VOLATILE ORGANIC COMPOUNDS AND CARDIOMETABOLIC DISEASE

University of Louisville Superfund Research Center

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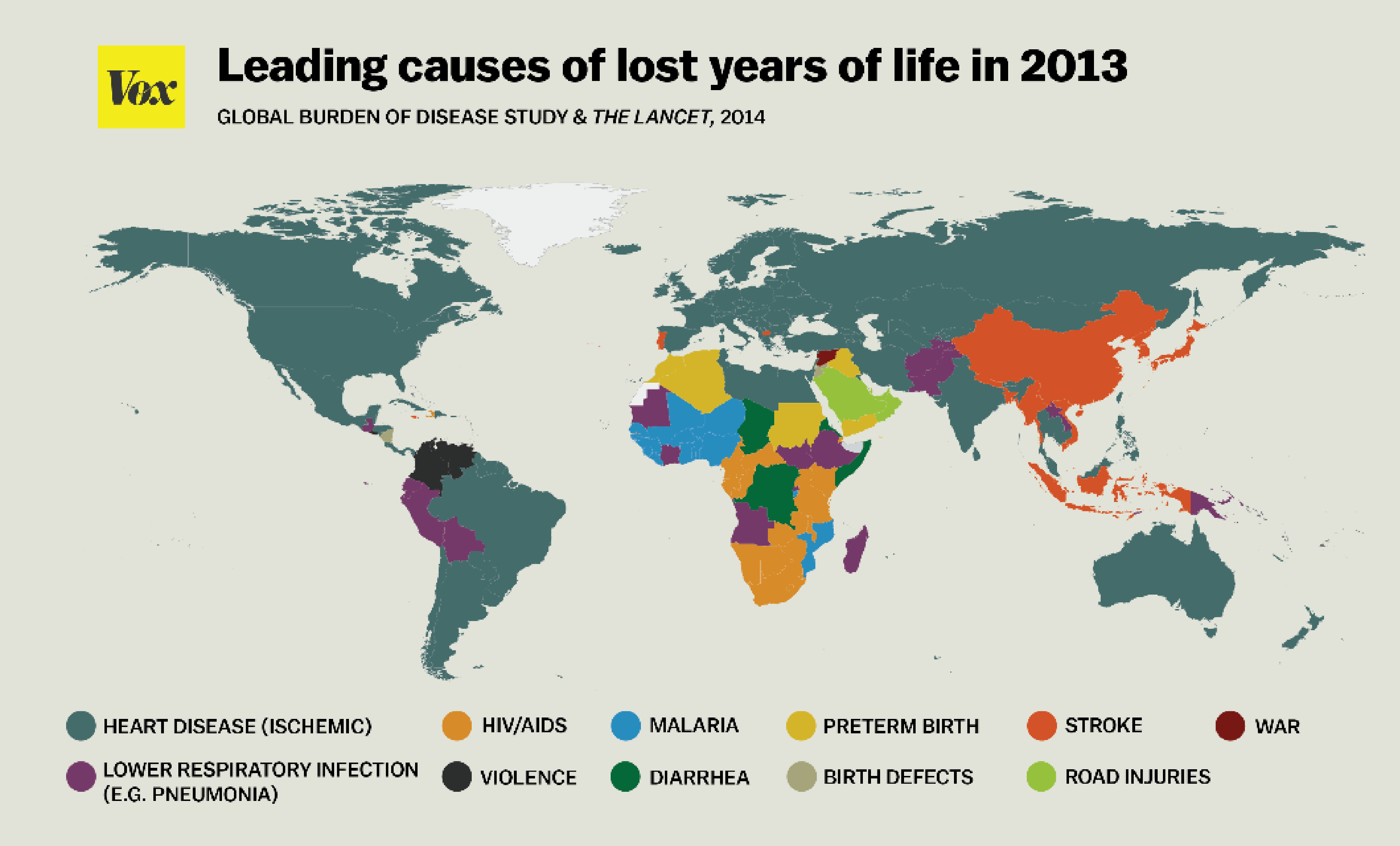
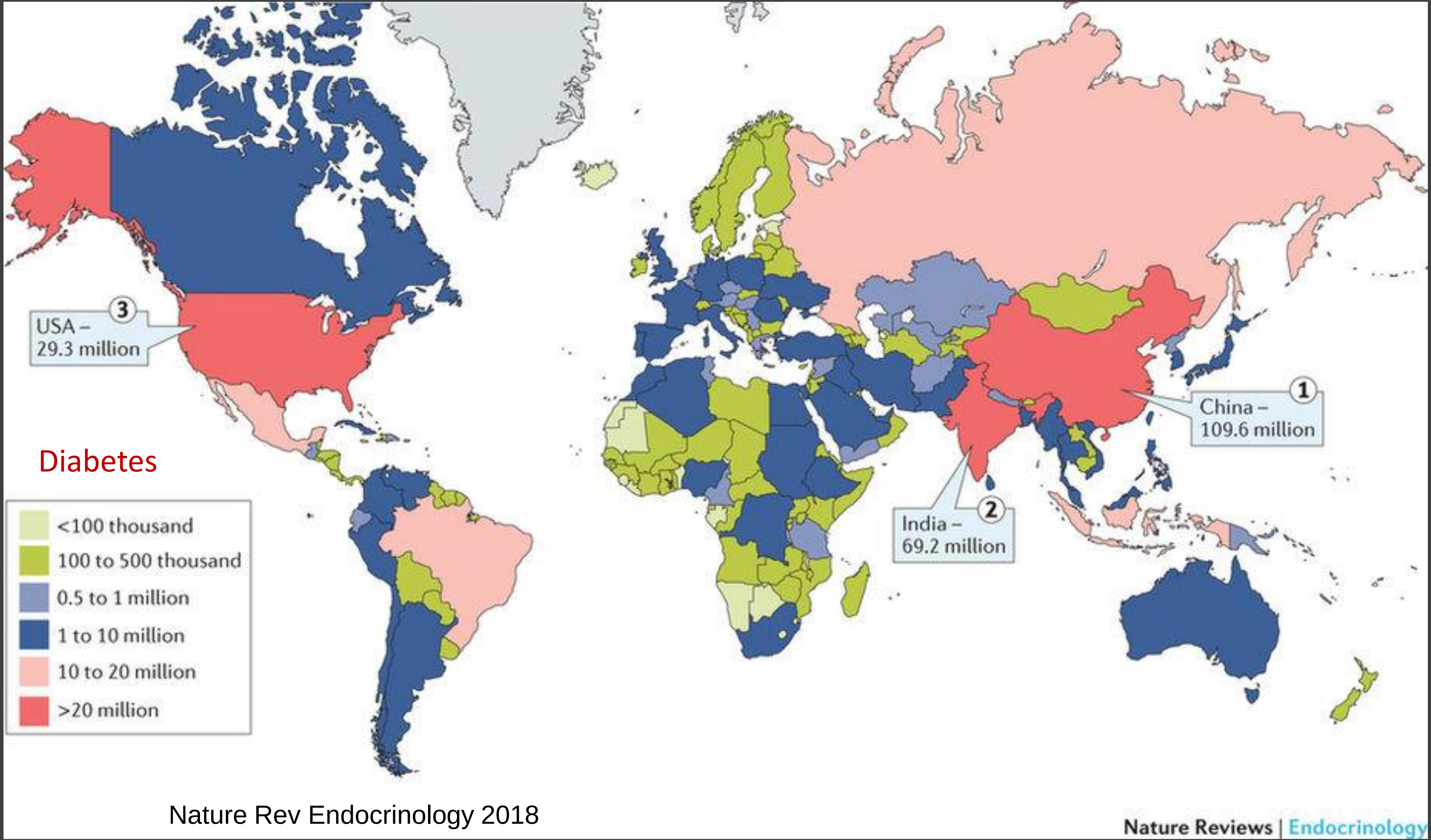
- John Fortner (Yale University), PI-Project 4

