PROJECT 3 ABSTRACT

EPA Grant #: RD83479701 **EPA Project Officer:** Mel Peffers/Sherri Hunt

Title: Long Term Metabolic Consequences of Exposures to Multipollutant Atmospheres in the Great Lakes Region

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Institution: The Ohio State University, Columbus, OH

Project Period: 12/1/2010 – 11/30/2015 **Project Costs:** $1,621,922

RFA: Clean Air Research Centers **Research Category:** Air Quality

Description: ***Objectives/Hypothesis*:** We have recently demonstrated that short-term exposure to concentrated ambient particulate matter (CAP) elicits the development of hypertension and insulin resistance (IR) that are facets of the cardiometabolic syndrome (CMS) often associated with obesity and diabetes. We hypothesize that long-term exposure to CAP, along with expose to the common gaseous air pollutant, ozone (O_3), interacts with host factors such as diet and genetic susceptibility, resulting in the development of CMS. Project 3 is an integral component of our Center's overarching theme that the major air pollutants, fine particulate matter ($PM_{2.5}$) and O_3, are 1) capable of eliciting multiple important adverse cardiometabolic health effects that are dependent on 2) the local multipollutant milieu, 3) an individual's pre-existing cardiovascular (CV) and metabolic condition, and 4) the interactive toxicity of $PM_{2.5}$ and O_3 coexposure.

Approach: Our proposed experiments are natural extensions of the human controlled exposure research outlined in Project 1 and the acute animal inhalation toxicology studies in Project 2. We will conduct long-term inhalation toxicology studies of obese and/or diabetic mice exposed to CAPs with or without O_3. In Aim 1, simultaneous chronic exposure of mice to CAP from two locations in Columbus OH, representing near-roadway/residential or transported/regional multipollutant atmospheres, will be examined alone and in combination with a high fat chow diet (HFC). The impact of CAP on various biological measures of CMS (e.g., glucose/insulin homeostasis, adipokines, insulin signaling, inflammation in adipose tissue) along with an analysis of CAP concentrations and components associated with these induced health effects will be evaluated in HFC-fed mice and in mice with a genetic propensity for developing Type II diabetes (KKA/y). In Aim 2, we will investigate the effect of CAP and O_3 co-exposures on the temporal development of IR and inflammation in fat (adipose) and lung tissues of KKA/y mice. We will also assess dose-response relationships of CAP and O_3 mixtures on IR and innate immune responses that are pivotal to the development of metabolic derangement characteristic of CMS. Based on data from Aims 1 and 2, we will design further experiments in Aim 3, which will help us to assess if and how CAP from multipollutant atmospheres may potentiate inflammatory cell (i.e., monocyte) activation and infiltration into various organs and tissues that may play important roles in mediating adverse systemic metabolic effects. We will contrast the results of health effect studies conducted at specified sites in Columbus, OH with those conducted in Dexter and Detroit, MI, to try to elucidate the components of these disparate multipollutant atmospheres that are most responsible for the enhancement of the CMS.

***Expected Results*:** Using state- of-the-art mobile inhalation exposure systems available at our laboratory (OASIS 1 and 2) and at Michigan State University (AirCARE 1 and 2), along with novel and high-resolution exposure characterization methods of our collaborators at The University of Michigan (Project 3) offers an unprecedented opportunity to elucidate relevant biological mechanisms responsible for the effects of ambient $PM_{2.5}$ and O_3 exposures on the pathogenesis of IR and other facets of the CMS. Insights from our studies will provide important guidance on how to better protect public health and susceptible populations, like those suffering from obesity and diabetes, from the harmful effects of environmental exposure to air pollutants in the Great Lakes Region and elsewhere.

Supplemental Keywords: obesity, insulin resistance, chronic exposure, inflammation, mice.