661 NEW FRONTIERS IN ENVIRONMENTAL SCIENCES AND HUMAN HEALTH: IMPLEMENTATION UPDATE ON THE NIEHS STRATEGIC PLAN.

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The NIEHS has begun work to implement its new Strategic Plan, "New Frontiers in Environmental Sciences and Human Health." With the Plan, the NIEHS is changing the way it approaches research, increasing the integration of clinical sciences into environmental health and the translation of basic and clinical research in environmental health into disease prevention strategies, therapeutics, and public health practice. NIEHS is emphasizing a dual approach balancing the work of interdisciplinary teams of scientists along with the very best individual investigator-initiated research. The vision of the NIEHS, supported by the Plan's goals, is to prevent disease and improve human health by focusing our research efforts on using environmental sciences to understand human biology and human disease. The Plan identifies seven major goals for the NIEHS: promoting clinical research in environmental health; using environmental sciences to understand human biology; fostering integrative approaches; promoting community-linked research, both domestically and globally; developing new approaches for studying the biology and measurement of exposure; creating new models for training the next generation of environmental health scientists; and fostering more widespread and effective partnerships to improve both the quality of the Institute's research and its ultimate public health impact. In this informational session, NIEHS and NTP leadership will discuss the Plan, describe recent accomplishments, present new program initiatives to advance the Plan's goals, and invite discussion from participants.

662 AIR POLLUTION AND ATHEROSCLEROSIS: IMPACT ON VASCULAR OXIDATIVE STRESS, DYSLIPIDEMIA, AND REMODELING.

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Cardiovascular disease remains a major health concern in the Western World, representing greater than 25% of all-cause mortality. Atherosclerosis, an inflammatory disease of the vasculature that causes or complicates many forms of cardiovascular disease, is greatly influenced by genetics and lifestyle, but environmental factors such as air pollution may cause or promote ongoing disease. Recent animal studies have begun to shed light on epidemiological findings of air pollution-related morbidity and mortality due to ischemic heart disease. Atherosclerosis is a complex disease, characterized by dyslipidemia, oxidative stress, inflammation, and vascular remodeling. Dysregulation of vascular cells can lead to remodeling and the development of vascular lesions or plaques that can obstruct flow in vital organs and erode or rupture to reveal procoagulant factors and induce intravascular clotting.
This symposium will explore mechanisms by which air pollutants, mainly particulate matter, can contribute to the vascular lesion progression via each of these various facets of atherogenesis. Studies presented will explore both biological pathways as well as components of air pollution that drive the vascular pathology. A more thorough understanding of the interactions between inhaled toxins and systemic vascular dysfunction may help identify susceptible individuals, highlight potential therapeutic targets, and determine contributing components of the complex pollutant mixture.

663 COMPARATIVE PROGRESSION OF ATHEROSCLEROSIS IN APOE-/- MICE EXPOSED TO ETS AND CAPS.

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There are many similarities in the nature and extent of the risks that have been associated with the inhalation of environmental tobacco smoke (ETS) and ambient air fine particulate matter (PM2.5). Population-based risk estimates for chronic exposures are significantly elevated for both of these complex mixtures for lung growth in children, and for cardiovascular disease and lung cancer in adults. For both complex mixtures, the effects seen in population studies have been questioned on the basis of the paucity of toxicological evidence establishing biological plausibility at the relatively low levels of ETS and PM at which humans have been exposed. In this study, we exposed ApoE knockout mice susceptible to atherosclerosis development to ETS at a nominal concentration of 500 ug/m3 for 6 hr/day, 5 day/wk, for 6 months. Atheroma progression and plaque characteristics (lesion cellularity, lipid core formation, and extent of macrophage and T-cell infiltration) were evaluated using non-invasive ultrasound biomicroscopy (UBM) and immunohistopathology and morphometric analysis. The results were compared to our previous subchronic CAPs inhalation study to evaluate whether ETS and CAPS caused comparable levels of alterations in atherogenesis.