CARDIOVASCULAR DISEASE IS THE LEADING CAUSE OF DEATH



DIABETES IS A GLOBAL HEALTH PROBLEM



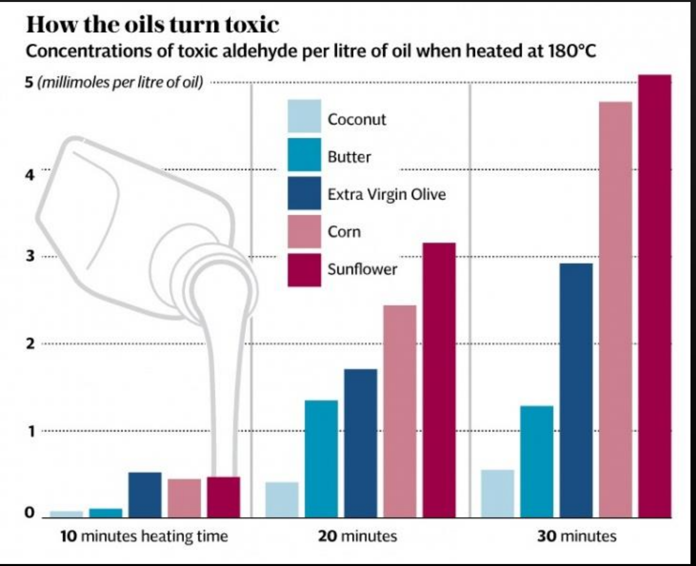
Nature Rev Endocrinology 2018

NEARLY 60 – 80%

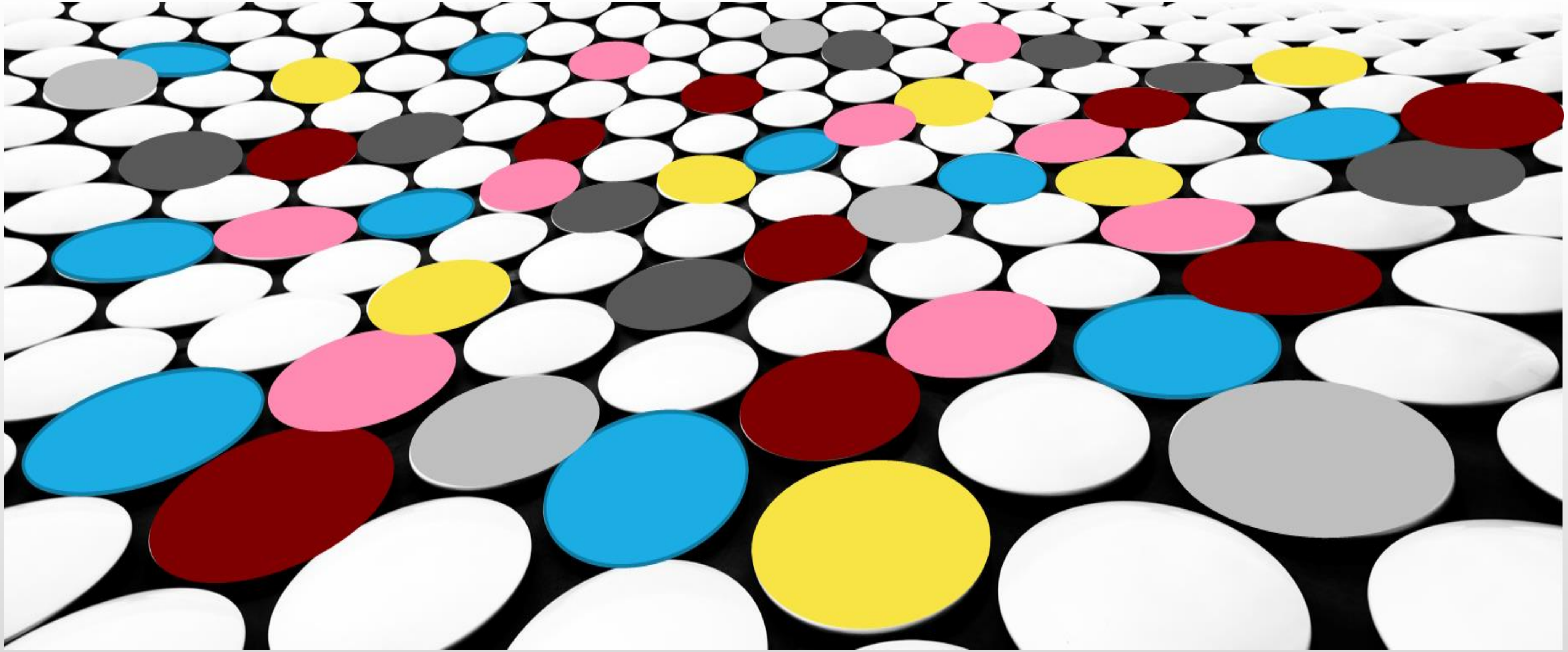
OF HEART DISEASE AND DIABETES

ARE ENVIRONMENTAL IN ORIGIN

Sources of VOCs



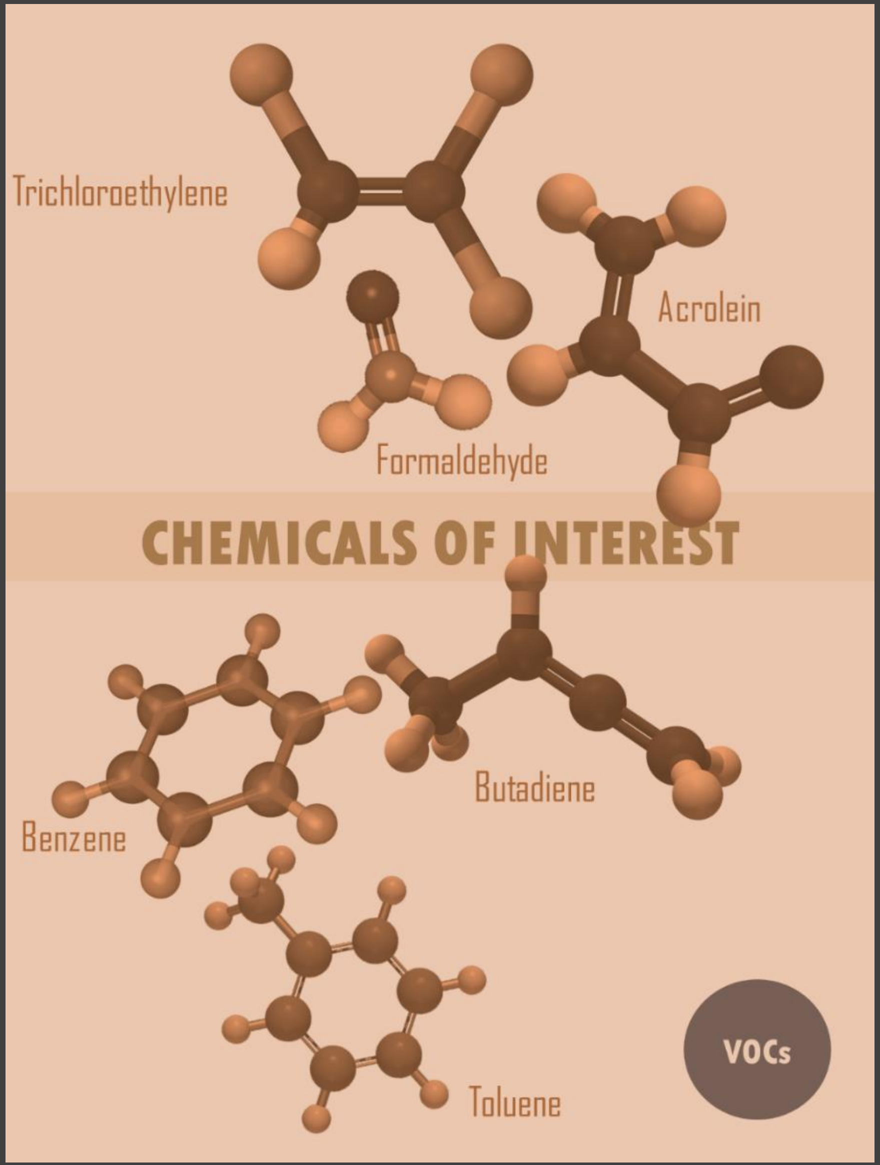
VOCs are ABUNDANT at SUPERFUND SITES



People living near the superfund sites have increased risk for diabetes and stroke

Priority Ranking of VOCs in ATSDR

- Vinyl Chloride (#5)
- Benzene (#6)
- Acrylamide
- Trichloroethylene (#16)
- Acrolein (#31)
- Acrylonitrile
- Xylene (#64)
- Toluene (#74)
- 1,3-Butadiene (#153)
- Propylene oxide
- N,N Dimethyl Formamide
- Ethylbenzene



HIGHLIGHTS OF THE PREVIOUS FUNDING CYCLE

Population Based Studies

- VOC (e.g. acrolein, crotonaldehyde, and 1,3-butadiene) exposure is associated with compromised vascular function and increase in systolic blood pressure
- VOC exposure induces endothelial injury and impairs repair capacity.
- Urinary VOC (e.g. benzene) metabolites are associated with an increase in liver injury markers

