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Tri City Concentrated Ambient Particle Study (Tri City CAPS)

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DOE-NETL Kickoff Meeting

September 8, 2005

Overview

- Introduction
- Background and Motivation
 - PM sources/components
 - Power plant- and traffic-derived PM
 - Concentrated ambient particles (CAPs)
- Study Objectives
- Study Methods
- Pilot Study Results: Detroit, Summer 2004
- Project Scope of Work
- Project Administration
 - Team
 - Schedule
 - Deliverables

Tri City Concentrated Ambient Particle Study

Cardiopulmonary Toxicity Induced by Ambient Particulate Matter: Inhalation Toxicology Studies Using a Mobile Particle Concentrator in Regions Dominated by Power Plant and Mobile Source Emissions

Study Basics

- EPRI Project Manager: Dr. Annette Rohr
- DOE Project Manager: Bill Aljoe
- Key Subcontractors:
 - Michigan State University (Dr. Jack Harkema)
 - University of Michigan (Dr. Jerry Keeler)
- Contract Period: July 12, 2005 to July 11, 2009

Tri City CAPS: Overview

- Primary Objective: Evaluate the potential for adverse cardiopulmonary effects from exposure to environmentally relevant coal-fired power plant and traffic-related PM
- Approach:
 - Station portable ambient particle concentrator at 3 locations during 2 seasons
 - Expose rats to CAPs for 8 hours/day for 13 days
 - Evaluate cardiopulmonary endpoints
 - Link responses to PM sources and components
- Status:
 - Fieldwork complete at first location/season; data analysis underway
 - Season 2 fieldwork in January 2006

Background and Motivation

- **Key issue:** increase our understanding of the *sources* and *components* of air pollution responsible for health effects.
- USEPA has a mass-based PM_{2.5} standard, but it is unlikely that all components are equally harmful

Toxicology: PM Sources/Components

- Single component studies:
 - **Sulfates/nitrates**: little effect in animals/human volunteers
 - **Acid aerosols**: some strong acids (eg. H_2SO_4) can cause pulmonary effects at high concentrations
 - **Metals**: Mostly instillation studies; Fe, V, Ni appear most potent
 - **Organic compounds**: Comprise 10-60% of PM mass, but little is known about health effects
 - **Ultrafines** ($d < 0.1 \mu\text{m}$): increased surface area
- Source-focused studies:
 - Exposure to specific sources: wood smoke, coal fly ash, diesel/gasoline exhaust particles
 - Factor analysis: Has not been used widely in toxicology; applied to CAPs data

Component-Focused Epidemiology Studies: Latest ARIES Findings

Cardiovascular Results (25 months)

	Unscheduled physician visits: Total CVD	Total CVD	ICD Response	CVD Mortality
Ozone	*			
NO ₂	*			
CO	*			
SO ₂				
OHC				
PM ₁₀				
PM _{coarse}				
PM _{2.5}				
Ultrafines				
SO ₄				
Acidity				
EC				
OC				
Metals				

Significant +ve association
 No significant association

* lag 3-5 days

Toxicity of Power Plant-Derived PM

- Two sources of information:
 - Studies examining the health effects of components of coal combustion emissions (e.g., sulfate, sulfuric acid)
 - Studies examining the health effects of coal fly ash
 - Primary CFA collected from ESPs
 - Inhalation exposure studies
- No information on the toxicity of secondary particles formed through SO₂ conversion in the atmosphere
- No assessment of the toxicity of actual plant emissions
- TERESA (cofunded by DOE-NETL) is evaluating power plant- and traffic-derived PM

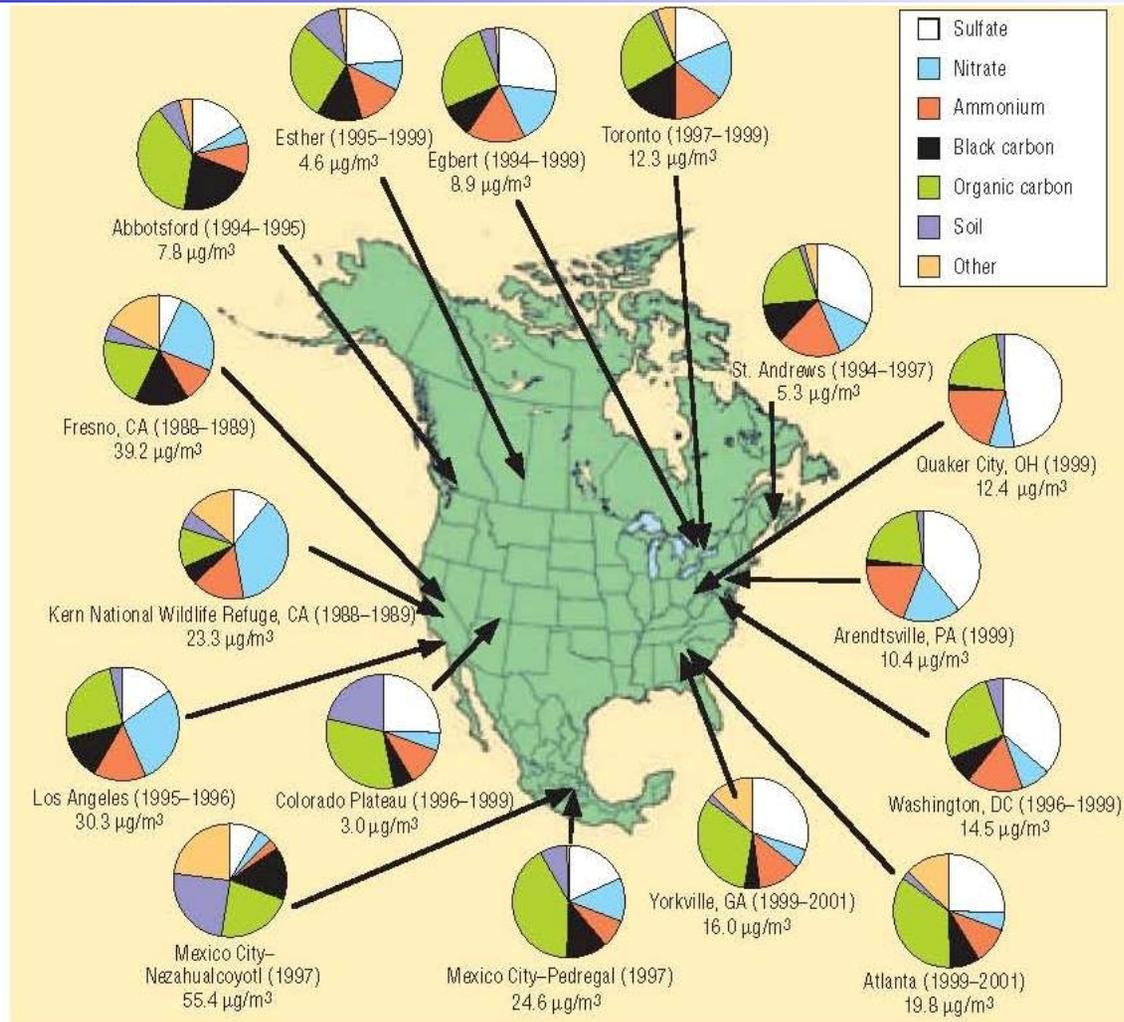
Toxicity of Traffic-Derived PM

- Many published studies on the toxicity of diesel exhaust particles (DEP)
- Much work on mutagenic potential, given PAH content
- Studies assessing allergic effects
- Little in the way of cardiovascular effects

Ambient Particle Concentrators

- Developed in mid-1990s
- Higher exposure concentrations (30 – 300X)
- Real-life particles
- Gases not concentrated
- Via inhalation
- Variable composition allows for “sub-experiments”