664 CARBON NANOTUBE RESPIRATORY EXPOSURE AND RISK FROM SYSTEMIC EFFECTS.

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The most attractive features of nanomaterials including their small size, large surface area, and reactivity might also be the main factors for their toxicity. In this regard, nanoparticles may induce not only higher damage at the penetration site but also can lead to unexpected distant responses as a result of their transclocation and reactivity through the body. Our research efforts are currently directed to evaluate the cardiovascular effects, including vascular inflammation, blood cell coagulation status, atherosclerosis, as well as the related molecular mechanisms associated with respiratory exposure to different forms of carbon nanotubes (CNT) using animal models. We demonstrated that pulmonary exposure to multiple doses of single wall-CNT induces severe lung toxicity and accelerates the progression of atherosclerosis in ApoE-/- mice. This response is accompanied by oxidative modification in the vascular wall and induction of markers which facilitate blood coagulation. The atherogenic effects might be a result of a systemic effects related to the lung toxicity and/or translocation of nanotubes into the systemic circulation.
The accumulation of toxicological data on engineered nanomaterials will allow for development of adequate risk assessment and regulations.

665 *IN VIVO* ENDOTHELIAL RESPONSE OF TIE2-GFP/APOE DEFICIENT MICE TO WHOLE DIESEL EXHAUST.

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Air pollution accelerates atherogenesis and cardiovascular disease. We examined the effect of diesel exhaust on endothelial gene expression in vivo, utilizing hypercholesteremic transgenic mice. Tie2-GFP mice expressing green fluorescent protein regulated by the endothelial-specific promoter Tie2 were crossed with apolipoprotein E knockout mice to generate Tie2-GFP/ApoE null mice. Tie2-GFP and Tie2-GFP/ApoE mice were exposed to diesel exhaust for 6 hours/day for 3 or 30 days at measured levels of diesel engine particulates from a Yanmar engine (0.3 and 1.0 mg/m^3). Within 24 hours of exposure, aortae (pooled from 4 animals) were dissected from the valve to the iliac bifurcation and rapidly processed by proteolytic dissociation followed by fluorescence activated cell sorting to yield > 50,000 cells of > 95% purity. Changes in abundance of endothelial transcripts were then examined comprehensively by microarray techniques. RNA representing > 10,000 cells was subjected to amplification by the Ovation system (Nugen, CA), prior to labeling and hybridization to arrays created from the Operon V3 long oligo set. Following each exposure level, several genes detected by microarray and confirmed by real-time PCR were consistently dysregulated by > 2-fold. After 3 days of exposure at 1.0 mg/m^3, increased expression of aryl sulfotransferase 1a and epoxide hydrolase 1 may reflect in vivo response to conditions of oxidative stress, and increased abundance of metal response element transcription factor-2 likely reflects the delivery of particulate-derived metals into the circulation. After 30 days of exposure at either 0.3 or 1.0 mg/m^3, dysregulation of gene expression of type 2 angiotensin II receptor, sulfotransferase-related protein 3, and beta-carotene-9',10'-dioxygenase was potentiated in the ApoE deficient mice. The gene regulation identified in these experiments implicates pathways important in enhancement of atherosclerosis by diesel exhaust.

666 ENVIRONMENTAL OXIDANT EXPOSURE CAUSES MITOCHONDRIAL DAMAGE ASSOCIATED WITH INCREASED ATHEROGENESIS.

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The etiology of atherosclerosis is understood as an inflammatory process of the artery wall involving oxidative stress exacerbated by metabolic defects in cholesterol or glucose metabolism. Stress factors such as diet, diabetes and smoking are well recognized as environmental or metabolic factors that play roles in atherogenesis. More recently, it has become clear that environmental oxidant exposure increases the risk for cardiovascular disease development. One potential mechanism by which environmental oxidant exposure acts to increase cardiovascular disease risk is

