State of California
AIR RESOURCES BOARD

Co-Exposure to Particulate Matter and Ozone: Pulmonary C-Fiber and Platelet in Activation Decreased Heart Rate Variability

RESEARCH PROPOSAL

Resolution 13-26

June 27, 2013

Agenda Item No.: 13-6-1

WHEREAS, the Air Resources Board (ARB or Board) has been directed to carry out an effective research program in conjunction with its efforts to combat air pollution, pursuant to Health and Safety Code sections 39700 through 39705;

WHEREAS, a research proposal, number 2763-276, entitled "Co-Exposure to Particulate Matter and Ozone: Pulmonary C-Fiber and Platelet Activation in Decreased Heart Rate Variability," has been submitted by the University of California, Davis; and

WHEREAS, in accordance with Health and Safety Code section 39705, the Research Screening Committee has reviewed and recommends for funding:

> Proposal Number 2763-276 entitled Co-Exposure to Particulate Matter and Ozone: Pulmonary C-Fiber and Platelet Activation in Decreased Heart Rate Variability," submitted by the University of California, Davis for a total amount not to exceed $600,782.

WHEREAS, the Research Division staff has reviewed Proposal Number 2763-276 and finds that in accordance with Health and Safety Code section 39701, the results of this study will improve understanding of the mechanisms and potential interactions between ozone- and PM2.5-induced effects on the cardiovascular system and can inform setting health protective ambient air quality standards.

NOW, THEREFORE BE IT RESOLVED that the Air Resources Board, pursuant to the authority granted by Health and Safety Code section 39703, hereby accepts the recommendations of the Research Screening Committee and Research Division staff and approves the following:

> Proposal Number 2763-276 entitled "Co-Exposure to Particulate Matter and Ozone: Pulmonary C-Fiber and Platelet Activation in Decreased Heart Rate Variability" submitted by the University of California, Davis not to exceed $600,782.

BE IT FURTHER RESOLVED that the Executive Officer is hereby authorized to initiate administrative procedures and execute all necessary documents and contracts for the research effort proposed herein, and as described in Attachment A, in an amount not to exceed $600,782.

I hereby certify that the above is a true and correct copy of Resolution 13-26, as adopted by the Air Resources Board.

Tracy Jensen

Tracy Jensen, Clerk of the Board

ATTACHMENT A

"Co-Exposure to Particulate Matter and Ozone: Pulmonary C-Fiber and Platelet Activation in Decreased Heart Rate Variability"

Background

Epidemiologic studies have consistently shown, contrary to expectations, that particulate matter (PM)-related health effects on the cardiovascular system are larger and more clinically significant than those on the respiratory system. Although these studies are the basis for the fine particulate matter (PM2.5) National Ambient Air Quality Standards (NAAQS), there are substantial gaps and uncertainties in our understanding of the biological mechanisms through which inhaled PM2.5 influences heart function. In contrast to the PM2.5 NAAQS, 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 also have cardiovascular effects, which have not been appreciated to date; however, little is known about potential biological mechanisms for these cardiovascular effects. More importantly, from a public health perspective, very little is known about whether or not there are interactions or synergies between mechanisms with concomitant exposure to ozone and PM2.5.

Objective

The objective of this study is to examine a hypothesized mechanistic pathway for the cardiovascular effects of ozone and PM2.5, and to examine whether the effects of co-exposure to these pollutants are additive or synergistic in laboratory animals.

Methods

The proposed experiments will address the hypothesis that co-exposure to PM2.5 and ozone leads to synergistic activation of pulmonary C-fibers and platelets. This activation will lead to alteration of autonomic nervous system control of the heart, which will be manifested as decreased heart rate variability (HRV). Further, concomitant exposure to PM2.5 and ozone is expected to lead to greater adverse responses in all endpoints in spontaneously hypertensive (SH) rats, compared to normal rats.

Platelet-related endpoints will include platelet activation, formation of platelet-monocyte and platelet-leukocyte aggregates, microthrombi, and the release of platelet-derived bioactive lipids. The influence of pulmonary C-fiber activation will be assessed by examining breathing pattern and heart rate variability, release of thromboxane-2 and serotonin, as well as immunocytochemical analyses of heart and lung tissues. Pathological analyses of lung tissues will include airway epithelial changes, extent of inflammation, number of immune cells in the lung inflammatory exudate, density of visible particles, vascular wall changes in the pulmonary arterioles, and density of platelets in arteriolar lumens. Pulmonary arteriolar constriction will be evaluated through assessment of vascular wall thickness. Heart tissues will be evaluated for

myocyte and vascular lesions. All endpoints will be examined using well established, standard methods.

Expected Results
The resulting data will help to elucidate the specific roles of platelets, the vascular endothelium, pulmonary C-fibers, and pulmonary vascular vasoconstriction in altering cardiovascular function. The results of this study will advance our understanding of the biological mechanisms mediating the cardiovascular and pulmonary effects of multi-pollutant exposures, and how different mechanistic pathways converge to induce adverse health effects.

Significance to the Board
The results of this study will improve understanding of the mechanisms and potential interactions between ozone- and PM2.5-induced effects on the cardiovascular system and can inform setting health protective ambient air quality standards.

Contractor:
University of California, Davis

Contract Period:
36 months

Principal Investigator:
Fern Tablin, VMD, Ph.D.

Contract Amount:
$600,782

Basis for Indirect Cost Rate:
The State and the University of California, Davis have agreed to a 10 percent indirect cost rate.

Past Experience with the Principal Investigator:
The Principal Investigator (PI) has been PI or Co-PI on three previous ARB-funded projects. Each project was successfully completed within the time and budget allotted. The results have been useful to the State in assessing the health effects of particulate matter exposure, and they have been published in quality journals.

Prior Research Division Funding to University of California, Davis:

Year	2012	2011	2010
Funding	$4,949,363	$1,394,560	$508,267

BUDGET SUMMARY

University of California, Davis

"Co-Exposure to Particulate Matter and Ozone: Pulmonary C-Fiber and Platelet Activation in Decreased Heart Rate Variability"

DIRECT COSTS AND BENEFITS				
1.	Labor and Employee Fringe Benefits	$	414,531	
2.	Subcontractors	$	0	
3.	Equipment	$	22,304	
4.	Travel and Subsistence	$	6,000	
5.	Electronic Data Processing	$	0	
6.	Reproduction/Publication	$	0	
7.	Mail and Phone	$	0	
8.	Supplies	$	99,358[1]	
9.	Analyses	$	6,000	
10.	Miscellaneous	$	0	
	Total Direct Costs			$548,193
INDIRECT COSTS				
1.	Overhead	$	52,589	
2.	General and Administrative Expenses	$	0	
3.	Other Indirect Costs	$	0	
4.	Fee or Profit	$	0	
	Total Indirect Costs			$ 52,589
TOTAL PROJECT COSTS				**$600,782**

[1] Supplies include the experimental model, and necessary supplies and materials to determine the effects of the exposures on the selected endpoints. The main items included in this category are rats, microscopy charges for histopathology, supplies for tissue and slide preparation, chemical reagents and antibodies, bioassay analysis kits, and general disposable laboratory plastic ware.