PM Composition Differs Markedly



From Samet et al., "Research Priorities for Airborne Particulate Matter in the United States", *ES&T* 39:299A-304A

Previous CAPs Studies

- MSU: pulmonary inflammation, epithelial cell remodeling, activation of inflammatory pathways in allergic rodents
- Harvard: pulmonary inflammation in bronchitic rats, changes in cardiac function in dogs, oxidative stress in rats
- NYU: changes in blood cytology and cardiac function in rats
- EPA (NC): increased neutrophils in BAL fluid, increased blood fibrinogen in humans
- Component/source analysis: Al/Si, Br/Pb, V/Ni, and S factors; road dust (Si, Al, Ca, Fe); EC, OC, Si,, Al, V, Br, Pb, Fe, Mn, Cu, Zn, Ti

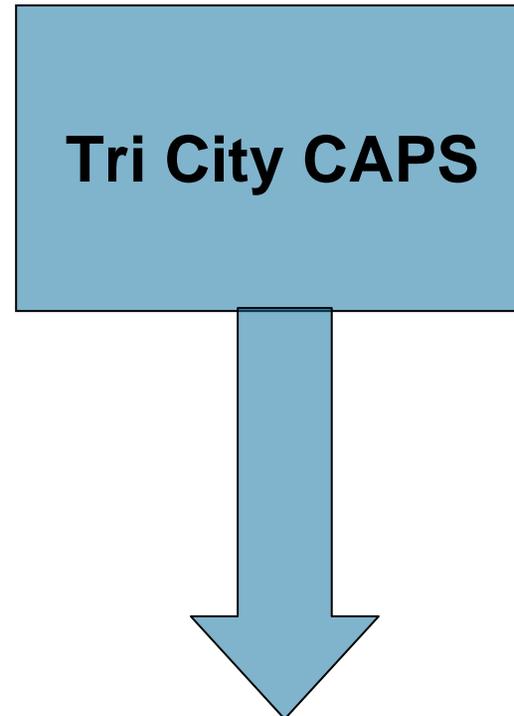
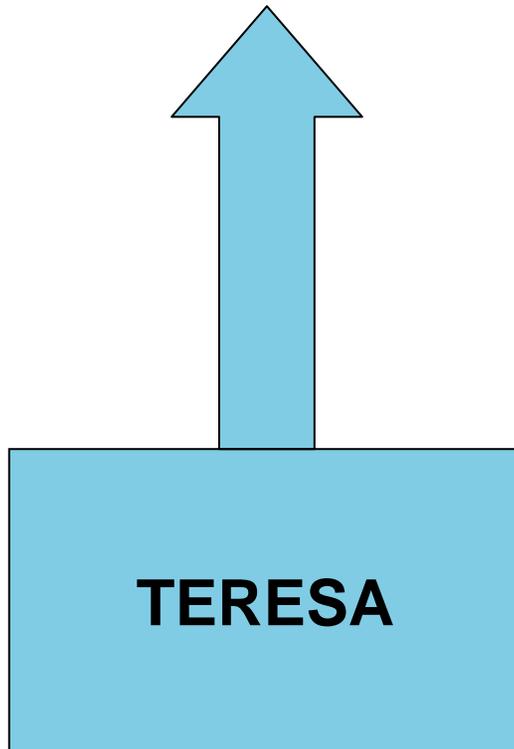
Why is Tri City CAPS Important?

- Highly innovative
 - First time a portable concentrator has been used for this application
 - Source attribution
- Enables us to tease out effects of different sources and components using real particles

First time ambient PM dominated by different sources has been evaluated in inhalation toxicology studies in a field setting

Complementary Approach to TERESA

Bottom-up approach
(start with controlled
sources)



Top-down approach
(start with ambient PM,
tease out effects of
specific sources)

Tri City CAPS Complements and Extends Previous CAPs Research

- Mobile concentrator: Almost all previous CAPs studies have used stationary concentrators, limiting study locations
- Exposure characterization: Many previous CAPs studies have not included extensive exposure characterization – no assessment of PM components
- Source apportionment: Very limited source attribution to date
- Rodent models proposed have been used in other CAPs/PM studies to aid direct comparison
- Toxicological endpoints to be studied are similar, if not identical, to other CAPs studies

Objectives

Primary Goal:

- **Evaluate the potential for adverse cardiopulmonary effects from ambient exposure to realistic coal-fired power plant and traffic-related PM**

Specific Objectives:

- Provide insight into toxicological mechanisms of PM-induced cardiopulmonary effects
- Generate toxicological data to directly correspond to epidemiology and exposure assessment data from concurrent studies being conducted at one of the project locations

Specific Aims

- Specific Aim 1:** Evaluate the cardiopulmonary toxicity of realistic coal combustion derived PM_{2.5} in normal and compromised rats
- Specific Aim 2:** Determine the relative cardiopulmonary toxicity of coal combustion-related PM_{2.5} and PM_{2.5} from other sources
- Specific Aim 3:** Identify the physical and/or chemical components of PM_{2.5} responsible for any cardiopulmonary effects observed
- Specific Aim 4:** Provide insight into the specific physiological mechanisms by which PM_{2.5} derived from coal-fired power plant emissions may induce cardiopulmonary effects through the use of both normal and susceptible rodent models
- Specific Aim 5:** Provide corresponding animal/toxicological data for direct comparison with a human health/exposure study being carried out at one of the study locations

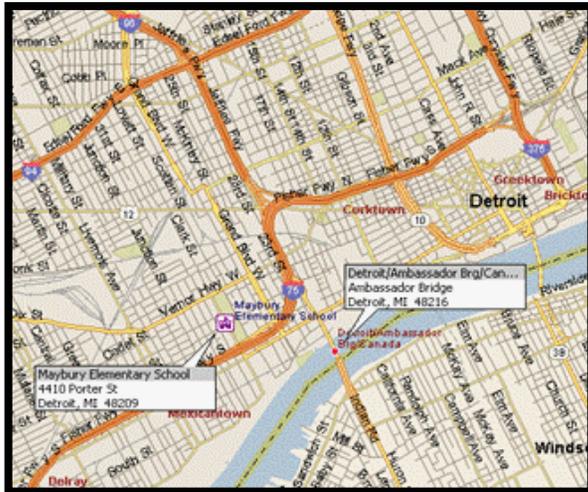
Methods

- Site selection
- Mobile toxicological laboratory
- Concentration of ambient particles
- Exposure characterization
- Source apportionment
- Animal exposures
- Toxicological assessment
- Data analysis

Location of Study Sites

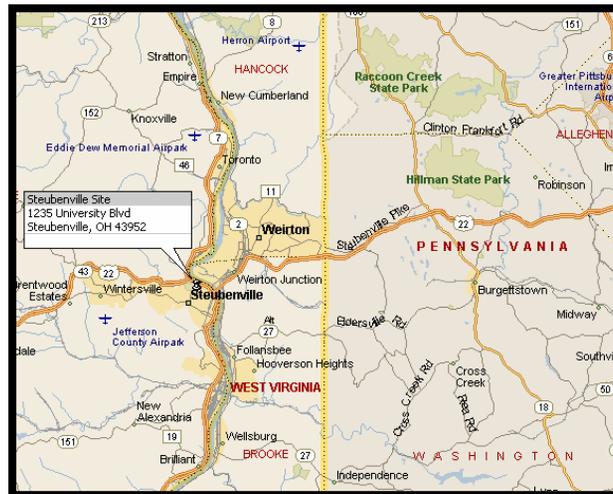
Downtown Detroit, MI

Dominated by diesel and gasoline emission-derived PM



Steubenville, OH

Dominated by power plant and local industrial emissions



Maurice K. Goddard State Park, NW PA

Rural site; dominated by power plant emissions



Downtown Detroit: Maybury Elementary School

- Located 0.5 mile from the Ambassador Bridge and 1 block from I-75
- History of toxicology/air quality monitoring work
- Previous epidemiological findings
- Linkage with DEARS (Detroit Exposure and Aerosol Research Study) and the Detroit Cardiovascular Health Study
- Straightforward site access, approval in place

