creased rates of cardiovascular morbidity and mortality. Remodeling of arterial extracellular matrix is a crucial step in the progression of atherosclerosis. We have previously reported that expression of vascular remodeling proteins, matrix metalloproteinases (MMPs), and vasoactive peptide endothelin-1 (ET-1), as well as reactive oxygen species (ROS) are found upregulated in ApoE-/- mice exposed to gasoline engine emissions (GEE). Thus, we tested the hypothesis that GEE exposure-induced ET-1 mediates ROS, and expression of MMPs in the vasculature. To determine the role of ET-1 in vascular ROS and MMP expression, ApoE-/- mice, on a high fat diet, were treated with either ETA receptor antagonist, BQ-123, (100 ng/kg/day via osmotic minipump) or vehicle, and concurrently exposed via inhalation for 6 h/d, for a period of 7 d to either GEE (60 μg PM/m3) or filtered air. Exposure to GEE resulted in a significant increase in aorta ET-1, MMP-2, and MMP-9 mRNA, as determined by real time PCR. Western blots and in situ zymography confirmed an increase in MMP-2 and -9 proteins and activity, respectively, in GEE-exposed aortas. Dihydroethidum staining and TBARs analysis of GEE-exposed aortas were indicative of elevated ROS. Effects of GEE on mRNA, protein, and TBARS levels were all significantly attenuated by BQ-123 treatment. Such findings suggest that exposure to gasoline emissions results in elevated vascular ET-1, which mediates, at least in part, upregulation of molecular pathways involved in vascular remodeling, inflammation, and the progression of atherosclerosis. Funded by NIH 5F32ES015404-02 (AKL) and EPA CF 826442-01-1(MJC).

740 CARBON NANOTUBE ACUTE LUNG EXPOSURE INDUCES PLASMINOGEN ACTIVATOR INHIBITOR 1.

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Plasminogen activator inhibitor (PAI)-1 is an inhibitor of fibrinolysis, the physiological process involved in blood clot degradation. Systemic release of PAI-1 has been associated with ischemic cardiovascular disease and poor prognosis of acute lung injury. We evaluated the induction of PAI-1 in the lung and systemic circulation of C57BL/6J mice exposed to high dose (40 μg) purified single walled carbon nanotubes (SWCNT, CNI, Inc.) or multi walled CNT (MWCNT, provided by Prof. Endo, Shinshu University, Japan) by pharyngeal aspiration. CNTs were dispersed by sonication in a dispersion solution (DS) containing mouse serum albumin and DSPC. Mice were sacrificed 4hr post-exposure and lung tissue, bronchoalveolar lavage (BAL), and blood were collected for biochemical and gene expression assessment. CNT exposure caused increased PAI-1 (~5-fold) gene expression in the lung while no increase was found in the whole blood. PAI-1 protein levels were significantly increased in the lungs of both CNT-treated groups (3.57±0.42 ng/ml DS; 7.45±0.68* SWCNT; 8.16±0.89* MWCNT, *p<0.05). A similar trend was demonstrated for the plasma PAI-1 protein levels (1.95±0.19 ng/ml DS; 2.36±0.57 SWCNT; 2.84±0.38 MWCNT) as well as plasma PAI-1 activity (0.33±0.10 DS; 0.64±0.16 SWCNT; 0.80±0.16* MWCNT, *p<0.05). The PAI-1 activation was accompanied by induction of lung inflammation including increased influx of neutrophils in the BAL, increased BAL LDH and albumin and elevated lung tissue gene expression of numerous inflammatory genes such as (IL-1β, MIP-2, MCP-1, and IL-6). Furthermore, acute CNT exposure induced MIP-2 and IL-1β gene expression in the blood cells from the systemic circulation. All these effects were more prominent and consistent in mice exposed to MWCNT compared to the mice exposed to SWCNT. In conclusion, CNT-induced acute lung inflammation was associated with a systemic response which may lead to disturbances in the coagulation cascade and vascular endothelial function.