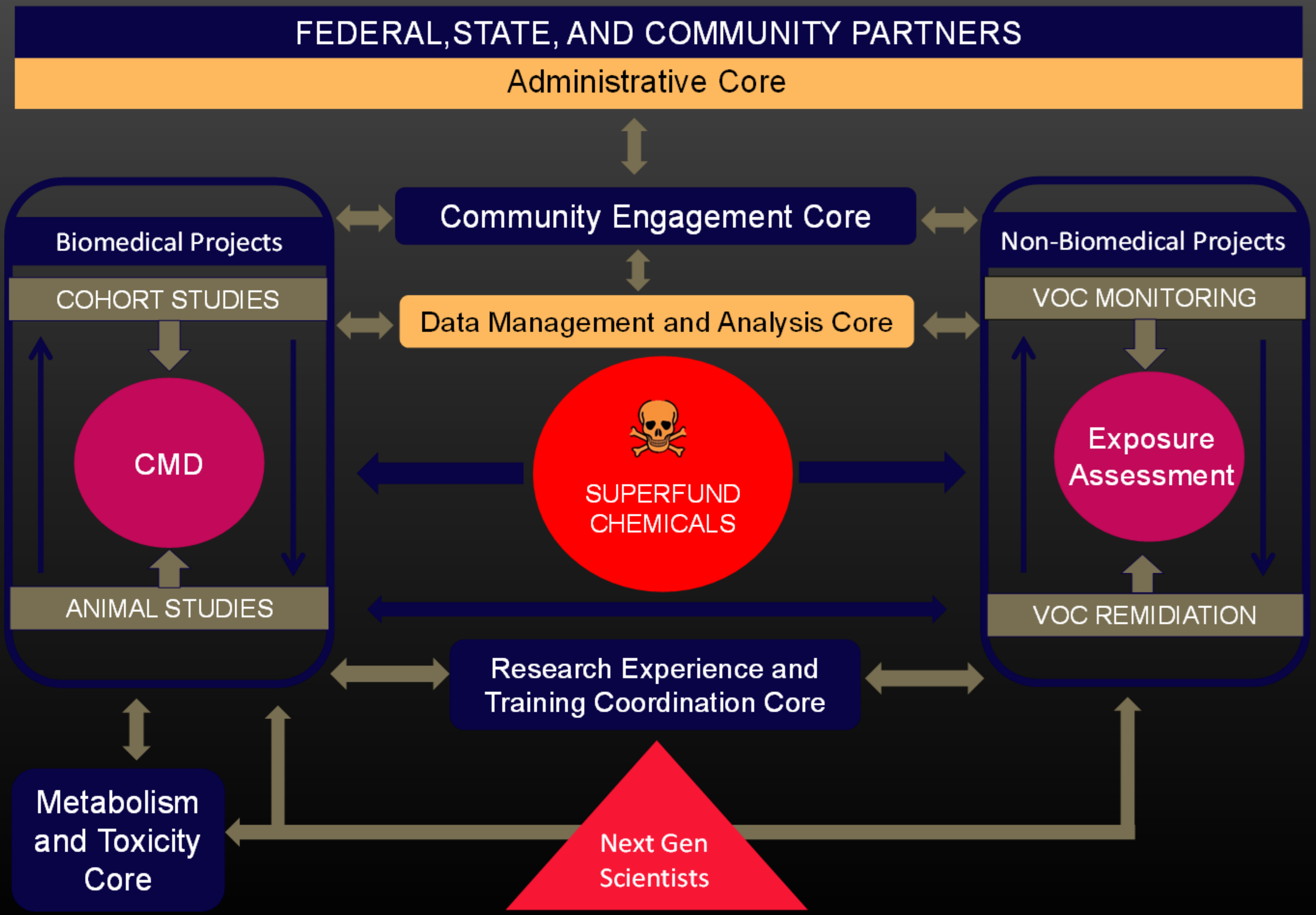
Pre-clinical Studies

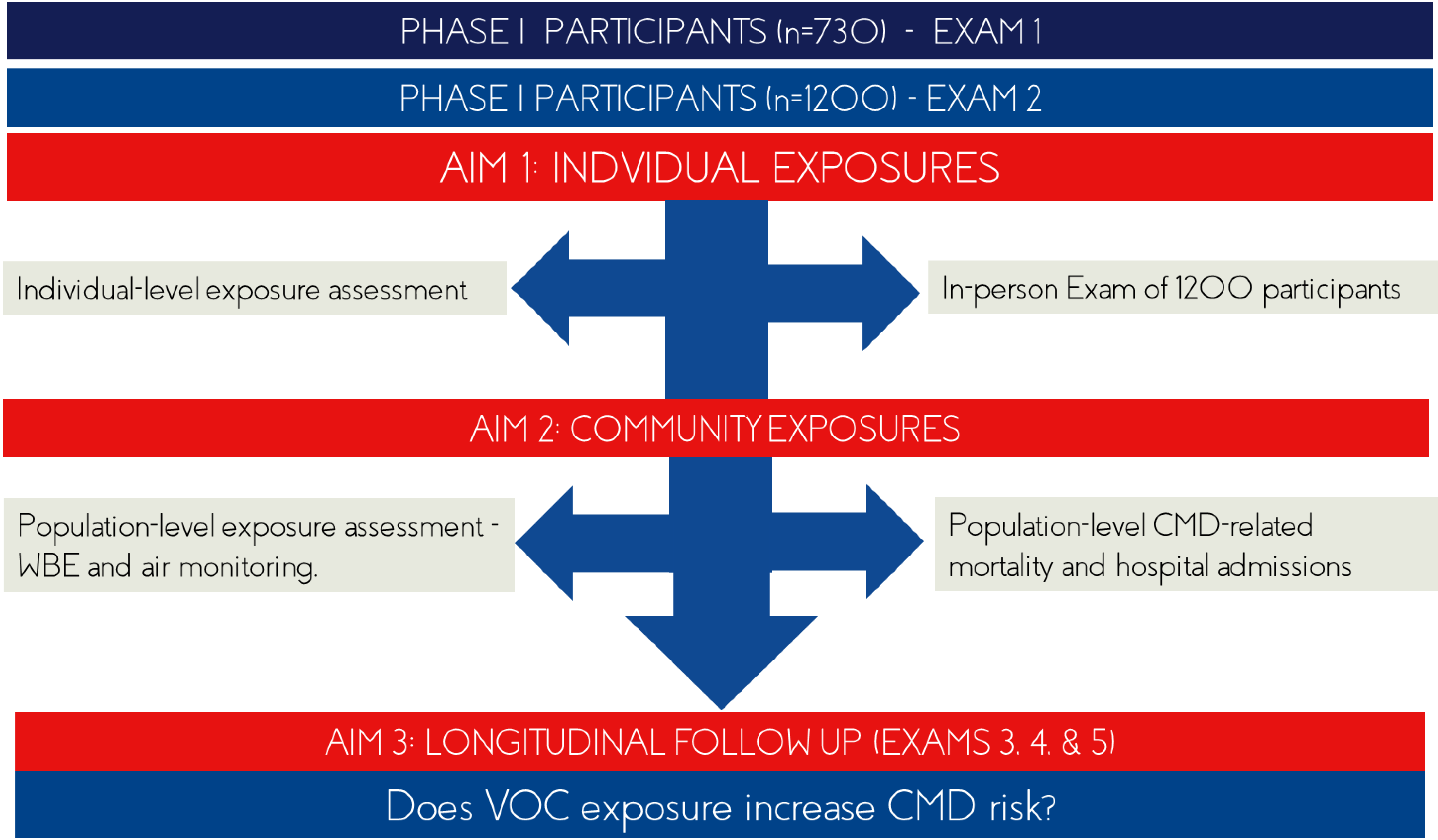
- Consistent with human studies, VOC (e.g. benzene, acrolein etc) exposure induces endothelial toxicity and impairs its repair mechanisms.
- Benzene exposure induces insulin resistance and promotes cardiac dysfunction.
- *In vitro* studies suggest that VOC exposure induces ER-stress and augments the expression of heat shock proteins as an adaptive response

Environmental Science and Engineering Studies

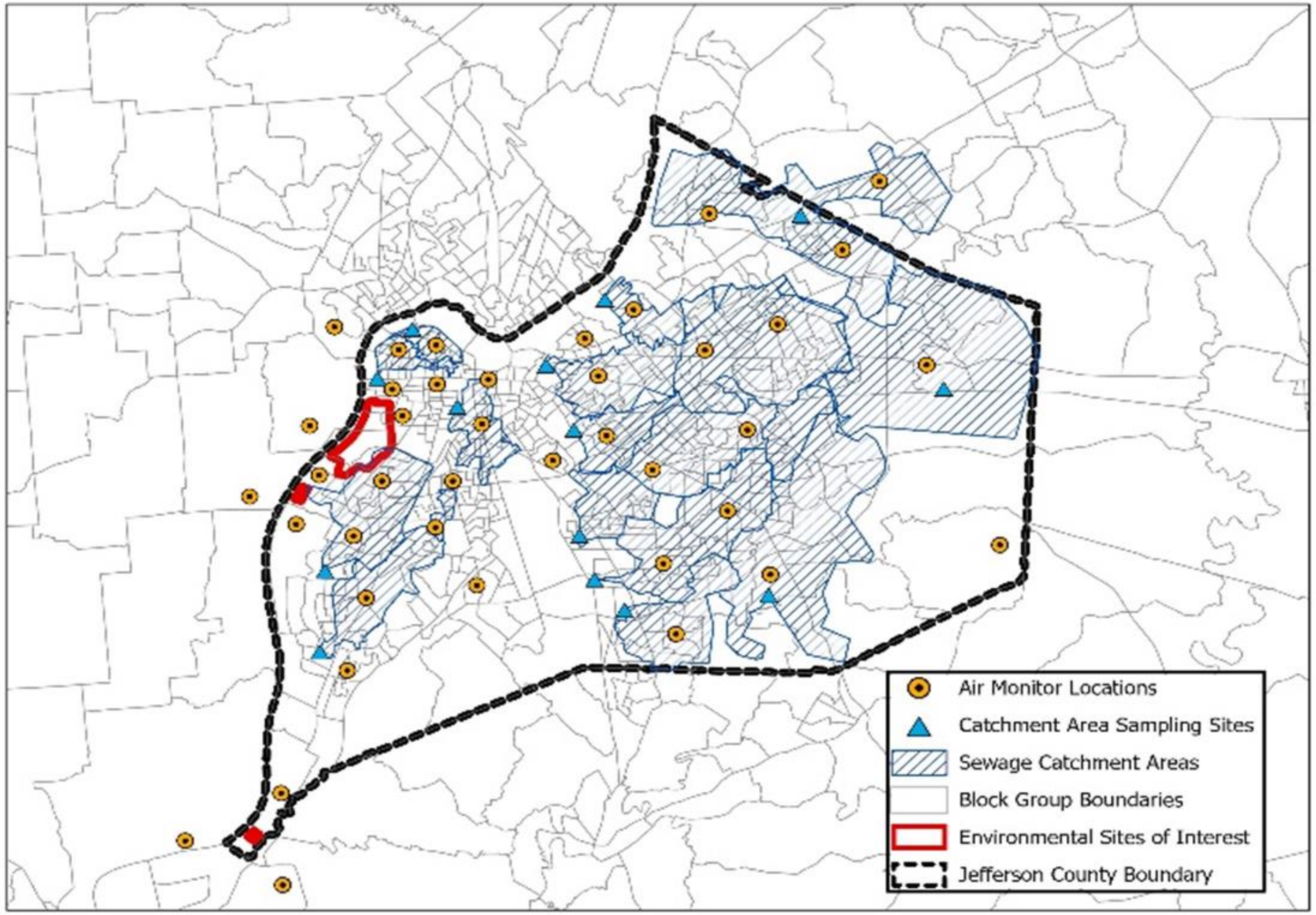
- Personal-level exposure to VOCs increased despite declining ambient air VOCs levels
- Developed LC-MS assays for measuring VOC metabolites in wastewater
- Built a multichannel portable GC-MS for real-time VOC measurements
- Developed Thiol-urea, Metal ion-, and Cesium-based censors for VOC

CENTER STRUCTURE




PHASE I PARTICIPANTS (n=730) - EXAM 1
PHASE I PARTICIPANTS (n=1200) - EXAM 2
AIM 1: INDVIDUAL EXPOSURES
Individual-level exposure assessment
In-person Exam of 1200 participants
AIM 2: COMMUNITY EXPOSURES
Population-level exposure assessment - WBE and air monitoring.
Population-level CMD-related mortality and hospital admissions
AIM 3: LONGITUDINAL FOLLOW UP (EXAMS 3. 4. & 5)
Does VOC exposure increase CMD risk?

