PROJECT 1 ABSTRACT

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

Title: Cardiometabolic Effects of Exposure to Differing Mixtures and Concentrations of $PM_{2.5}$ in Obese and Lean Adults

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Project Period: 12/1/2010 – 11/30/2015 **Project Costs:** $1,543,442

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

Description: ***Objectives/Hypothesis:*** We have discovered an important interaction between key aspects of the cardio-metabolic syndrome (CMS) and exposure to fine particulate matter ($PM_{2.5}$). Brief exposure to concentrated ambient $PM_{2.5}$ (CAP) for 2 hours triggers arterial narrowing (vasoconstriction), increased diastolic blood pressure (BP), and impairment of proper blood vessel function (vascular endothelial function (VEF)) 1 day after exposure – the latter occurring in a location-dependent manner suggesting that particle constituents are important determinants of these health effects caused by multipollutant exposures. Two pathways were implicated in these responses - 1) changes in autonomic nervous system (ANS) balance responsible for the increased BP and 2) systemic inflammatory responses for the slower impairment in VEF. Though these findings help us understand how $PM_{2.5}$ might cause acute cardiovascular (CV) changes, several important issues remain to be clarified. Moreover, our previous studies also suggest that a more-encompassing, yet unappreciated, convergence might exist between $PM_{2.5}$ exposure and the CMS. Not only could obesity enhance the susceptibility to adverse health effects induced by $PM_{2.5}$ exposure, but $PM_{2.5}$ might promote the development of metabolic insulin resistance (IR), a central factor in the cause of obesity and the CMS itself. Our objectives are to investigate: 1) if exposure to CAP mixtures are capable of acutely instigating metabolic IR in addition to elevating diastolic BP and impairing VEF; 2) whether obesity confers enhanced susceptibility for these responses; 3) details of the mechanisms responsible for health effects; 4) the nature of the dose-response relationships even at concentrations below current 24-hour $PM_{2.5}$ standards; and 5) if CAP derived from 2 dissimilar multipollutant ambient $PM_{2.5}$ atmospheres cause differing CMS responses and the specific pollutants responsible.

Approach: We will achieve these aims by examining the BP and VEF responses, along with additional outcomes, in obese versus lean adults, caused by CAP exposures in 2 separate locals comprised of dissimilar $PM_{2.5}$ mixtures (industrial/urban versus a near-roadway/residential). The concentrations of CAP will be varied to include levels from below 35 to above 100 $\mu g/m^3$. Using state-of-the-art physiological testing and biomarkers, the mechanisms responsible for the alterations in CMS responses will be explored. The role of the ANS in the BP increase and the effectiveness of a prophylactic measure, $\alpha+\beta$ adrenergic blockade, in preventing this response will also be tested. Finally, we will evaluate whether exposure to CAP can acutely elicit metabolic IR.

***Expected Results*:** This project will address questions with humans exposed to real-world $PM_{2.5}$, thereby providing findings of tremendous public health importance. The expected results will elucidate new insights into: the susceptibility of obese individuals to multipollutant atmospheric exposures, the extent of concentration-response relationships, the mixtures of $PM_{2.5}$ and their constituents responsible for health effects, and the mechanisms underlying the CV responses. Finally, we will explore the evidence for a novel $PM_{2.5}$ health effect – instigation of metabolic IR.

Supplemental Keywords: metabolic syndrome, vascular, pollution mixtures, human subjects