W 2363 Discriminatory Circulating Peptides from Different Inhalation Exposures–Biomarker and Cerebrovascular Implications

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Mechanisms underlying the diversity of systemic health impacts following different inhalation exposures may, in part, relate to a complex make-up of inducible peptides released into circulation. With developed mass spectrometric methods, we have revealed an induced sero-peptidome following pulmonary exposure. Distinct signatures are revealed in response to carbon nanomaterials, ozone, and secondhand smoke exposures, with both dose-dependent and -independent responses. The diversity in sero-peptidome response offered advantages for biomarker model development, providing the ability to build selective models based on the nature of exposure. Studies also show altered cerebrovascular permeability based on the inhalation exposure and the translocation of induced peptides into the central nervous system. Furthermore, behavioral deficits in juvenile animals exposed to secondhand smoke were correlated with inhalation-induced peptides. Novel software being developed in our laboratory provides improved sero-peptidome characterization and reflects an associated with an immune/inflammatory response. Thews findings provide novel perspectives on the origins of systemic toxicity arising indirectly from pulmonary exposures to inhaled particulates.

W 2364 Early Endothelial Bioactivity of Serum After Diesel Exhaust Inhalation: A Driver of Latent Impairment in Left Ventricular Pressure in the Heart?

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Adverse cardiovascular effects of air pollution are often associated with increases in systemic proinflammatory mediators, although causative linkage between circulating factors and deleterious outcomes following exposure remains elusive. The purpose of this study was to examine the plausibility of serum-bound factors as initiators of an air pollution-induced pathologic sequelae that begins with endothelial injury and ultimately manifests as cardiac dysfunction. We hypothesized that serum taken from diesel exhaust (DE)-exposed rats that develop cardiac dysfunction would alter aortic endothelial function *in vitro*. To assess cardiac function *in vivo*, left ventricular pressure (LVP) assessments were conducted in rats one day after a single 4-hour whole body exposure to 150 or 500 µg/m3 DE or filtered air. To assess impacts of serum *in vitro*, rat aortic endothelial cells (RAEC) were exposed to diluted serum (10%) collected 1-hour after exposure from a separate cohort of similarly exposed rats for measures of VCAM-1, cell viability, nitric oxide synthase (NOS) levels, and mRNA expression of key mediators of inflammation. Exposure of rats to 150 or 500 µg/m3 DE increased heart rate (HR) after exposure relative to rats exposed to filtered air, suggesting a shift towards increased sympathetic tone. LVP and HR in DE-exposed rats (500 µg/m3 DE) failed to recover to normal levels after challenge with the sympathomimetic dobutamine, suggesting dysregulation of mean arterial pressure, a response consistent with impaired post-exercise recovery of cardiac function in humans exposed to air pollution. Serum from DE-exposed rats caused a decrease in NOS activity (150, 500 µg/m3 DE) and cell viability (500 µg/m3 DE), and an increase in VCAM-1 (500 µg/m3 DE) in RAECs relative to cells treated with serum from rats exposed to filtered air. Thus, cardiac responses after DE exposure may stem from a shift in autonomic balance and/or endothelial dysfunction that may in part be triggered by exposure-induced increases in circulating proinflammatory mediators. Proteomic and lipid assessments in rat sera are currently being conducted to confirm the presence of a proinflammatory milieu and to identify potential causative factors (this work is supported in part by NIH R01 ES019311 and K99 ES024392; this abstract does not reflect EPA policy).

W 2365 Vascular Effects after Exposure to Particles: Systematic Literature Review and Plasma Bioactivity in Carbon Black-Exposed ApoE Knockout Mice

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Pulmonary exposure to combustion-derived particulate matter (PM) and certain nanomaterials is hazardous to the vascular system in experimental animals. A systematic review of the literature shows airway exposure to air pollution particles and nanomaterials is associated with similar effect size on atherosclerosis progression, augmented vasoconstriction, and blunted vasorelaxation responses in arteries. These effects have typically been attributed to either translocation of particles or spill-over of inflammatory or oxidation products from the lungs to the circulation. However, vasomotor dysfunction and progression of atherosclerosis occur at doses that are not associated with pulmonary and systemic inflammation in animals. Likewise, there is only a very modest increase in systemic inflammation markers in humans who have been exposed to air pollution particles. A new line of research has developed the notion of serum bioactivity, i.e. the presence of mediators in serum that causes vascular effects. We assessed plasma bioactivity in apolipoprotein E knockout (ApoE -/-) mice that were exposed once a week for 10 weeks to 0, 8.53 or 25.6 µg nanosized carbon black alone or spiked with lipopolysaccharide (0.2 µg/mouse/exposure). The exposure caused pulmonary inflammation, whereas the glutathione status was unaltered in lung tissue. There was no convincing evidence of plaque progression in the aorta and the brachiocephalic artery. However, the plasma of exposed ApoE-/- mice contained vasoactive mediators that mediated vasoconstriction in aorta rings from naïve C57BL/6 mice. This effect was abolished by treatment with the serotonin receptor antagonist Ketanserin. The same effect was not observed in lipopolysaccharide-exposed mice, indicating that pulmonary inflammation was not the main driver of plasma bioreactive mediators. This observation corroborates with earlier findings of vasomotor dysfunction in aorta of ApoE-/- mice after exposure to carbon black. In humans, such an increased tendency of vasoconstriction in blood vessels with atheromas may be reduce blood flow, leading to ischemic episodes and symptoms of heart failure.