741 THE AORTA, BUT NOT LUNG OR HEART, IS THE TARGET OF SUBCHRONIC DIESEL-INDUCED INJURY AND INFLAMMATION.

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Cardiovascular abnormalities have been noted in individuals exposed to diesel exhaust (DE) or traffic air pollution; however, the mechanisms are unknown. We postulated that long-term episodic exposure of rats to DE would differentially affect the three target organs: lung, heart, and aorta. We exposed healthy male Wistar Kyoto rats (12-15 wks old), nose-only, to either fresh air or bulk DE from the tail pipe of 30 kW Deutz engine (2.0 mg/m3), 5 h/d, 1 d/wk for 16 wks. We analyzed gene expression by real-time PCR which reveal contributions of inflammation, oxidative stress, microvascular thrombosis and vasoconstriction. Minimal pulmonary inflammation was noted following DE exposure. Gene expression in the lung and the heart did not change except for a ~2-fold induction in atrial and brain natriuretic peptide mRNA in the lung. However, remarkable changes were noted in the aorta. While the inflammation and oxidative stress genes (MIP-2, HO-1) were induced ~3-fold over control, the most remarkable induction was noted for markers of thrombosis (tissue plasminogen activator inhibitor (~22-fold), tissue plasminogen activator (~9-fold), thrombomodulin (~4-fold), and van Willebrand Factor (~3-fold). The expressions of endothelin (ET) and its receptors were also induced (ET, ~9-fold; ET receptor A, ~3-fold and receptor B, ~2-fold) but not angiotensin-2. Surprisingly, the expression of natriuretic peptides was inhibited in the aorta following DE exposure. These data demonstrate that aorta is the target of DE-induced injury. Episodic DE exposure produces remarkable vascular abnormalities while sparing the heart and the lung. The aortic injuries and thrombosis produced by ambient levels of DE in healthy individuals may secondarily lead to cardiac physiological alterations. (Does not reflect US EPA policy). Supported in part by EPA NCBA/SEE Program and EPA/UNC Cooperative Agreement #CT829471.

742 CHANGES IN ENDOTHELIAL TUBE CELL-CELL BORDERS IN RESPONSE TO DIESEL EXHAUST PARTICLES.

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Several epidemiological studies link exposure to diesel exhaust particles (DEP) with adverse cardiovascular events. Other studies show that inhaled DEP gain access to the bloodstream. The mechanisms for how DEP gain access to the capillary lumen and how they cause cardiovascular problems are unclear. To elucidate possible mechanisms, we have used human umbilical vein endothelial cells (HUVEC) plated on plastic and Matrigel as in vitro and organ culture model systems. DEP collected from a Japanese diesel engine (gift of Dr. Sagai), were diluted and sonicated (to about the size of PM2.5) in 0.05% TWEEN/PBS for 5 min. DEP at concentrations of 1, 10, and 100 in 1 ml medium were added to 150,000 cells in monolayer culture or as capillary endothelial tubes. After 24 or 48 hr exposures, proliferation and cytotoxicity assays were used to examine cell viability of monolayer cultures, TUNEL assays were used to determine the extent of apoptosis of treated capillary tubes, and confocal microscopy was used to evaluate the redistribution of VE-cadherin in the cell-cell borders of tubes. At 100 ug/ml DEP, over 80% of the cells die within 48 hr. Cells treated with 1 ug/ml DEP doubled every 24 hr, as do untreated cells. However, 10 ug/ml DEP delayed doubling. TUNEL assays indicated that some cell death was occurring at this concentration. In addition, Z-stacks of confocal images revealed that DEP not only accumulated on the surface of capillary tubes, but also penetrated into the lumen. VE-cadherin was observed to redistribute in response to DEP. Endothelial cell borders were slightly affected at 1 ug/ml, more affected at 10 ug/ml, and were almost totally disrupted at 100 ug/ml. Our results suggest that DEP gain access to the bloodstream by altering the endothelial cell junctions.

743 EXACERBATION OF ATHEROSCLEROSIS BY URBAN AND RURAL CONCENTRATED AMBIENT PM.

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A number of epidemiologic studies have demonstrated a link between particulate matter (PM) and cardiovascular morbidity and mortality. We have previously shown acute and cumulative effects of daily inhalation exposures to concentrated ambient particles (CAPs) in Sterling Forest, NY in a mouse model of atherosclerosis. Although PM from sources rich in nickel and vanadium were found to be responsible for changes in heart rate (HR) and heart rate variability (HRV), the sources responsible for atherosclerosis changes were not clearly demonstrated. In the HEI's NPACT initiatives (National Particle Composition Toxicological initiatives), we are conducting subchronic CAPs inhalation studies in mice in diverse U.S. locations in order to identify the PM components that are most responsible for acute and cumulative cardiovascular system effects. In this study, we simultaneously compared the effects of CAPs in Sterling Forest to those encountered in Manhattan, where there are substantial increments of Ni and elemental and organic carbon in the ambient PM in addition to the long-range transport PM that is present in both locations. Male mice lacking apolipoprotein, 3-month old, n=12/group, on normal rodent chow, were exposed to CAPs, simultaneously, in our Sterling Forest laboratory in Tuxedo and in Mt. Sinai School of Medicine in Manhattan for 6 hr/d, 5d/w, for 6 months (avg. conc. 170±130 μg/m3). Atherosclerotic lesions in the brachiocephalic and left common carotid arteries were measured by serial non-invasive ultrasound biomicroscopy at 3 and 6 months of exposure. The plaque size in both the brachiocephalic and left common carotid arteries was significantly increased at 3 months of CAPs exposure. At this time point,

