metal involvement in PM associated increases in morbidity and mortality. [This is an abstract of a proposed presentation and does not necessarily reflect official EPA policy. Supported by NIEHS T32-ES07126.]

916 ULTRAFINE IRON OXIDE AND SOOT PARTICLES INDUCE OXIDATIVE STRESS IN THE LUNGS OF HEALTHY ADULT RATS.

Y. M. Zhou, C. Y. Zhong, I. M. Kennedy and K. E. Pinkerton. *UC Davis, ITEH, Davis, CA.*

To better understand the adverse health effects of ambient particulate matter (PM), the physicochemical characteristics of PM need to be assessed for their potential role to induce biological response. As critical constituents of PM, transition metals may be responsible for the health effects associated with PM exposure. Iron-mediated oxidative stress has been hypothesized to be involved in many pathological and physiological processes. The purpose of our study was to examine the effects of ultrafine iron oxide particles in combination with soot, and soot alone in the respiratory system of adult rats. Sprague-Dawley rats were exposed by inhalation to a combination of iron and soot particles (50 mg /M3 iron, 200 mg /M3 soot), soot (250 mg /M3) or filtered air (FA) 6 hr /day for 3 days. The mass median aerodynamic diameter (MMAD) of particles was 70 - 80 nm. Following exposure, bronchoalveolar lavage fluid (BALF) was collected to examine cell viability, cell differentiation, protein concentration and LDH activity. NO, MDA, GST, GSH, GSSG, glutathione redox ratio (GRR) and total antioxidant power (FRAP assay) were also measured in BALF and lung tissue. No changes in protein concentration, LDH, cell viability and cell differentiation in BALF were observed following exposure to the combination of iron and soot particles as well as exposure to soot alone. However, exposure to the combination of iron and soot particles resulted in significant increases in GST activity (in BALF), GSSG (in BALF), GRR (in BALF and lung) and a significant decrease in total antioxidant power (in BALF and lung) compared with FA controls. In contrast, no significant changes were found with exposure to soot alone compared with FA controls. We conclude that exposure to iron in the presence of soot particles significantly induced oxidative stress in the lungs of adult rats. These data support the hypothesis that particles containing transition metals play an important role in PM air pollution health effects.

917 IDENTIFICATION, BY CDNA MICROARRAY, OF A-RAF AND PROLIFERATING CELL NUCLEAR ANTIGEN AS GENES INDUCED IN RAT LUNG BY EXPOSURE TO DIESEL EXHAUST.

H. Sato[1,2], K. T. Suzuki[2], M. Sagai[3], T. Imanari[2] and Y. Aoki[1]. *[1]National Institute for Environmental Studies, Environmental Health Sciences Division, Tsukuba, Japan, [2]Chiba University, Faculty of Pharmaceutical Sciences, Chiba, Japan and [3]Aomori University of Health and Welfare, Faculty of Health Sciences, Aomori, Japan.*

Diesel exhaust particles (DEP) contain various carcinogens and mutagens, and chronic exposure to diesel exhaust (DE) induces pulmonary cancer in experimental animals. We reported that mutation frequency was significantly increased in Big Blue(R)transgenic rat lung caused by exposure to DE at the concentration of 6 mg/m^3 as suspended particulate matter (SPM) for 4 weeks (SOT 39th Annual Meeting). Although, the genotoxicity of DEP and DE has been investigated intensively, it is not clear which oncogenes are involved in pulmonary cancer caused by exposure to DE. Mutations of ras oncogenes and tumor suppresser gene p53, which are detected in lung tumor cells, were not found in adenocarcinomas, adenosquamouscarcinomas and squamous cell carcinomas induced in the lungs of rats by chronic exposure to DE. On the other hand, mutations in K-ras oncogenes were detected in adenocarcinonmas in the lungs of rats, induced by intratracheal instillation of DEP. Although mutations in oncogenes induced by DEP have been investigated, the oncogenes whose expression is elevated by exposure to DE have not been identified. In order to identify the oncogenes and related genes which are involved in carcinogenesis caused by DE, we systematically surveyed the genes whose expression are elevated in F344 rat lung by exposure to DE containing 6 mg/m^3 as SPM for 4 weeks, using cDNA microarrays (CLONTECH). The expression of each gene was confirmed by northern blot analysis. Expression of A-raf and proliferating cell nuclear antigen (PCNA) mRNAs was induced in rat lung by exposure to DE.These results suggest that A-raf and PCNA might contribute to pulmonary carcinogenesis in rats.

918 GENE EXPRESSION OF PULMONARY INFLAMMATORY CYTOKINES IN RATS DIRECTLY EXPOSED TO DIESEL EXHAUST PARTICULATE.

N. N. Sun[1], S. Wang[1], D. E. Foster[2] and M. L. Witten[1]. *[1]University of Arizona, Center for Toxicology, Tucson, AZ and [2]University of Wisconsin, Engine Research Center, Madison, WI.*

Using a on-line in vivo exposure system to freshly generated diesel exhaust particulates (DEP), we investigated the acute effects of DEP on gene expressions of inflammatory cytokine in lungs. Young female Fischer 344 rats (150g) were randomly assigned to three groups, 1) control (room air), 2) sham control, and 3) DEP (200-300 μg/m^3). Animals were nose-only exposed to DEP or room air one hour/day for 5 days. The expression of GM-CSF, TNF-α, IL-1β,IL-6, and TGF-β genes were detected by RT multiplex PCR technique and normalized against GAPDH expression. DEP had a significant activation effect on TNF-α mRNA expression to a marked degree. But, no significant induction for GM-CSF, IL-1β, IL-6, and TGF-β were observed at this time point. The result indicates that freshly generated DEPs may be important in the induction of cytokines such as TNF-α relevant lung inflammation. Previous research in our laboratory has determined a key role for TNF-α in initiating cytokine cascade and DEP exposure may also have key role for TNF-α.

