State of California
AIR RESOURCES BOARD

Cardiovascular Effects of Multi-Pollutant Exposure: Mechanisms and Interactions

RESEARCH PROPOSAL

Resolution 13-24

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 2764-276, entitled "Cardiovascular Effects of Multi-Pollutant Exposure: Mechanisms and Interactions" has been submitted by the University of California, Irvine; and

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

> Proposal Number 2764-276 entitled "Cardiovascular Effects of Multi-Pollutant Exposure: Mechanisms and Interactions" submitted by the University of California, Irvine, for a total amount not to exceed $740,429.

WHEREAS, THE Research Division staff has reviewed Proposal Number 2764-276 and finds that in accordance with Health and Safety Code section 39701, the results of the study will provide insight into: (1) the relative importance of primary versus secondary PM, (2) the role of semi-volatile components in the PM2.5 fraction, and (3) the extent of interaction or synergy between PM2.5 and ozone for development and progression of atherosclerosis.

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 2764-276 entitled "Cardiovascular Effects of Multi-Pollutant Exposure: Mechanisms and Interactions" submitted by the University of California, Irvine not to exceed $740,429.

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 $740,429.

I hereby certify that the above is a true and correct copy of Resolution 13-24, as adopted by the Air Resources Board.

/s/

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Tracy Jensen, Clerk of the Board

ATTACHMENT A

"Cardiovascular Effects of Multi-Pollutant Exposure: Mechanisms and Interactions"

Background

Previous research by this investigator and others has demonstrated that when mice from a strain having genetic impairment of lipid metabolism and increased susceptibility to development of atherosclerotic plaques are exposed daily for two months to concentrated ambient particles (CAPs, fine and ultrafine) plaque development is accelerated. Also, there is a more rapid progression of atherosclerosis than in the same strain of mice exposed to clean air. The investigator's recently completed ARB-funded study extended previous findings by examining the role of particle associated semi-volatile compounds in atherosclerotic progression. The results suggested that much of the atherosclerotic potential of ultrafine particles (UFP) lies in the semi-volatile constituents, in that removal of the semi-volatiles from the aerosol blocked acceleration of atherosclerotic plaque development. To date no studies have investigated the atherosclerotic potential of O_3 exposure, concurrent exposure to PM2.5 and O_3, or the role of PM2.5-associated semi-volatile compounds in conjunction with ozone exposure.

Objective

The objective of this study is to investigate the atherosclerotic potential of ambient PM2.5 from the Irvine, California area. Both intact particles and particles denuded of the semi-volatile constituents of PM2.5 will be used with and without concurrent exposure to ozone in a mouse model of atherosclerosis. The principal goals are to elucidate the role of the semi-volatile components of PM2.5 and ozone in the progression of atherosclerosis, and the extent to which concomitant ozone exposure interacts with disease progression.

Methods

Acute and chronic cardiopulmonary inflammation, vascular injury, and myocardial function will be examined using genetically susceptible mice implanted with electrocardiogram (ECG) telemetry devices. There will be six experiments, each with several exposure conditions. Experiment 1: filtered air, CAPs, CAPs + 0.2 ppm ozone, and 0.2 ppm ozone without CAPs during a period of high ambient photochemical activity (ozone 0.07-0.12 ppm). Experiment 2: filtered air, CAPs, CAPs + 0.2 ppm ozone, and 0.2 ppm ozone without CAPs during a period of low ambient photochemical activity (ozone 0.03 – 0.06 ppm). Experiment 3: filtered air, 0.2 ppm ozone, denuded CAPs, and 0.2 ppm ozone + denuded CAPs during a period of high ambient photochemical activity (ozone 0.07-0.12 ppm). Experiment 4: filtered air, 0.2 ppm ozone, denuded CAPs, and 0.2 ppm O_3 + denuded CAPs during a period of low ambient photochemical activity (ozone 0.03 – 0.06 ppm). Experiment 5: filtered air, 0.2 ppm ozone, volatile phase gases, and the volatile phase gases + ozone during a period of high ambient photochemical activity (ozone 0.07-0.12 ppm). Experiment 6: filtered air, 0.2 ppm ozone, volatile phase gases, and the volatile phase gases + ozone during a period of low ambient photochemical activity (ozone 0.03-0.06 ppm).

Groups of 16 animals will be exposed for five hours per day, 4 days per week for 8 weeks to each of the exposure conditions using an in-vivo rodent exposure system, in combination with a VACES particle concentrator that incorporates a thermal denuder.

Endpoints will include markers of inflammation, histological examinations for evidence of vascular and myocardial pathology, ventricular hypertrophy and biomarkers of lipid, protein and DNA oxidation, all using standard methods. The *in vivo* biological responses will be correlated with physical and chemical composition of the particles and the *in vitro* potential of these particles to produce free radicals and induce cytotoxicity.

Expected Results
The results of the study will provide insight into: (1) the relative importance of primary versus secondary PM, (2) the role of semi-volatile components in the PM2.5 fraction, and (3) the extent of interaction or synergy between PM2.5 and ozone for development and progression of atherosclerosis.

Significance to the Board
People are typically exposed to mixtures of air pollution, in contrast to the single pollutant approach used with National Ambient Air Quality Standard development. The United States Environmental Protection Agency (U.S. EPA) has recently adopted a multi-pollutant perspective, particularly with reference to NAAQS implementation and development of emissions reduction regulations. The results of this project will contribute to ARB's and U.S. EPA's efforts to strengthen the biological support for epidemiological associations between PM2.5 exposure and adverse health effects. The results will also address concerns about potential confounding of ozone effects by concomitant PM2.5 exposure that add uncertainty to interpretation of ozone epidemiological studies. This, in turn, will contribute to ensuring that future revisions to the PM and ozone NAAQS are adequately health protective.

Contractor:
University of California, Irvine

Contract Period:
48 months

Principal Investigator:
Michael T. Kleinman, Ph.D.

Contract Amount:
$740,429

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

Past Experience with the Principal Investigator:
This investigator has successfully completed many ARB-funded projects over the past 15 years.

Prior Research Division Funding to the University of California, Irvine:

Year	2012	2011	2010
Funding	$519,997	$285,000	$274,931

B U D G E T S U M M A R Y

University of California, Irvine

"Cardiovascular Effects of Multi-Pollutant Exposure: Mechanisms and Interactions"

DIRECT COSTS AND BENEFITS				
1.	Labor and Employee Fringe Benefits	$	495,827	
2.	Subcontractors	$	0	
3.	Equipment	$	20,000	
4.	Travel and Subsistence	$	2,794	
5.	Electronic Data Processing	$	0	
6.	Reproduction/Publication	$	1,000	
7.	Mail and Phone	$	1,000	
8.	Supplies	$	122,925[1]	
9.	Analyses	$	20,000	
10.	Miscellaneous	$	11,389	
	Total Direct Costs			$674,935
INDIRECT COSTS				
1.	Overhead	$	0	
2.	General and Administrative Expenses	$	65,494	
3.	Other Indirect Costs	$	0	
4.	Fee or Profit	$	0	
	Total Indirect Costs			$ 65,494
TOTAL PROJECT COSTS				**$740,429**

[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 mice, ECG telemetry implants, filters for air quality analysis, supplies for tissue and slide preparation, chemical reagents and antibodies, bioassay analysis kits, and general disposable laboratory plastic ware.