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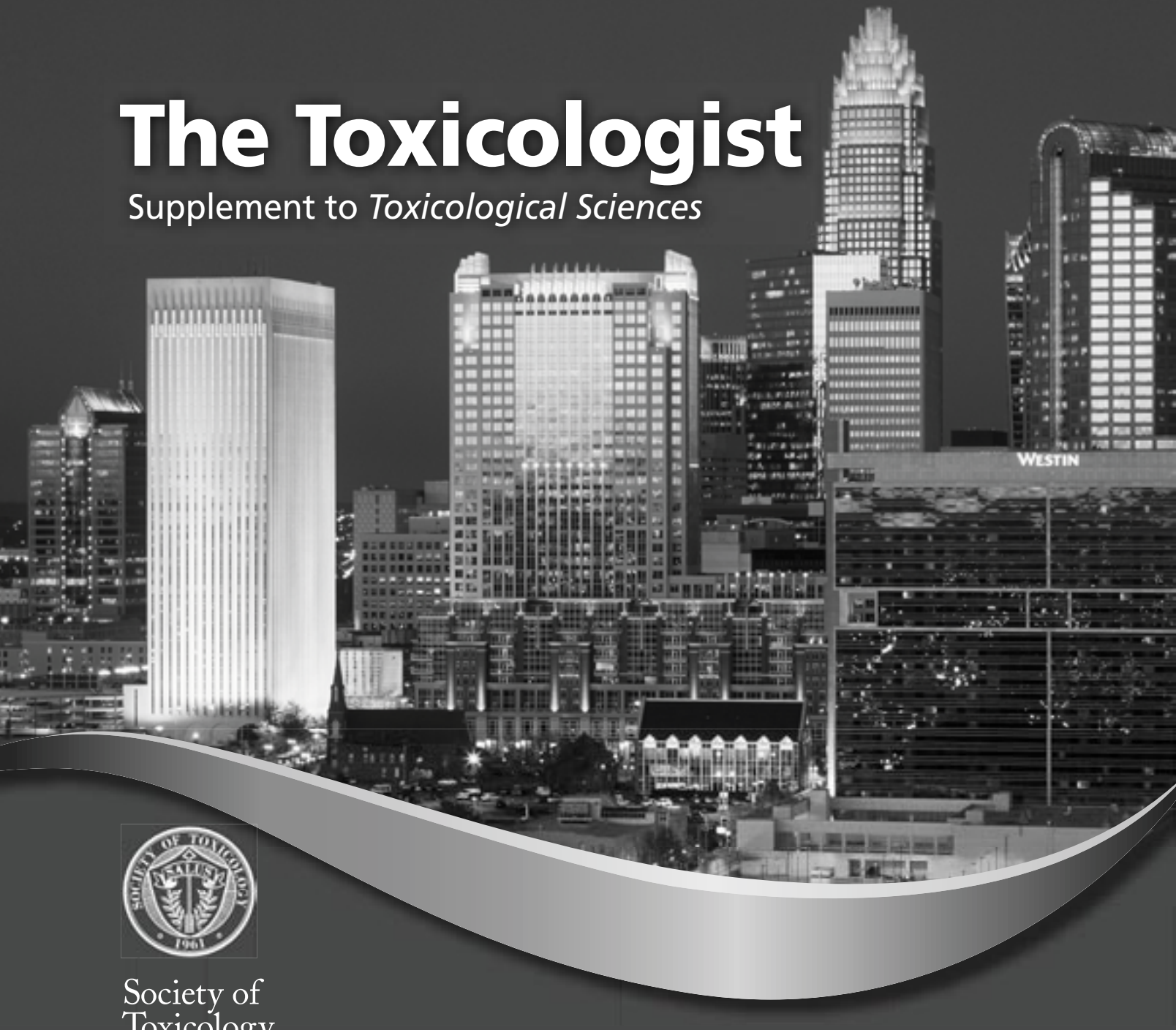

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Preface

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An alphabetical Author Index, cross referencing the corresponding abstract number(s), begins on page 449.

The issue also contains a Keyword Index (by subject or chemical) of all the presentations, beginning on page 480.

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

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