Steubenville: Franciscan University of Steubenville

- Located in a highly industrialized area including coke plants, metal smelting and processing plants, and coal-fired power plants
- Location of a number of field studies, including the Harvard Six Cities Study and ongoing studies being carried out by the Harvard School of Public Health, the University of Michigan, and CONSOL
- Straightforward site access; site currently being used by Dr. Keeler and site approval in place

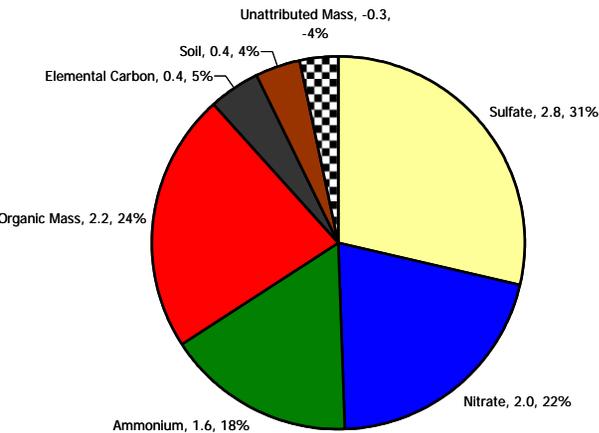
Northwest PA: Maurice K. Goddard State Park

- Located in an area heavily impacted by regional sulfate and power plant emissions
- Upwind of Pittsburgh: low urban impact and no industry in the immediate vicinity of the site
- IMPROVE (Interagency Monitoring of Protected Visual Environments) monitoring location; PM compositional data are readily available
- Straightforward site access

Regional Differences in PM Composition

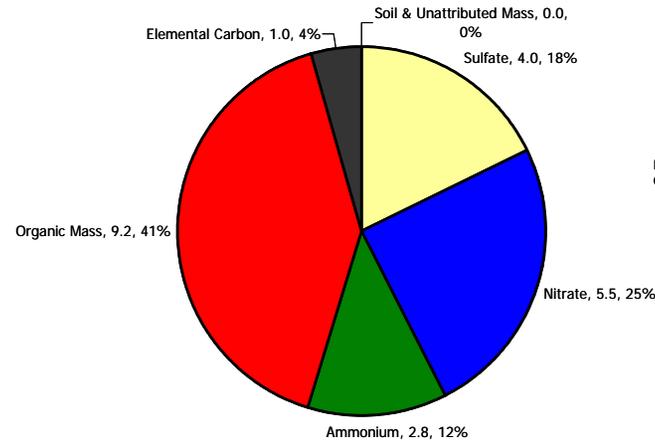
Maurice K. Goddard Park, PA

Winter 2002



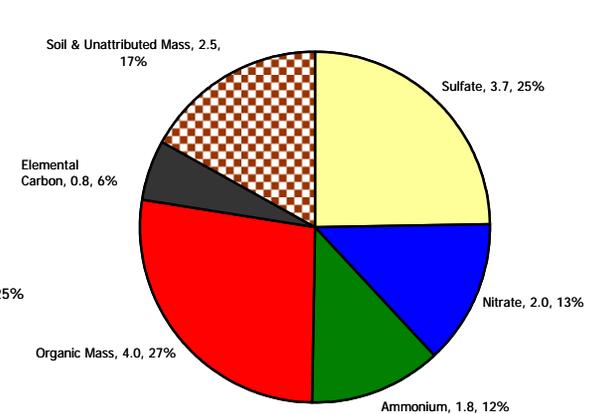
Detroit, MI

Winter 2003



Steubenville, OH

Winter 2001-2002



Yellow = Sulfate

Red = Organic Carbon

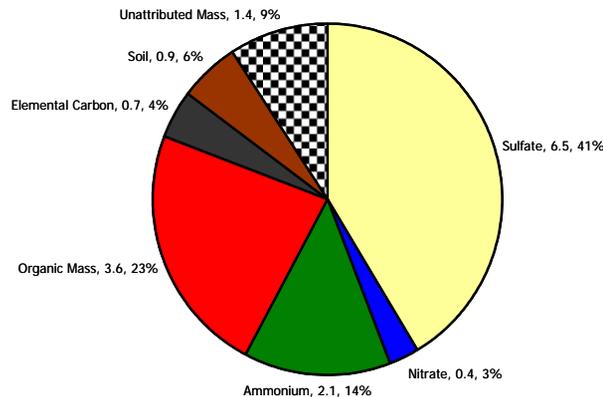
Black = Elemental Carbon

Blue = Nitrate

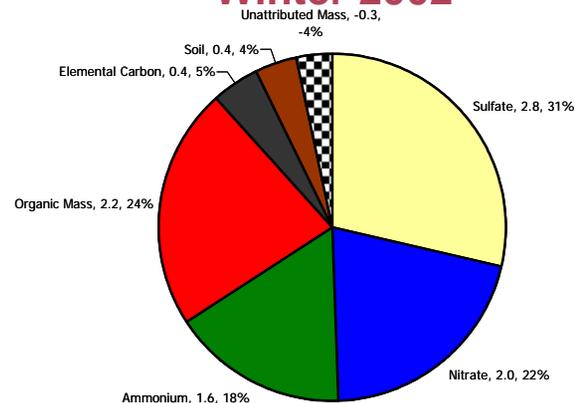
Summer and Winter Sampling Seasons

- Different meteorological regimes
- Different wind patterns can transport PM/precursors from different geographical regions
- Warm temperatures can influence formation of photochemical oxidants (e.g., ozone), enhancing formation of secondary particles
- Cooler temperatures favor condensation of ammonia and nitric acid to form ammonium nitrate

**Maurice K. Goddard Park
Summer 2002**



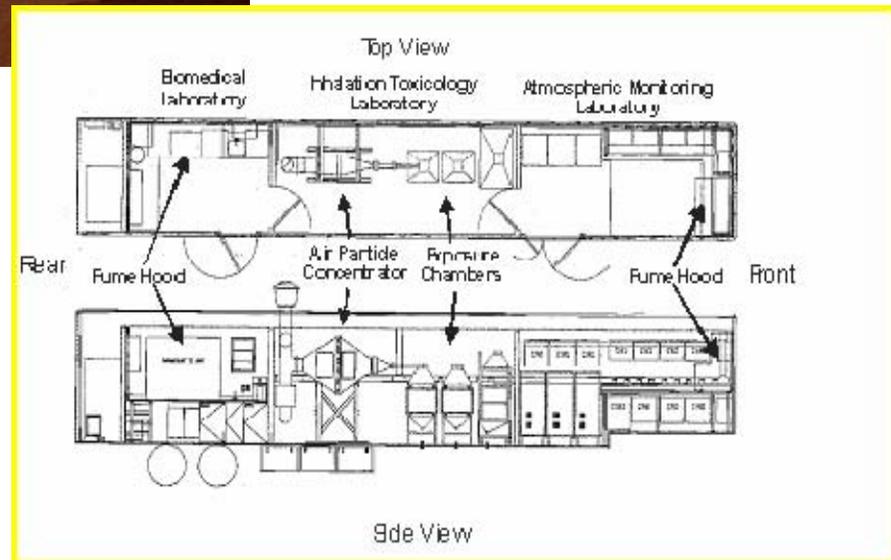
**Maurice K. Goddard Park,
Winter 2002**