919 RESPIRATORY EXPOSURE OF MICE TO DIESEL EXHAUST PARTICLES DECREASED THE SPLEEN ANTIBODY-FORMING CELL RESPONSE.

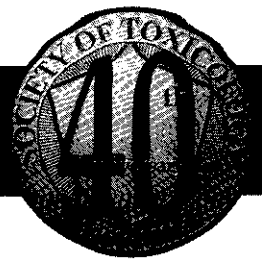
H. M. Yang, L. Butterworth, A. E. Munson and B. J. Meade. *National Institute for Occupational Safety and Health, Morgantown, WV.*

Many studies have demonstrated that exposure to excess diesel exhaust particles (DEP) may augment respiratory hypersensitivity responses. The potential immunosuppression of DEP was investigated in this study using a murine model. Female B6C3F1 mice (~8 weeks old) were intratracheally instilled with either saline vehicle, 1, 5 or 15 mg/kg of DEP 3 times every two weeks. Positive control mice received cyclophosphamide (25 mg/kg/day, i.p.) for 4 consecutive days prior to sacrifice. The mice were sacrificed 2 or 4 weeks after the first instillation of DEP. Four days prior to sacrifice, all mice were immunized with sheep red blood cells (sRBC) intravenously. End points included body, spleen, lung, thymus and liver weights; spleen antibody-forming cell (AFC) response to sRBC; and phenotypic analysis of subpopulations of splenocytes. Exposure of mice to the high dose of DEP resulted in an increase in lung weights. In mice exposed to DEP for 2 weeks, the number of anti-sRBC IgM AFC in the spleen was decreased approximately 40% at all tested concentrations. Suppression was only observed in mice exposed to the high dose of DEP following 4 weeks of exposure. An evaluation of the spleen leukocyte subpopulations revealed a decrease in the absolute numbers of total, CD4$^+$ and CD8$^+$ T cells in mice exposed to DEP. Suppression of the AFC response following DEP exposure was also observed *in vitro* using Mishell-Dutton assay. In summary, pulmonary exposure of mice to DEP resulted in the altered spleen leukocyte subpopulations and decreased systemic T cell dependent humoral immune responses. The possible underline mechanisms of DEP-induced immunomodulation are under investigation.

920 ROLE OF MATRILYSIN IN THE ACUTE LUNG INJURY INDUCED BY OIL COMBUSTION PARTICLES.

K. L. Dreher[1], W. Y. Su[2] and C. L. Wilson[3]. *[1]USEPA, Research Triangle Park, NC, [2]Duke University, Durham, NC and [3]Washington University, St. Louis, MO.*

Mechanisms by which combustion particles and ambient air particulate matter (PM) mediate their adverse health effects remains a critical uncertainty in ambient air PM health risk assessment. Matrix metalloproteinases (MMPs) normally function in wound repair but have been implicated in the pathogenesis of a variety of lung diseases such as idiopathic fibrosis, emphysema, and asthma. Residual oil fly ash (ROFA) and ambient air PM have been shown to induce pulmonary gene and protein expression of various MMPs (Am. J. Physiol. Lung Cell Mol. Physiol. 279:L152-L160, 2000; Inhal. Toxicol. 12 (Suppl. 2) 105-119, 2000). However, the roles which MMPs play in ROFA and ambient air PM-induced lung injury are unknown. This study examines the role which matrilysin (MMP-7) plays in ROFA-induced acute lung injury. MMP-7 knockout (MMP-7 -/-) and wildtype (MMP-7 +/+) mice were exposed to ROFA by intratracheal instillation (dose: 50 μg ROFA/mouse). Bronchoalveolar lavage fluid (BALF) samples were recovered from mice at 6h and 24h post-exposure and examined for biomarkers of lung injury. No differences in pulmonary edema, cytotoxicity or inflammation were observed between MMP-7 -/- and MMP-7 +/+ mice at 6h post-exposure. However, at 24h



Society of Toxicology

40th Annual Meeting

An Official Journal of the
Society of Toxicology
Supplement

TOXICOLOGICAL SCIENCES
Formerly Fundamental and Applied Toxicology

The Toxicologist

Abstracts of the 40th Annual Meeting

Oxford University Press

Volume 60, Number 1, March 2001

Preface

This issue of *The Toxicologist* is devoted to the abstracts of the presentations for the symposium, platform, poster discussion, workshop, roundtable, and poster sessions of the 40th Annual Meeting of the Society of Toxicology, held at the Moscone Convention Center, San Francisco, California, March 25–29, 2001.

An alphabetical Author Index, cross referencing the corresponding abstract number(s), begins on page 451.

The issue also contains a Keyword Index (by subject or chemical) of all the presentations, beginning on page 479.

The abstracts are reproduced as accepted by the Program Committee of the Society of Toxicology and appear in numerical sequence.

Copies of *The Toxicologist* are available at $45 each plus $5 postage and handling (U.S. funds) from:

Society of Toxicology
1767 Business Center Drive, Suite 302
Reston, VA 20190-5332

http://www.toxicology.org