In collaboration with Project 3. we will establish passive sampling based "VOCore Network" at clinical study participant residences across Jefferson County which includes Louisville.



Preliminary design for the 40-site VOCore air monitoring network and sewage sampling sites in Jefferson County

BIOMARKERS OF EXPOSURE AND BIOMARKERS OF HARM

Table 1: Data and biomarkers collected from participants
Physical Exam - Height, Weight, Waist Circumference, Blood Pressure, Arterial Stiffness, body composition (InBody)
Demographic Information - Address, occupation, diet, exercise, tobacco & alcohol use, stress, well-being, exposure history
CVD risk assessment -Plasma – LDL, HDL, cholesterol, triglyceride, TMAO
Liver disease – Serum K18, liver enzymes, FIB-4, NAFLD Fibrosis Score, TGFβ, and liver toxicity miRs (FirePlex® - abcam)); urinary bile acids
Glucose control and systemic injury - HbA1c, HETEs, and HODEs, plasma miRs, hepatokines
Inflammation -IL-6, hs-CRP, TNFα, MCP-1, IL-8, sCD4L, endothelin, HA, sICAM, sVCAM, HSPs
Circulatory markers - Mononuclear cells, EPCs, platelet-monocyte aggregates, circulating microparticles
Stress: Plasma cortisol and urinary catecholamine metabolites
Exposure Assessment – Urinary VOC metabolites, creatinine

Complementary studies in Project 2 will examine the plausibility that individual VOCs are sufficient to induce cardiometabolic toxicity and delineate the underlying cellular and molecular mechanisms.

Project 3: Platforms for Airborne VOCs Monitoring with Application to Surveillance, Source Apportionment, and Exposure Estimation

The Need…

- **Develop** novel technologies for quantitative analysis of trace VOCs
- **Demonstrate** the use of these technologies and robustly characterize indoor/outdoor contrast and in-home determinants for exposures to target Superfund-relevant VOCs.

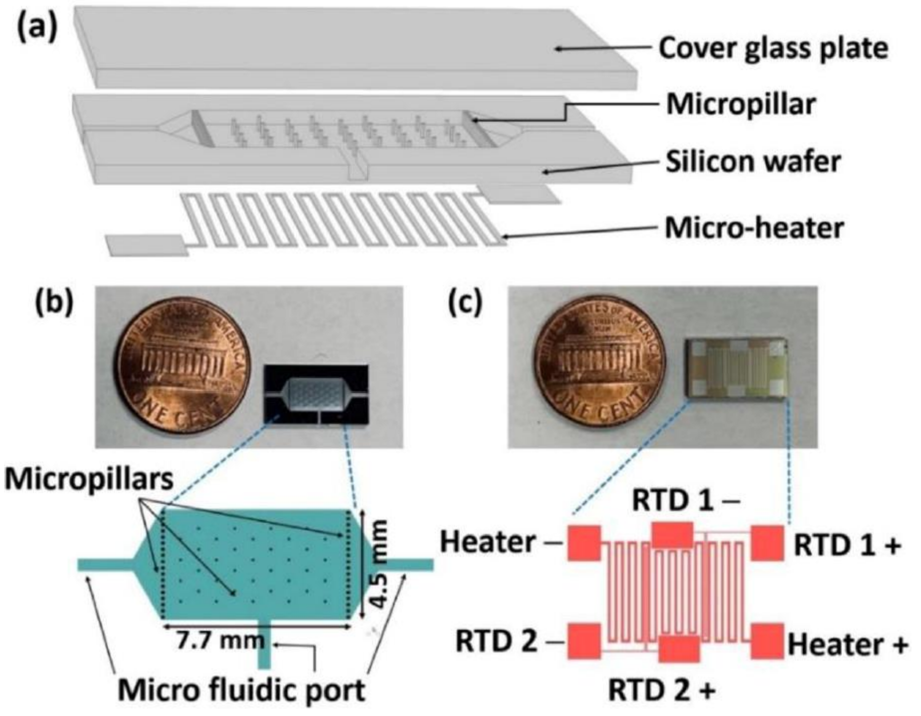
Gas sensor arrays for on-site measurement of target airborne VOCs

- Develop microfabricated gold-based gas sensors to measure target VOCs
- Develop gas sensor arrays to measure target VOCs
- Conduct field validation of the sensors/sensor arrays

Indoor/outdoor residential VOC monitoring to identify drivers for VOC exposures

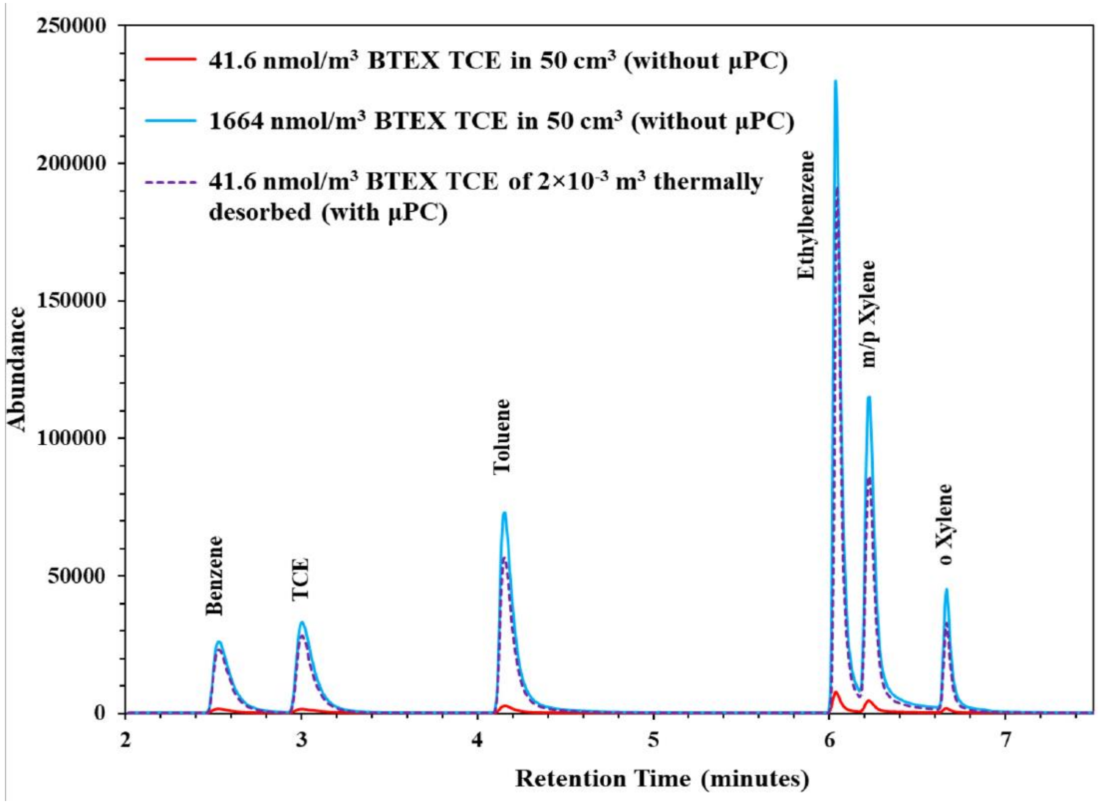
- Optimize the recently developed **M**ultichannel **O**rganics **I**n-situ envi**R**onmental **A**nalyzer (MOIRA) instrument for indoor/outdoor VOC monitoring
- Conduct indoor/outdoor monitoring of target airborne VOCs at several homes using passive sampling (VOCore network) and MOIRA