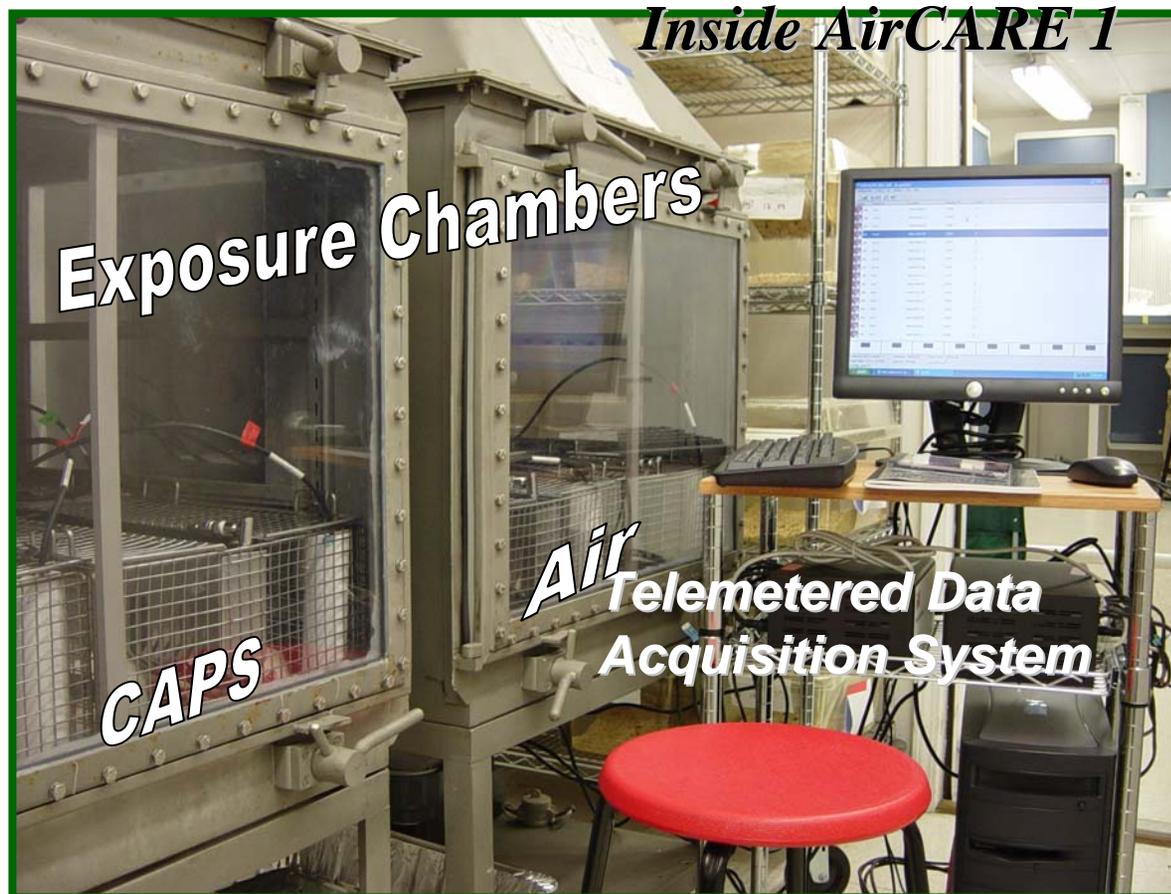
Mobile Toxicological Laboratory: AirCARE1

- Only one of its kind in the US
- Specialized 53-ft long transport trailer with >400 sq. ft of laboratory floor space
- Extensive instrumentation for air quality and meteorological parameter monitoring
- Whole-body inhalation exposure chambers attached to a Harvard/EPA fine ambient air particulate concentrator
- Freezer, refrigerator, bench space, fume hood, and water distiller
- On-board electric power, water & HVAC systems

AirCARE1



AirCARE1: Exposure Chambers and Telemetry Hardware



Concentration of Ambient Particles

- Harvard/EPA Ambient Fine Particle Concentrator (HAPC)
- Series of three virtual impactors; output flow from the third stage of ~50 LPM (15 LPM for characterization, 35 LPM to exposure chambers)
- PM_{2.5} concentrated approximately 30X without altering the physicochemical characteristics of the aerosol

Exposure Characterization

- Acidity
- Sulfate
- Nitrate
- Ammonium ion
- Elemental carbon
- Organic carbon
- Elements (total and water soluble)
- CO
- NO_x
- SO₂
- Ozone

PM Measurements and Analyses

Measurement	PM Property	Sampling Media	Sample Duration (hr)	Analytical Method
TEOM	Mass	-	Continuous	
APS 3320	Size (0.5-20 μm)	-	Continuous	
Aethelometer	Black carbon	-	Continuous	
SMPS 3936	Size (0.01-.6 μm)	-	Continuous	-
MOI	Size (10 stages)/Mass & Trace elements	Teflon	8	Gravimetric/ICP-MS
Filter (PM _{2.5})	Trace elements	Teflon	8	Gravimetric/ICP-MS
Filter (PM _{2.5})	Soluble trace elements	Teflon	8	Gravimetric/ICP-MS
PM _{2.5}	Trace elements		Semi-continuous	Slurry sampler
Annular Denuder-Filter Pack System	Acid gases & aerosols and major ions	Teflon/Glass /denuders	8	IC/pH
Filter	Elemental & organic carbon	Quartz	8	TOA

High Frequency Aerosol Slurry Sampler

- Allows for 30-minute (semicontinuous) collection of elemental data
- Particles are grown by condensation of water vapor to allow separation from the air stream
- Use of high-resolution ICP-MS analysis to perform sub-hourly multi-elemental analysis of PM_{2.5}
- Samples analyzed for a suite of 20+ trace elements (including As, Se, Pb, Zn, Cu, Mg, Mn, Al, V, Ni, Co, etc.), and major ions

Source Apportionment

- Critical part of Project: will enable us to determine how different PM sources contribute to health effects
- Use unique high temporal resolution (30 min) aerosol composition (trace elements, sulfate, nitrate, EC, OC), size, and gaseous pollutant dataset
- Multivariate receptor modeling techniques, e.g., Positive Matrix Factorization (PMF), UNMIX
- Identify source types with the chemical composition profile of each factor
- Use known indicator species or elemental ratios (EC/OC ratios also useful)
- HYSPLIT4 Model (Hybrid Single-Particle Lagrangian Integrated Trajectory) to calculate backward air mass trajectories from exposure sites

Potential Elemental Indicators

Source Category	Indicators
Motor Vehicles	Fe, Zn, Mn, Cu, Pb, S, EC, OC
Coal Combustion	S, Se, As
Oil Combustion	V, Ni
Waste Incinerators	Sb, Pb, Zn, Hg
Iron-Steel Production	Fe, Mn, Pb
Cu Smelters	Cu, Zn, As, Pb
Marine	Mg, Sr, Na
Soil	Al, Sc, Mn, Ti, Sr

Animal Exposures

- 11-12 week old male spontaneously hypertensive (SH) rats and Wistar-Kyoto (WKY) rats
- Surgically implanted with telemetry transmitters for continuous ECG/heart rate/temperature recording
- Two stainless steel whole body inhalation chambers: one for CAPs, one for air
- Eight SH and 8 WKY rats exposed in each chamber at the same time
- Expected CAPs concentrations: 300-700 $\mu\text{g}/\text{m}^3$
- 8 hour exposures for 13 consecutive days

Summary of Exposure Groups

Exposure Site	Rat Strain	Number of Animals in Each Exposure Group			
		Summer		Winter	
		CAPs	Filtered Air	CAPs	Filtered Air
Detroit, MI	SH <i>(compromised)</i>	8	8	8	8
	WKY <i>(healthy)</i>	8	8	8	8
Steubenville, OH	SH	8	8	8	8
	WKY	8	8	8	8
MK Goddard State Park, NW Pennsylvania	SH	8	8	8	8
	WKY	8	8	8	8