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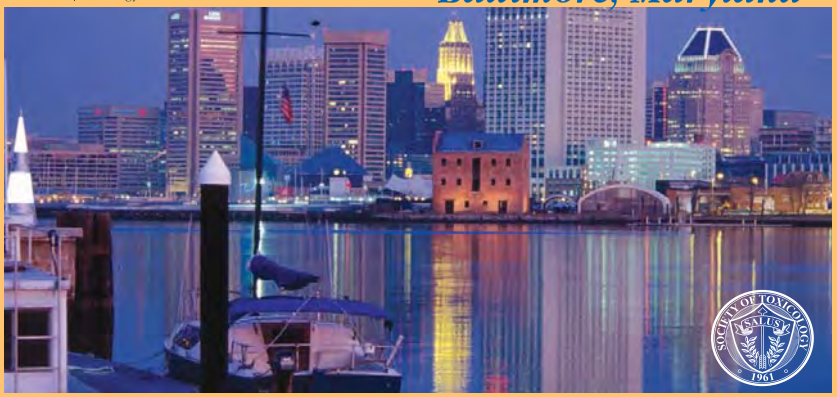

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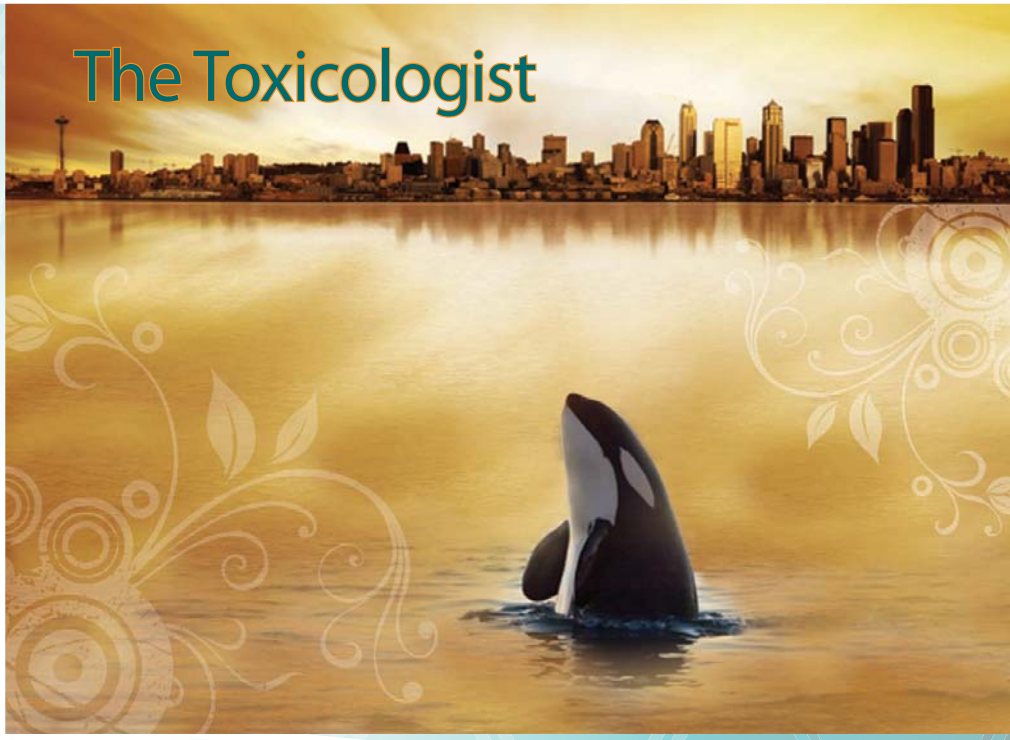

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