Integration of a Micropreconcentrator (µPC) with Solid-Phase Microextraction (SPME) for Analysis of Trace VOCs by GC-MS



Micropreconcentrator (µPC):

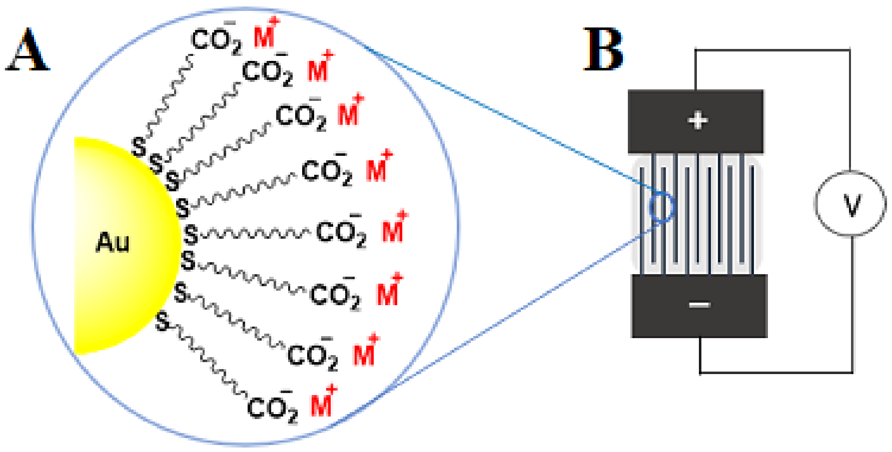
(a) three-dimensional view of layers
(b) front side of the µPC showing cavity and micropillars
(c) backside heater and RTD of the µPC

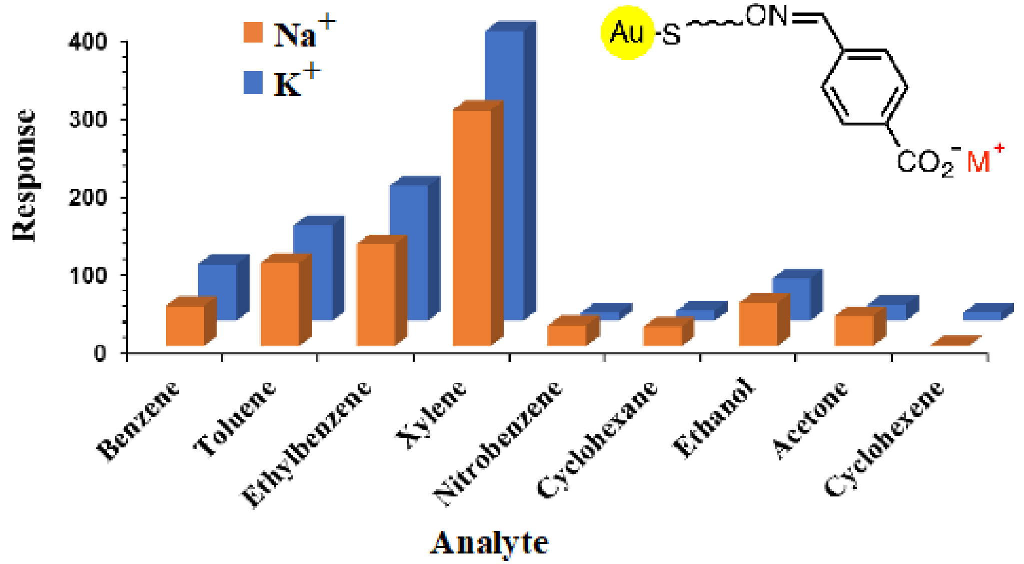


Detector signals for SPME of f BTEX samples with (dashed line) and without (solid lines) µPC

S Halder *et al.* (2022)

Harnessing Cation-π Interactions of Metallated Gold Monolayer Protected Clusters (MPCs) to Detect Aromatic VOCs





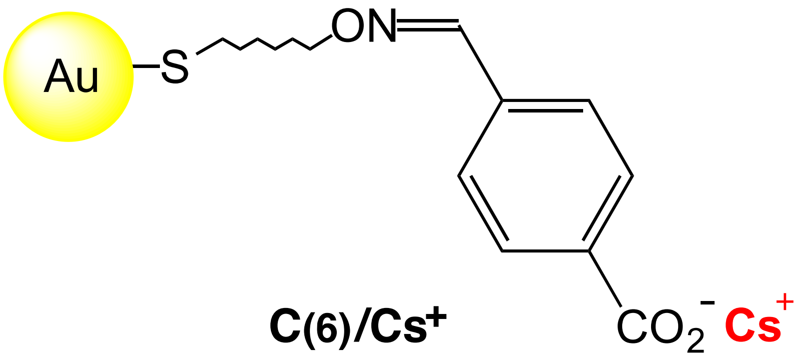
A. metal ion-carboxylate linked Au MPCs (M+ = alkali metal)
B. chemiresistor structure with interdigitated electrodes. The Au MPCs are drop-cast onto the chemiresistor electrodes to create a closed circuit

Chemiresistor response to VOCs at a concentration of 5 ppm. Sensors were prepared from Au MPCs-M+, where M+ = Na+ or K+

PK Adhihetty *et al.* (2023)

Developments in Progress…

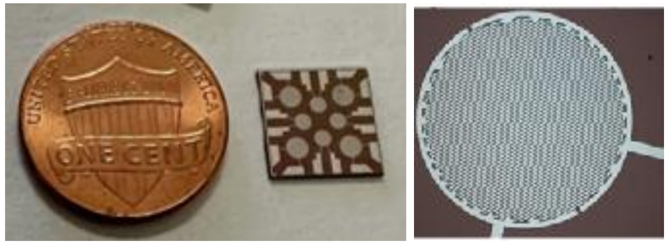
A Cesium Ion-Based Chemiresistor for Sensing Trichloroethylene in Air



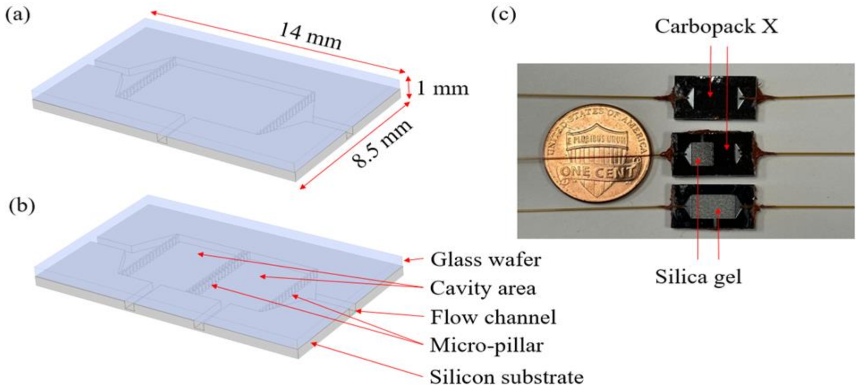
C(6)/Cs^+

PK Adhihetty *et al.,* in preparation

Sensor Array and Micropreconcentrator Fabrication



Sensor chip array and interdigitated electrodes



Microfabricated preconcentrators (µPC):