Selection of Toxicological Design

- *In vivo* assessments: more costly, but allow assessment of effects on the whole organism and consider natural exposure routes
- Inhalation exposures are more realistic than intratracheal instillation
- Rats are used extensively in inhalation toxicology research; straightforward procurement, care, and handling and inexpensive to purchase

Selection of Rodent Models

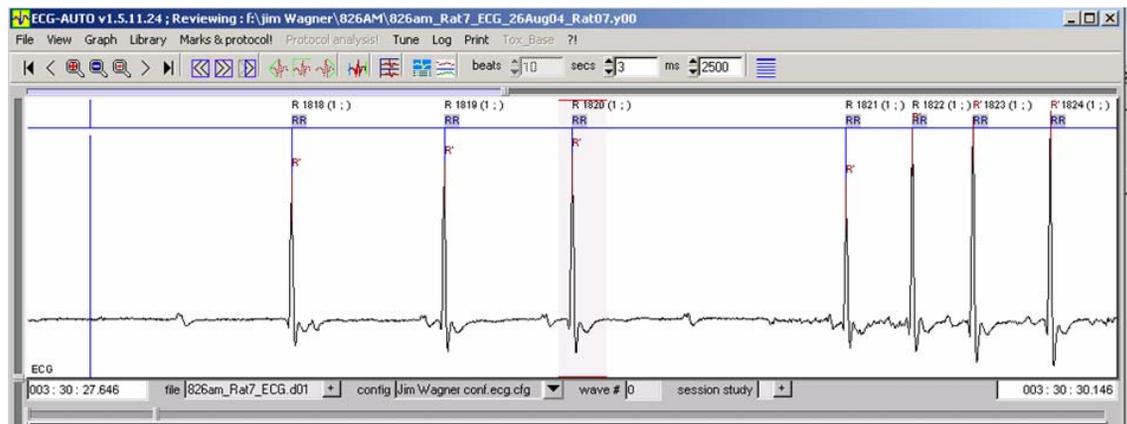
- Normal: Wistar-Kyoto (WKY)
- Compromised: Spontaneously Hypertensive (SH)
 - Derived from WKY (reference strain)
 - Model of human cardiovascular disease
 - Vascular resistance and activation of renin-angiotensin system
 - Cardiac hypertrophy (risk factor for adverse cardiac events)
 - Genetically predisposed to develop systemic hypertension
 - Pulmonary vascular changes and borderline pulmonary hypertension, increased plasma fibrinogen, immune cell activation, and systemic oxidative stress
 - Commonly used in PM research, along with pulmonary hypertensive, monocrotaline-treated (MCT) rat

Selection of Toxicological Endpoints

- Heart rate, temperature, heart rate variability (HRV)
 - HRV refers to variation in beat-to-beat intervals
 - A healthy heart in resting state has a large HRV
 - Decreased variability may indicate cardiac disease, e.g., reduced HRV known to be good predictor of poor clinical outcome after an MI
- Bronchoalveolar lavage
- Blood/plasma analysis
- Histopathology (heart/lung)

Telemetry and ECG Data Collection

- Continuous ECG readings before/during/after exposure
- Data analysis
 - Subjective ECG waveform review: Visual inspection for waveform morphology changes and ectopic beats
 - Automated ECG analysis: Physiostat® ECG Analysis Data Analysis Software
 - Heart Rate Variability: R-R intervals for all normal beats used to calculate time-domain (SDNN, rMSSD) and frequency domain (LF/HF) measures



Post-Exposure Endpoints

- Rats sacrificed 24 hours after last CAPs exposure
- Heart, airway tissues, and blood removed for analysis
- Complete clinical analysis of blood
- Standard techniques to identify alterations in cardiac and pulmonary tissues
- Bronchoalveolar lavage fluid (BALF) analyzed for cellularity and markers of inflammation and injury

Plasma Analysis

Plasma analysis for markers of inflammation/cardiac injury:

- Troponin I: Marker of myocardial injury and ischemia
- C-Reactive Protein: Index of inflammation; sensitive predictor of myocardial events and outcome
- Myeloperoxidase: Recently shown to be an even more sensitive predictor of myocardial events than CRP
- Asymmetric Dimethylarginine (ADMA): Healthy rats exposed to CAPs showed increases in plasma ADMA
 - High ADMA levels inhibit nitric oxide production
 - Could promote vasoconstriction and exacerbate hypertension in SH rats
 - Endpoint relevant to the Detroit Cardiovascular Health Study – brachial artery diameter

Data Analyses

- Descriptive analyses: type and magnitude of endpoints expressed as the mean group value \pm SE ($n = 8/\text{group}$)
- Analysis of variance (ANOVA) using the factors of exposure (air vs. CAPs) and strain (SH vs. WKY) for each site
- Correlations of CAPs characteristics with toxicological endpoints by Pearson Product Moment analysis within each strain, using CAPs mean values for entire 13-day exposures
- Correlations of CAPs physicochemical characteristics with ECG endpoints comparing mean 30-minute data points
- ECG endpoints collected during evening hours compared to mean CAPs data from the entire 8-hour exposure
- Time series analysis to detect potential lag effects of CAPs exposures with ECG metrics

Pilot Study, Maybury Elementary School, Detroit, August 15-29, 2004

- 13 day exposures
- 4 groups of animals: SH-CAPs, SH-sham, WKY-CAPs, WKY-sham
- $n=4$ for each group



Exposure Characterization: PM Components

CAPs concentrations 103–918 $\mu\text{g}/\text{m}^3$ (mean = 507 $\mu\text{g}/\text{m}^3$)

