawley rats were dosed intratracheally with saline (control) or ROFA at a dose of 1 mg/100 g b wt. Three days later, ~500,000 *Listeria monocytogenes* were intratracheally instilled into the ROFA-treated and saline control rats. Bronchoalveolar lavage was performed on the right lungs at 3, 5, and 7 days after exposure to *L. monocytogenes*. The cells recovered were differentiated, and chemiluminescence, an index of macrophage activation, was measured. At the same time points, the left lung and spleen were removed, homogenized, and cultured on brain heart infusion agar at 37°C. Colony forming units were counted after an overnight incubation. Pre-exposure to ROFA significantly ( $p < 0.05$ ) delayed the pulmonary clearance of *L. monocytogenes* as compared to the saline control rats. ROFA had no effect on the influx of neutrophils into the lungs but caused a significant ( $p < 0.05$ ) decrease in macrophage chemiluminescence as compared to saline control rats. We have demonstrated that acute exposure to ROFA slowed the pulmonary clearance of *L. monocytogenes*. This is most likely due to a ROFA-induced suppression of macrophage activation, perhaps related to the elemental composition of the particles. Therefore, in an occupational setting, inhalation of ROFA may lead to increased susceptibility to pulmonary infection.

**1483** METAL-CONTAINING PARTICULATE MATTER-INDUCED AUTOXIDATION OF SYNTHETIC LUNG EPITHELIAL LINING FLUID.

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Oxidative stress has been implicated in the toxicity of metal-rich particulate matter (PM). Lung epithelial lining fluid (ELF) contains several antioxidants and serves as the first line of defense against inhaled toxins and infective agents. We used synthetic ELF (sELF) as a model system to study the role of residual oil fly ash (ROFA, an ambient PM containing soluble transition metals) in autoxidation of ELF constituents and the effects of antioxidants on this process. sELF was formulated based on literature data and our own measured values of human bronchoalveolar lavage. Oxygen-18 labeling was used to trace the extent of oxidation by measuring <sup>18</sup>O incorporated into sELF components after exposure of sELF (200 µL, pH 7.4) containing ROFA (0-200 µg/mL) to 20% <sup>18</sup>O<sub>2</sub> (24°C, 4 h). Ascorbate, urate, total glutathione, and non-protein sulfhydryls were also measured. ROFA induced autoxidation of sELF significantly in the presence of ascorbate and this effect was slightly enhanced by glutathione. Ascorbate became inhibitory at high concentrations. Catalase, superoxide dismutase, and glutathione peroxidase had no significant effect on the autoxidation at normal and 2X reported physiological concentrations. The consumption of ascorbate was ROFA-dose-dependent, while urate, total glutathione, and non-protein sulfhydryls were not depleted under any condition studied. Compared with maximum possible binding of ROFA metals to sELF components, oxygen incorporation was 2-9X higher (on a nmol/mL basis). These results suggest that ROFA-induced oxidative stress might be a significant contributor to toxicity and that ascorbate and glutathione act as pro-oxidants in this process. (Supported by EPA/UNC CT #902908. This abstract does not represent EPA policy.)

**1484** SURFACE CHARGE AND SIZE AS CONTRIBUTING FACTORS TO PARTICULATE MATTER (PM) TOXICITY.

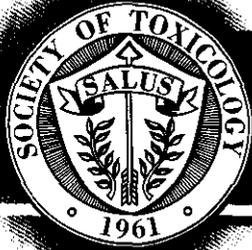
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The heterogeneous composition of PMs has complicated identifying which physicochemical component(s) contribute to their inflammatory effects. In vitro exposure of airway cell targets to various urban and industrial PM pollutants results in differential inflammatory changes (e.g., cytokine release, oxidative burst). In this study, nine PMs from various urban, natural and industrial sources (e.g., urban air particles, diesel, woodstove, oil fly ash) were described in terms of their surface charge (i.e., zeta potential) and particle size. The different PMs were examined in field suspension (fine and coarse particles) and after 0.22 µm filtration (ultrafine particles). The zeta potentials of suspended field PMs (1-30 µm in diameter) did not differ significantly across sources, but were dependent on the vehicle milieu. For example, zeta potential values of PM suspended in 1 mM KCl (pH 7.4) ranged from averaged values of -27 to -42 mV, whereas, when suspended in serum-supplemented culture media, their zeta potentials ranged from -6 to -12 mV. In contrast, the zeta potentials of the ultrafine particles (i.e., after 0.22 µm filtration) were highly variable, ranging from averaged values of +13 mV to -109 mV in 1 mM KCl (pH 7.4). Exposure of mouse sensory neurons and human bronchial epithelial cells (i.e., BEAS-2B) to the individual suspended field PM or to their filtrates produced a differential release of the proinflammatory cytokine IL-6. Collectively, these data suggest that both surface charge and particle size are contributing factors to the inflammatory effects of PMs seen in cultured airway target cells. Although charge appears not to be the discriminative factor for the differential inflammatory effects of PM >1 µm, it may be relevant for the ultrafine PM fraction. (This abstract has been reviewed by NHEERL and does not necessarily reflect EPA policy).

**1485** CHANGES IN HEART RATE VARIABILITY IN YOUNG AND ELDERLY HUMANS EXPOSED TO CONCENTRATED AMBIENT AIR PARTICLES.

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Epidemiology studies have shown an association between ambient air particles (PM) and mortality in the elderly related to cardiovascular causes. In addition, a recent study has shown an association between PM and decreased heart rate variability in elderly residents of a retirement village. The purpose



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# Preface

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**An alphabetical Author Index, cross referencing the corresponding abstract number (2), begins on page 423.**

**The issue also contains a Keyword Index (by subject or chemical) of all the presentations, beginning on page 448.**

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