Poster No. 5

Title: Mitochondrial and Plasma Associated Metabolic Perturbations Due to Low Dose, Chronic Exposure to the Organochlorine Pesticide Endosulfan I

Presented by: Doug I. Walker

Authors: Douglas I. Walker and Kurt D. Pennell, Department of Civil and Environmental Engineering, School of Engineering, Tufts University; W. Michael Caudle, Department of Environmental Health, School of Public Health, Emory University; James R. Roede, Department of Pharmaceutical Sciences, Skaggs School of Pharmacy, University of Colorado; Dean P. Jones, Department of Medicine, Clinical Biomarkers Laboratory, Emory University

Abstract:

Traditional in-vitro and in-vivotoxicological testing has relied on acute dosing methods and set endpoints to investigate the health effects occurring from exposure to environmental agents. While these tests are useful to identify hazardous agents, it is often challenging to extrapolate these results to relevant, environmental exposures and the associated effects on human health. High-resolution mass spectrometry-based metabolic profiling (metabolomics) enables a system-based understanding of exposure related phenotypes. In this study, metabolic profiling with broad chemical coverage was applied to an animal exposure model to elucidate how the liver mitochondrial and plasma metabolome is altered due to low dose, 30-day exposure. Ten wild type male mice were orally gavaged with 1 mg/kg of the alpha isomer of endosulfan (endosulfan I) at 24-hour intervals for 30-days in addition to 10 control mice fed blank vehicle that were housed under identical conditions. Following the exposure period, experimental and control mice were sacrificed, and blood plasma along with intact liver mitochondria (isolated via differential centrifugation) were analyzed using dual chromatography with high resolution mass spectrometric detection. After removing m/z features found in less than 10% of samples, 3,792 features were common to mitochondria and plasma while an additional 2,440 were detected only in mitochondria and 2,653 were detected only in plasma. To identify specific m/z features associated with endosulfan I exposure, control and experimental metabolic profiles were compared using multiple hypothesis testing at a false discovery rate (FDR) of 0.05. For the m/z features present in greater than 70% within each individual group, plasma had more significant differences (611) than mitochondria (285); of these, 41 overlapping m/z features were present in both metabolic profiles. Pathway enrichment analysis of the mitochondrial significant features exhibited associations with fatty acid, vitamin D3, and methionine metabolism, with a slight enrichment in metabolites associated with the urea cycle. A similar analysis of the plasma metabolome found enrichment in glycerol related pathways, which included glycosphingolipid, n-glycan degradation, vitamin B6, glutathione and glycerophospholipid metabolism. Only alterations present to fatty acid metabolism were present in both the plasma and mitochondria. These results show that endosulfan I impacts mitochondrial function and has additional widespread metabolic effects. The results highlight use of high performance metabolic profiling to determine the metabolic phenotype associated with low dose, chronic exposure to environmental chemicals.