CARDIOVASCULAR EFFECTS OF MULTIPOLLUTANT EXPOSURE: MECHANISMS AND INTERACTIONS

I. OBJECTIVE

Many studies have reported a significant association between fine PM2.5 and adverse cardiovascular effects. In addition, several recent studies have suggested that ozone exposure, well-known to induce respiratory effects, may also have cardiovascular effects. There remain significant gaps in understanding the mechanistic pathways through which inhaled particulate matter and ozone exposure affect heart function. It is also unknown whether effects of concurrent exposure to PM2.5 and ozone are additive or synergistic. Therefore, the objectives of this study are to: 1) to elucidate the mechanistic pathways through which PM2.5 and ozone exposure induce cardiovascular effects, and 2) to determine whether there are additive or synergistic interactions between these two air pollutants.

II. BACKGROUND

National ambient air quality standards (NAAQS), which are updated at five year intervals, are based on reviews of the scientific literature on the health effects of exposure to air pollutants. Among the six pollutants for which there are NAAQS, only those for particulate matter are primarily based on epidemiologic associations. Epidemiologic studies have consistently shown, contrary to expectations, that PM-related health effects on the cardiovascular system are larger and more clinically significant than those on the respiratory system. While some published studies have provided important data that have addressed this issue, there remain substantial gaps and uncertainties in our understanding. To date, mechanistic studies investigating how inhaled PM induces adverse health effects have focused on generic, non-specific modes of action (e.g., oxidative stress and inflammation) that are not unique to air pollution.

In contrast, the ozone NAAQS is primarily based on human exposure studies that have investigated the relationship between well-defined ozone exposures and changes in clinical endpoints, primarily of the respiratory system. Several mechanistic pathways are known through which ozone exposure causes respiratory health effects. Recent research suggests that ozone exposure may have cardiovascular effects, which have not been appreciated to date; however, little is known about potential biological mechanisms for ozone-induced cardiovascular effects. In addition, although humans are exposed to a complex mixture of ambient air pollutants, little is known as to whether or not there are interactions or synergisms among various ambient pollutants.

Previous research results indicate that exposure to fine and ultrafine PM increases inflammatory cytokines and activates platelets in the systemic circulation, although the source of the cytokines and mechanistic pathway through which platelets are activated are unclear.

Activated platelets can release biomarkers that directly affect heart muscle function. Recent data suggest that inhaled PM2.5 may directly activate nerve fibers (C-fibers) in the airway walls that are known to cause airway constriction and hyperresponsiveness. Ozone exposure is known to activate the same airway nerve fibers, producing bronchoconstriction and airway hyperresponsiveness. Furthermore, it is also known from non-air pollution studies that activation of C-fibers can influence the function of the heart muscle. The possible convergence on the heart muscle of both the mechanistic pathways originating with activated platelets in the central circulation, and activation of C-fibers in the airways by inhaled air pollutants (PM2.5, ozone, or a mixture of pollutants) has not been investigated. In addition, the information cited above hints at possible interactive effects related to concurrent exposure to PM2.5 and ozone.

This project is important to the ARB, as well as to the United States Environmental Protection Agency (U.S. EPA), for the following reasons. First, the results of this study will strengthen the biological support for epidemiological associations between PM2.5 exposure and adverse health effects, and will reduce uncertainty in the database. Few studies have investigated biological pathways other than oxidative stress and inflammation, and even fewer have investigated whether or not there are interactive effects with concurrent exposure to multiple air pollutants. Therefore, studies, particularly in experimental animals, are needed to elucidate the biological pathways through which PM- and ozone-related health effects are mediated.

Second, the results of this study will contribute to ensuring that future revisions to the PM and ozone NAAQS are adequately health protective by strengthening biological support for, and reducing uncertainty in, our understanding of the relationship between exposure to PM and adverse health outcomes. In addition, the study will help to define the parameters of cardiovascular disease that increase vulnerability to air pollution exposure. Strong NAAQS and identification of vulnerability factors are both important components of ARB's mission to promote and protect public health.

Third, although the NAAQS are based on single pollutants, people are always exposed to mixtures of air pollution. Consequently, it is of particular interest to determine whether concurrent exposure to PM2.5 and ozone induces greater adverse cardiovascular effects than exposure to either pollutant alone. U.S. EPA has recently adopted a multipollutant perspective, particularly with reference to NAAQS implementation and development of emissions reduction regulations. Because PM2.5 and ozone have been identified as responsible for the majority of adverse health effects associated with air pollution exposure, this project will focus on these two pollutants. The results of this study could help guide development of more efficient future emission control strategies and methodologies that reduce emissions of more than one pollutant simultaneously, while also contributing to development of health protective NAAQS.

Finally, this study could potentially leverage findings from previous ARB-funded studies, for example by using established analytical techniques, exposure models, or baseline data from individual component studies.

III. Scope of Work

Submissions must provide the following elements:

- An hypothesized mechanistic pathway for PM2.5- and ozone-induced cardiovascular dysfunction. Submitters must include a detailed description or diagram of the hypothesized pathway, and a literature review supporting the hypothesis. They must also clearly indicate the parts of the mechanistic pathway their proposed study will address.
- Description of, and justification for, the proposed animal model(s). This section should also provide the number of groups of animals proposed, and the number of animals in each group.
- Description of the proposed exposure protocol using PM2.5, ozone and a mixture of both. The description should include method, duration, dose/concentration, and number of days of exposure.
- Description of the proposed endpoints and the methods for measuring them. Proposed endpoints may be biochemical and/or physiological, but must address the specific hypothesis proposed, and be oriented toward demonstrating the influence of PM2.5 and ozone exposure on cardiac function.
- Description of the statistical methodologies to be used to analyze the results. This section should include the specific statistical tests to be employed, and estimates of the statistical power of the analyses. Submitters should also describe the methods to be used to determine whether or not the data are normally distributed, and if not, what alternative statistical methods will be used. Evidence for participation of, or consultation with, a biostatistician is also required.

IV. Deliverables

- Quarterly Progress Reports
- Final Report
- Additional deliverables to be determined in consultation with ARB

V. Timeline

It is anticipated this project will be completed in 36 months from the start date. Note that this allows 30 months for completion of all work through delivery of a draft final report; the last 6 months are for ARB and RSC review of the draft final report and delivery of a revised final report and data files to the ARB.