(a) single compartment µPC

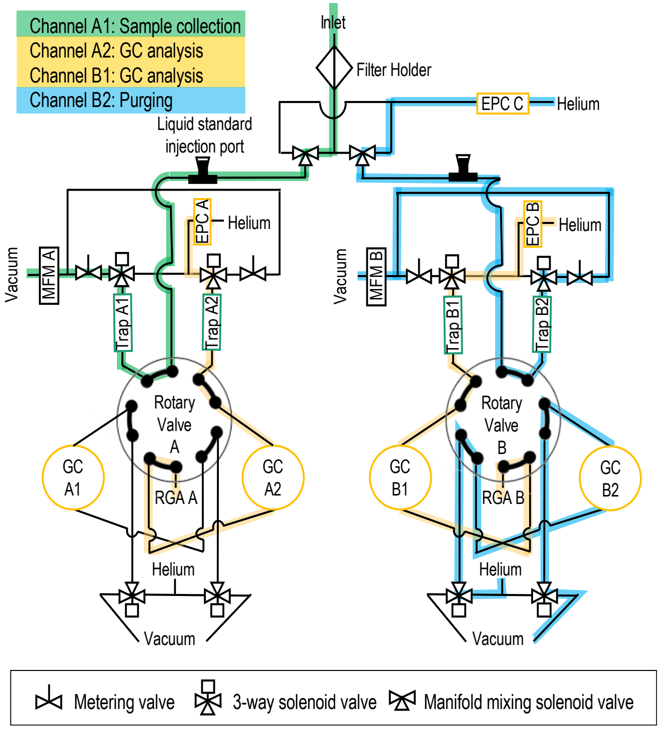
(b) dual-compartment µPC

(c) packing and comparison to US coin

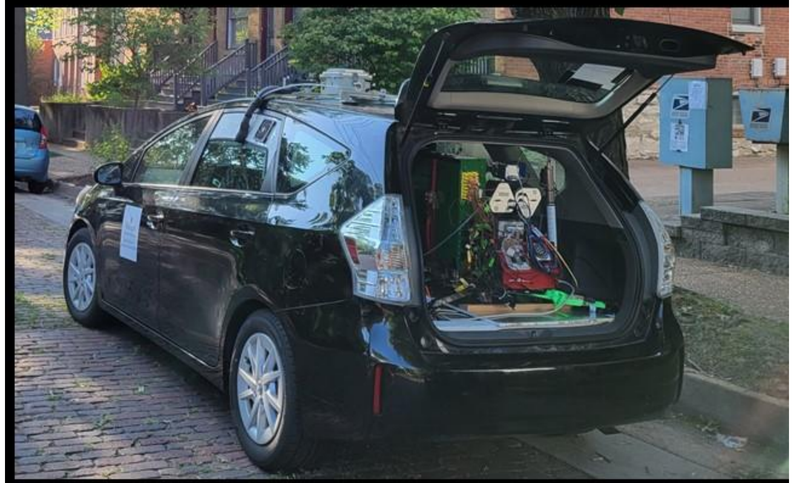
Multichannel Organics In-situ enviRonmental Analyzer (MOIRA)

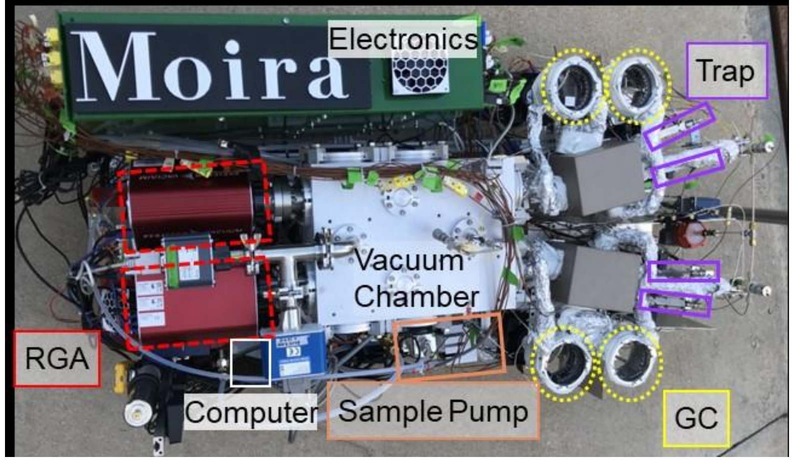
Developed by Brent Williams with PhD student Audrey Dang

- Mobile platform
- Staggered sample collection and analysis by
  - four thermal desorption collectors
  - four miniature gas chromatography (GC) heaters
  - two compact residual gas analyser (RGA) mass spectrometer (MS) detectors
- ➢ Continuous measurements at 10 min time resolution