W 2366 Increasing the Utility and Acceptance of Chemical Specific Adjustment Factors—International Experience

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The application of chemical-specific toxicokinetic (TK) or toxicodynamic (TD) data to address interspecies differences and human variability in the quantification of hazard has potential to reduce uncertainty and better characterize variability compared to the use of traditional default uncertainty factors. This workshop will summarize the state of the science since the introduction of the WHO/IPCS guidance on chemical-specific adjustment factors (CSAF) in 2005, including the impact of more recent guidance, such as the IPCS guidance on physiologically-based pharmacokinetic modeling (PBPK), and the US EPA guidance on data-derived extrapolation factors. The session also illustrates how CSAF principles complement ongoing research initiatives to develop more innovative testing and assessment strategies based on additionally evolving frameworks to consider Adverse Outcome Pathways/mode of action and combined exposures. A summary of lessons learned from an analysis of approximately 100 case studies identified in the literature and information provided by regulatory agencies globally illustrates the nature of evolution of CSAF in regulatory application. It also identifies associated challenges, including adequacy of supporting data and assessments in which CSAF were considered but not adopted. Based on this analysis, recommendations for relevant interdisciplinary research and engagement are included. The session ends with a panel discussion on enhancing uptake of CSAF in chemical risk assessment, including an opportunity for the audience to discuss principal aspects with representatives from key stakeholder groups. Researchers, biological modelers, and risk assessors interested in increasing their knowledge concerning the application of relevant toxicological data to reduce uncertainty associated with interspecies differences or human variability will find this session of interest. The content of the session also is relevant to regulators interested in expanding their knowledge of the scope of application and nature of supporting data considered most valuable in the development of CSAF over the last couple of decades.

W 2367 Analysis of International Experience on CSAFs and Potential Path Forward

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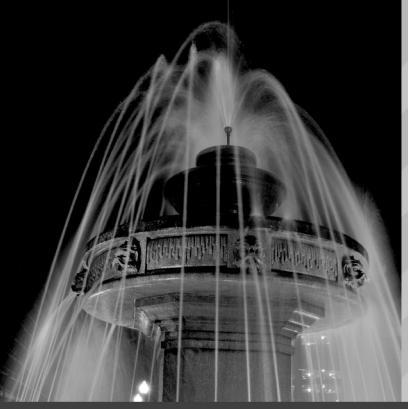
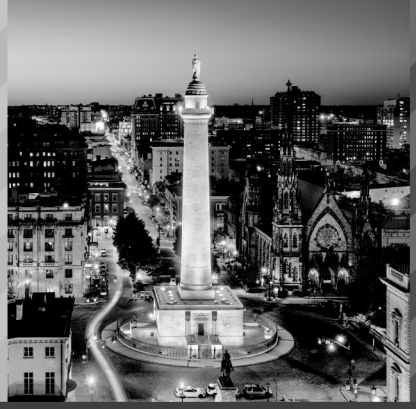
Chemical Specific Adjustment Factors (CSAF) offer opportunity to apply information on toxicokinetics and dose-response relationships for early key events in Adverse Outcome Pathways (AOPs) to dose-response characterization in chemical specific mode of action analysis. However, recent analysis of case studies released since the introduction of the IPCS Guidance on CSAF indicates that while there has been progress in incorporating toxicokinetic data in the development of CSAF, there are very few examples of the application of data on early toxicodynamic key events generated in, for example, *in vitro* studies. Analysis also indicates that while there have been a number of proposals for (particularly) toxicodynamic adjustments based on chemical-specific data from the research community, uptake in regulatory context has been rather limited. The limited extent of this progress is considered, in the context of potential limitations of the original guidance and more recent international experience in the documentation and assessment of AOPs and PBPK models, by collaborating teams of the research and





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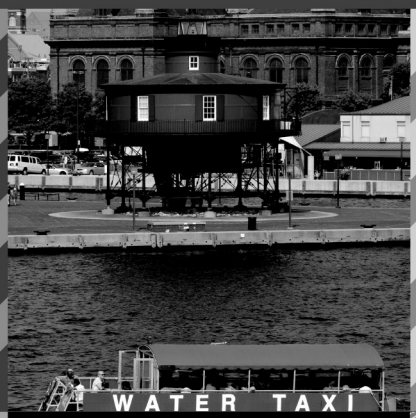

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