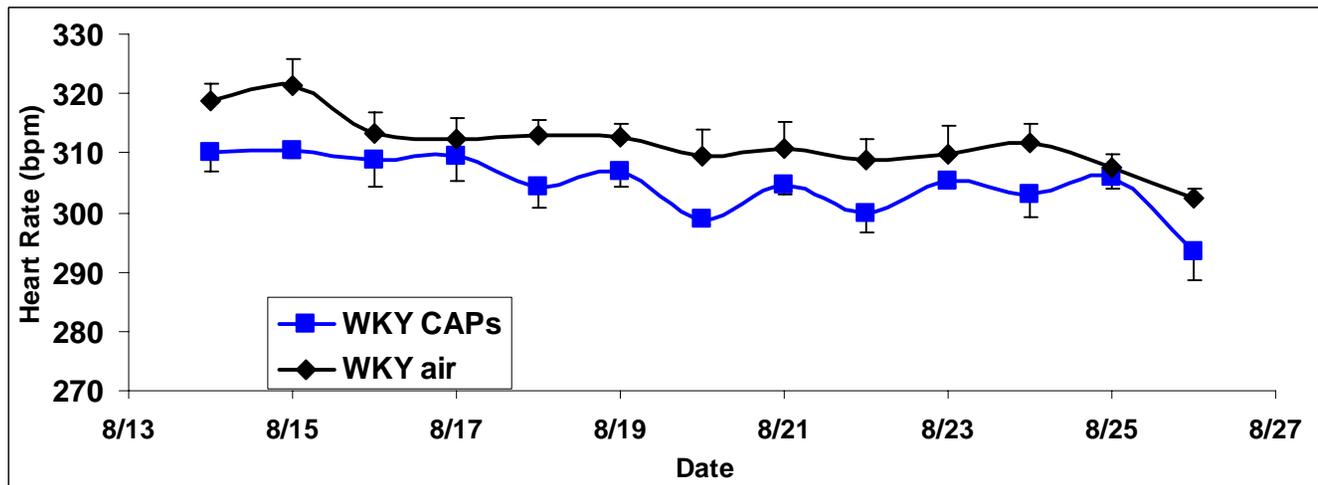
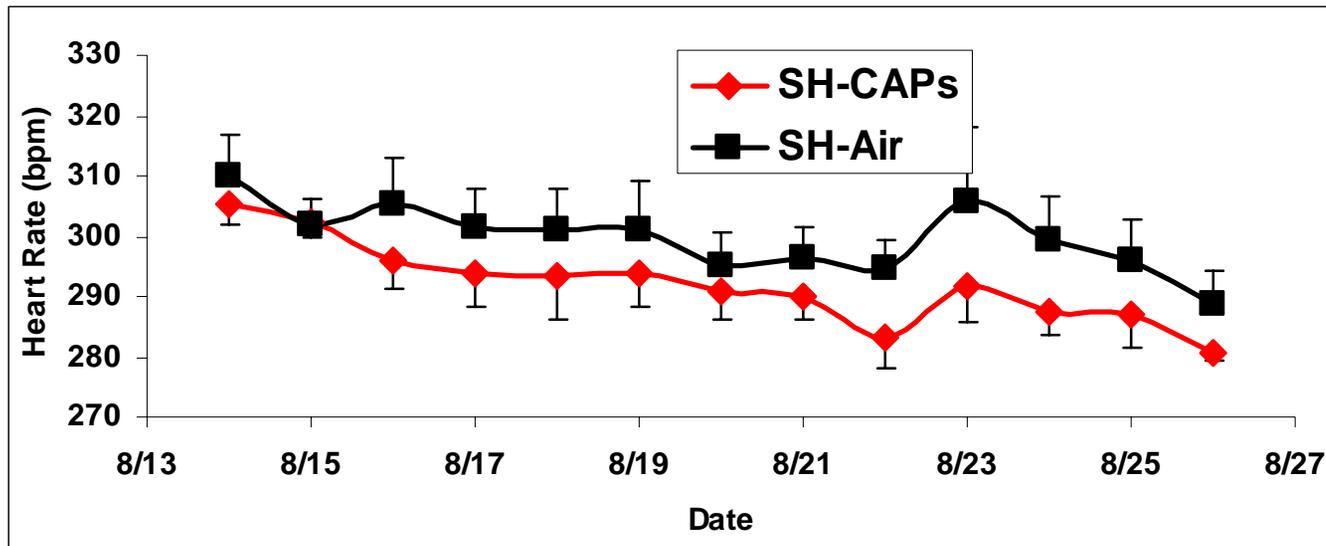
$\mu\text{g}/\text{m}^3$	8/14	8/15	8/16	8/17	8/18	8/19	8/20	8/21	8/22	8/23	8/24	8/25	8/26	Mean
Mass	253	270	560	481	918	226	522	103	311	721	817	541	869	507 ± 266
OC	102	85	246	194	266	157	166	49	102	205	199	106	192	159 ± 66
EC	6	3	24	19	12	8	19	5	11	12	6	5	8	11 ± 6
Sulfate	65	38	89	117	268	16	48	5	39	140	205	99	244	106 ± 86
Nitrate	8	9	45	26	53	9	44	3	14	23	18	22	22	23 ± 16
Ammon.	21	14	42	40	80	9	26	4	13	45	56	37	68	35 ± 23
Crustal	16	18	63	55	38	28	66	19	44	45	41	37	46	40 ± 16
Unid'd	35	102	51	31	201	0	153	18	89	251	291	236	288	134 ± 108

Exposure Characterization: Trace Elements (units of ng/m³)

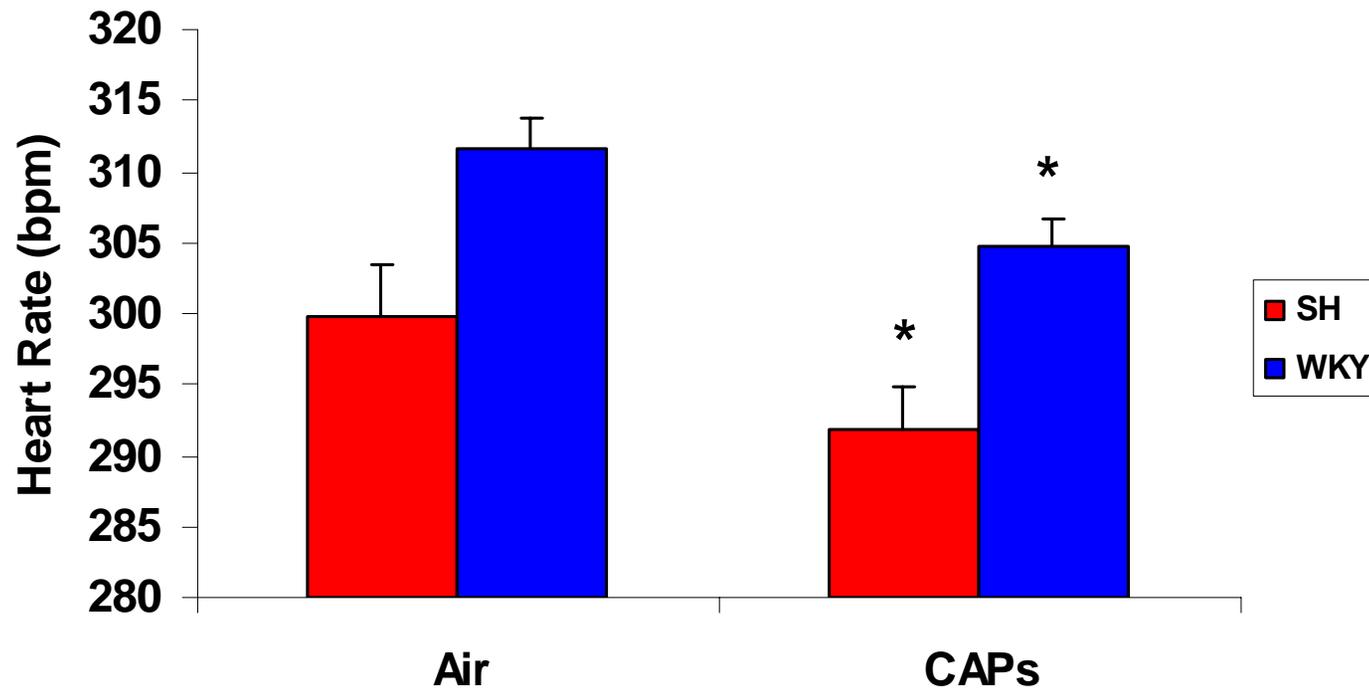
Rb	5	±	2
Sr	33	±	18
Mo	8	±	4
Cd	5	±	2
Ba	412	±	107
La	25.9	±	42.2
Ce	15.4	±	23.3
Sm	0.2	±	0.1
Pb	145	±	79
Mg	892	±	452
Al	2239	±	758
P	385	±	90

S	38868	±	29442
V	28	±	37
Cr	21	±	14
Mn	200	±	137
Fe	6517	±	4101
Co	1.4	±	0.6
Ni	16	±	12
Cu	91	±	43
Zn	955	±	672
As	24	±	18
Se	139	±	228

Heart Rate Decreases Over the 13-Day Exposure Period

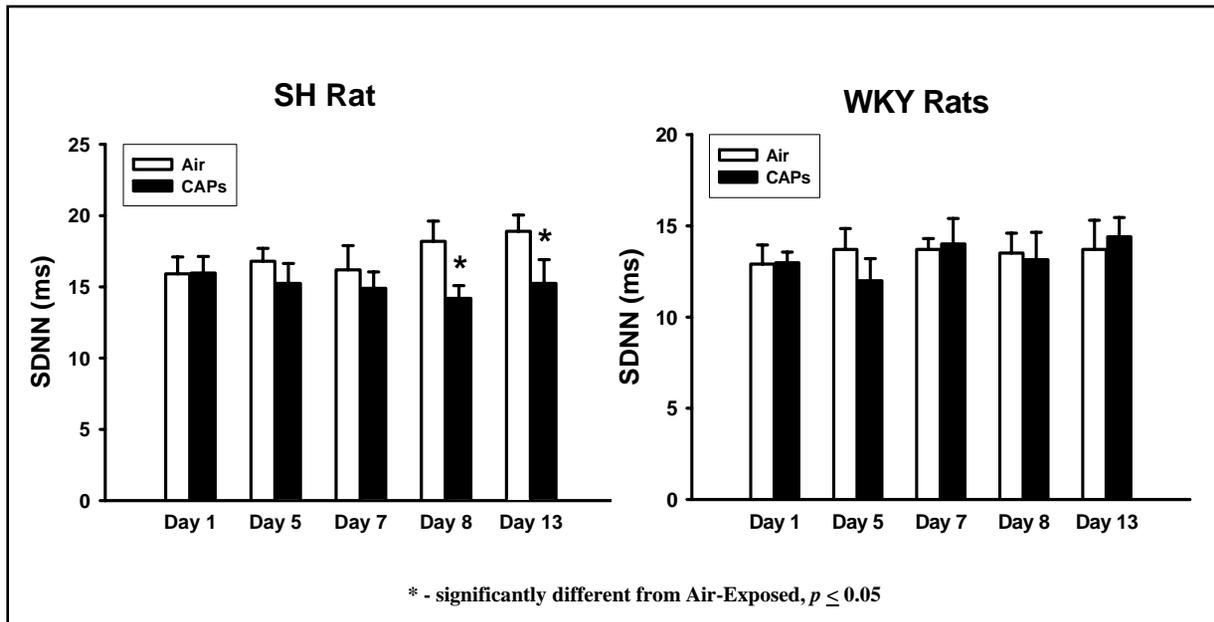


CAPs Exposure Causes Reduction in Heart Rate



Heart Rate Variability Changes with CAPs Exposure

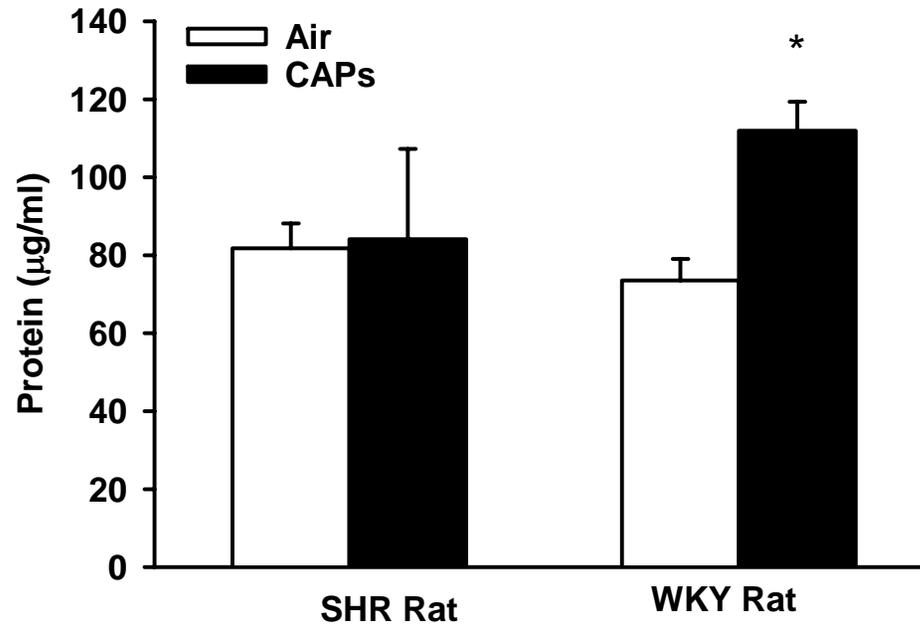
- Data selected from Days 1, 7 and 13 (first, middle, and last day of exposure), Day 5 (highest mass), and Day 8 (lowest mass)
- CAPs caused significant decreases in SDNN in SH rats on Days 8,13
- Similar pattern for r-MSSD
- CAPs-induced decreases in HRV appear to be cumulative, or delayed in onset



Bronchoalveolar Lavage Fluid

Protein in BALF

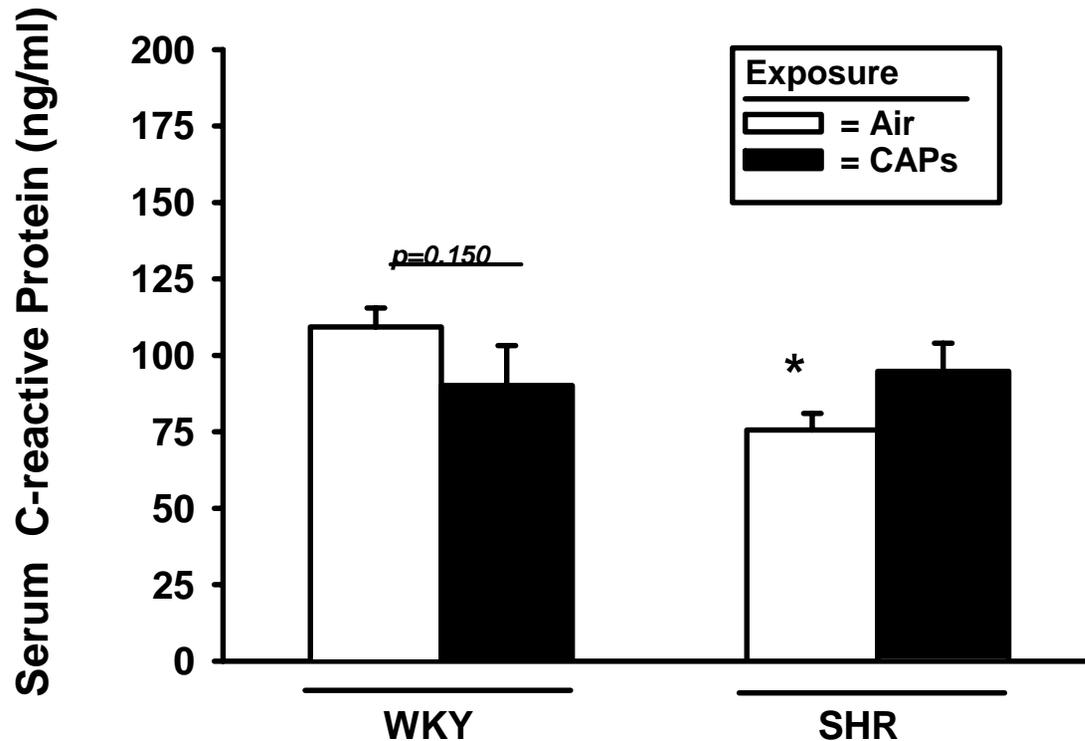
SHR and WKY Rats exposed to Concentrated Air Particles (CAPS) for 2 weeks
Detroit, MI August 2004



* = Significantly different from respective group within the same strain, ($p \leq 0.05$)

Plasma Analyses

Effect of CAPs Exposure on Serum C-reactive Protein
in Wistar Kyoto (WKY) and Spontaneously Hypertensive Rats (SHR)
(13 Day Exposure; EPRI Detroit 2004)



* significantly different from same strain exposed to Air, $p \geq 0.05$.

Remaining Analyses

- Lags: evaluate impact of earlier exposures on later responses
- Finer temporal resolution: utilization of continuous mass (TEOM) and HR/T data to evaluate rapid, short-term responses
- PM composition: utilization of PM component data (sulfate, nitrate, EC, OC, metals)

Application of Pilot Results to Full Study

- Increase sample size
- Work out kinks in nighttime ECG data collection

Project Scope of Work

Task 1: Field Experiments at Site 1, Season 1

- Subtask 1.1: Mobile Concentrator/Laboratory Setup
 - Performance check of concentrator and exposure chambers
 - Installation of power drop/meter
 - Setup/testing of exposure characterization instrumentation
 - Installation of ECG monitoring hardware
- Subtask 1.2: Particle Concentration and Animal Exposures
 - Use of Harvard/EPA fine ambient air particulate concentrator to generate exposure PM concentrations of 300-700 $\mu\text{g}/\text{m}^3$
 - 8 hour exposures for 13 consecutive days

Task 1: Field Experiments at Site 1, Season 1 (continued)

- Subtask 1.3: Exposure Characterization
 - PM components: acidity, sulfate, nitrate, ammonium ion, EC, OC, and trace elements (total and water soluble)
 - Semicontinuous slurry sampler to obtain finer time resolution for trace metals and EC/OC
 - CO, SO₂, NO_x, ozone, and meteorological parameters
- Subtask 1.4: Toxicological Assessments
 - Continuous ECG recording throughout study period
 - Processing of ECG data for heart rate, waveform morphology, rhythm analysis, QT and QTc, and heart rate variability
 - Histological analysis on heart and airway tissues
 - Bronchoalveolar lavage fluid (BALF) analysis
 - Blood analysis
 - Plasma analysis

Task 2: Field Experiments at Site 1, Season 2

- Subtask 2.1: Mobile Concentrator/Laboratory Setup
- Subtask 2.2: Particle Concentration and Animal Exposures
- Subtask 2.3: Exposure Characterization
- Subtask 2.4: Toxicological Assessments

Task 3: Data Analysis for Site 1

- Source apportionment analyses:
 - Multivariate receptor modeling techniques (PMF and UNMIX)
 - HYSPLIT4 Model
 - Specific chemical tracers
- Toxicological data analyses:
 - ANOVA using factors of exposure and strain
 - Correlations of CAPs physicochemical characteristics with toxicological endpoints by Pearson Product Moment analysis within each strain
 - Time series analysis to detect potential lag effects of CAPs exposure with ECG metrics
 - Merging of source contribution data with ECG and other toxicological data

Remaining Task Structure Same as for Site 1

- Task 4: Field Experiments at Site 2, Season 1
- Task 5: Field Experiments at Site 2, Season 2
- Task 6: Data Analysis for Site 2
- Task 7: Field Experiments at Site 3, Season 1
- Task 8: Field Experiments at Site 3, Season 2
- Task 9: Data Analysis for Site 3

Task 10: Integrated Data Analysis for All Sites

- Employ analytical methods used in Tasks 3, 6, and 9 to make comparisons across sites and within treatment groups

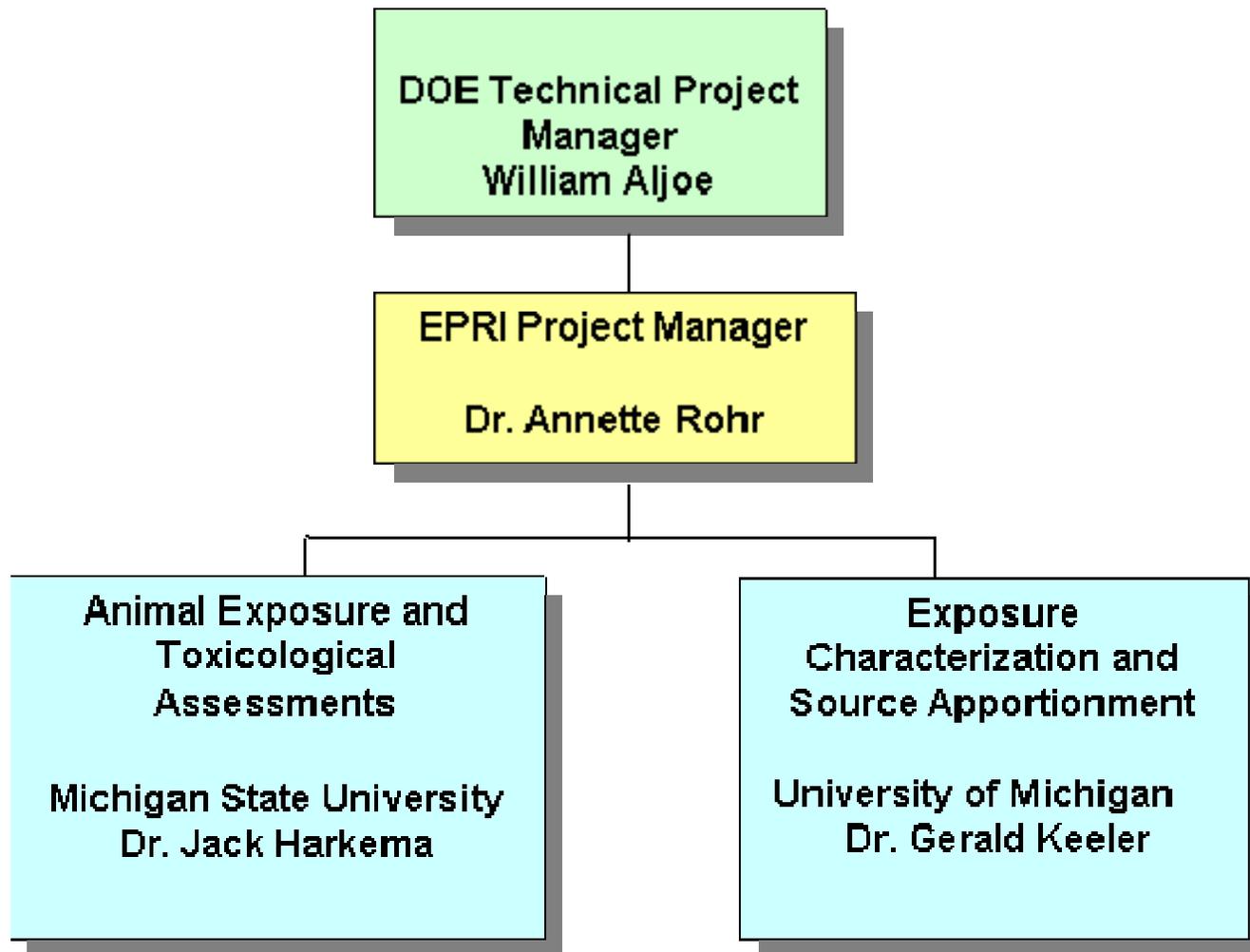
Task 11: Project Management and Reporting

- All planning, management, and coordination activities associated with the project
- EPRI will:
 - Coordinate all field, laboratory, data management, and data analysis activities of the subcontractors
 - Be responsible for all deliverables and briefings

Project Administration

- Project Team
- Project Schedule
- Project Deliverables

Project Team



Milestones

Milestone/Deliverable	Date
Project Kickoff Meeting	09/08/05
Management Progress Reports	Quarterly throughout project period
Complete Field Experiments at Site 1	06/30/06
Topical Report, Site 1	12/31/06
Complete Field Experiments at Site 2	06/30/07
Topical Report, Site 2	12/31/07
Complete Field Experiments at Site 3	06/30/08
Topical Report, Site 3	12/31/08
Final Briefing to DOE	03/31/09
Draft Final Report	06/30/09
Final Report	09/30/09

Deliverables

- Sixteen quarterly progress reports (beginning 10/30/05)
- Three topical (site-specific) reports on the toxicological results
- Comprehensive final report
- Approximately 7 manuscripts for peer-reviewed journals:
 - Description of toxicological results for the Detroit site
 - Description of toxicological results for the Steubenville site
 - Description of toxicological results for the Goddard State Park site
 - Integration of cardiac function results across the three sites
 - Integration of histopathology results across the three sites
 - Integration of blood and plasma results across the three sites
 - Integration of the overall Project results with DEARS and the Detroit Cardiovascular Health Study results

EPR

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