MOIRA flow paths





AJ Dang *et al.*, in preparation

Example MOIRA Time Series from a Residential Indoor Study

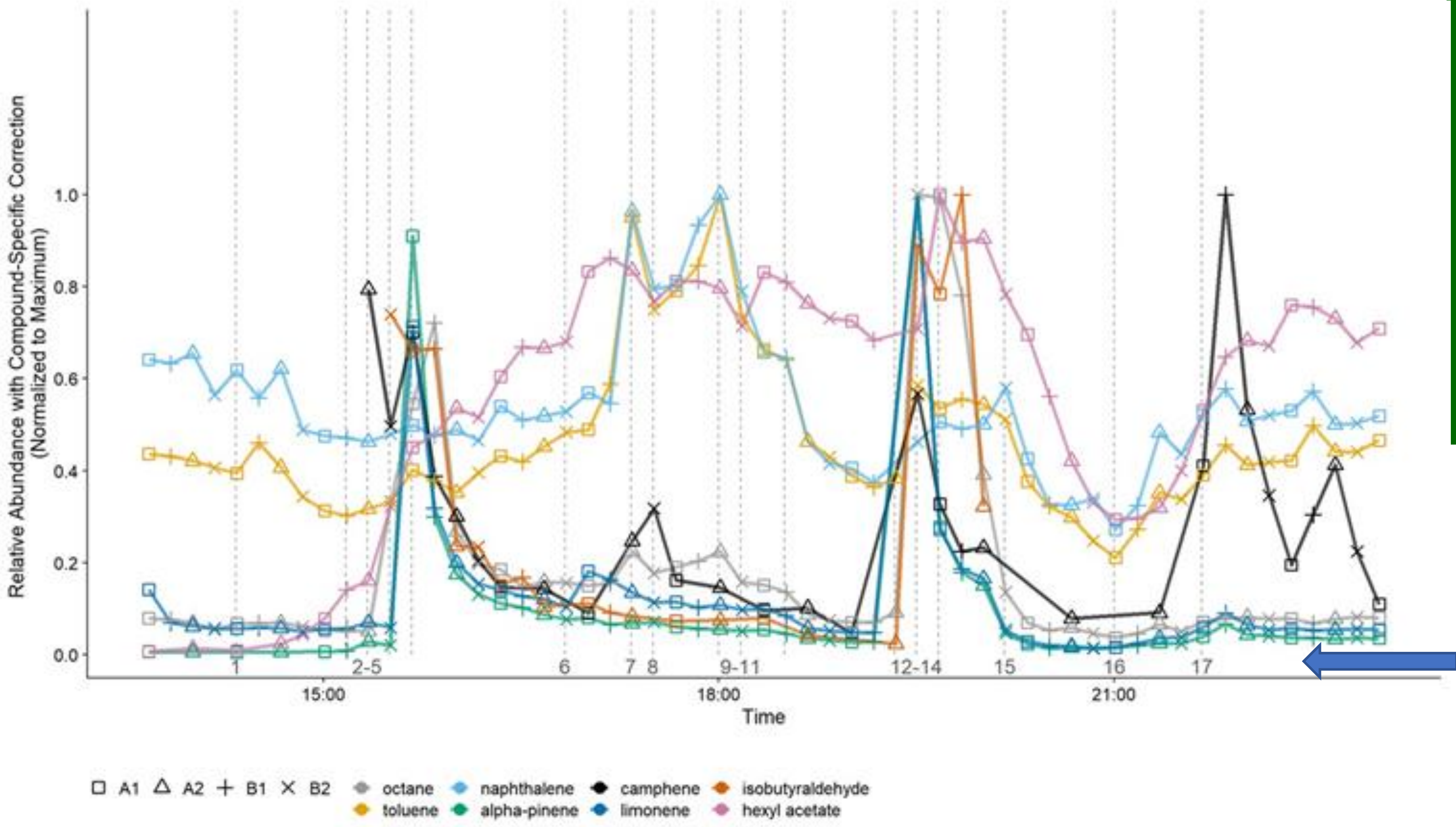


Figure shows eight of the more than 100 compounds quantified

Powerful approach to identify determinants of indoor exposures using source apportionment

Numbers correspond to various activities, e.g. window opening/closing, cooking, cleaning kitchen surfaces

Also demonstrated MOIRA capabilities for mobile measurements driving on public roads

Project 4: Develop and demonstrate novel, material-driven processes for advanced VOC treatment

The Need…

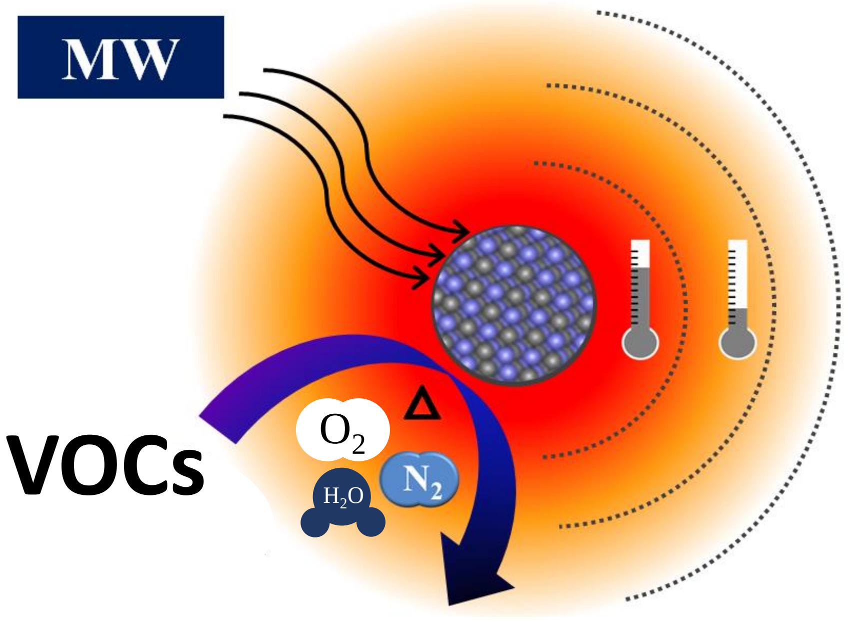
- **Develop** novel technologies to TREAT VOCs
- **Demonstrate** the potential of new, material-based treatment technologies and robustly characterize with Superfund-relevant VOCs.

*Project 4 is new for Center Year 6.

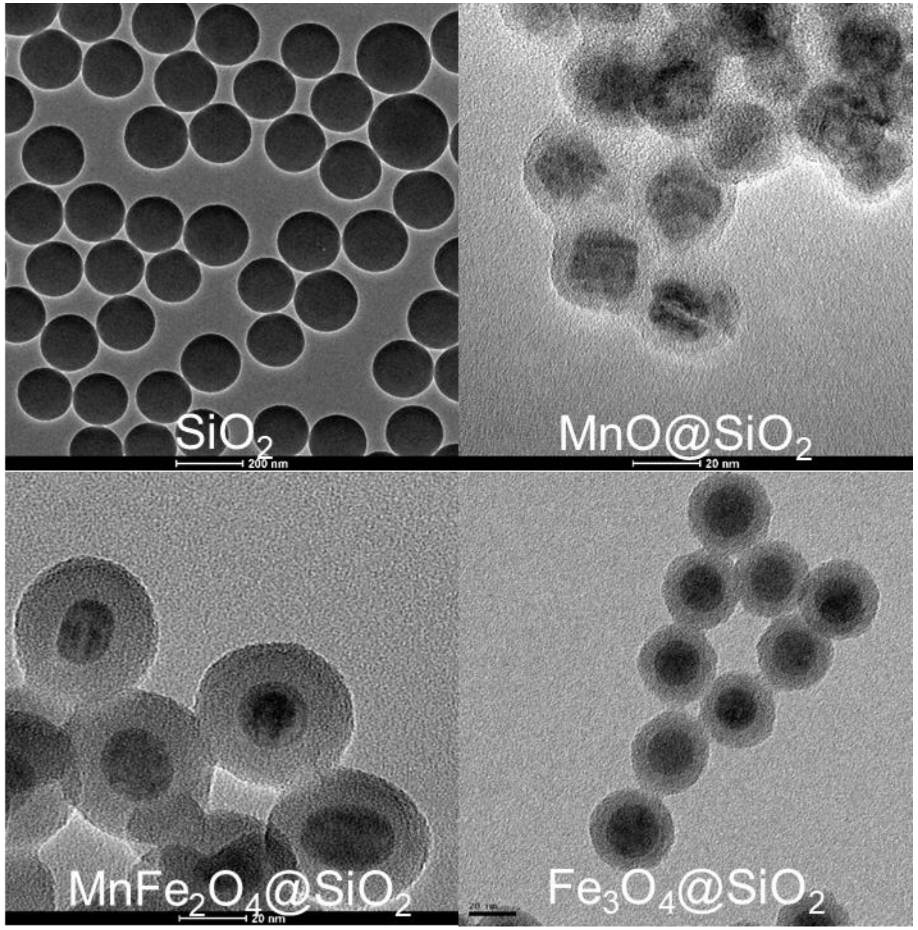
Approach…

- **Aim 1** will focus on VOC treatment with a unique class of hyperthermic nanoparticles (NPs), which are defined by their capacity to emit heat when subjected to external electromagnetic (EM) irradiation.
- **Aim 2** will focus on the development and characterization of materials and related processes to achieve synergistic photothermocatalytic effect(s) for advanced VOC degradation via oxidation pathways to environmentally benign products, such as CO_2 and H_2O, at significantly reduced temperatures compared to conventional thermocatalytic oxidation.
- **Aim 3** will focus on the development, characterization, and demonstration of multifunctional material-based membrane treatment of VOC (i.e. flow through treatment processes).

Project 4
Objective 1: Development of Thermocatalytic Materials for VOC degradation

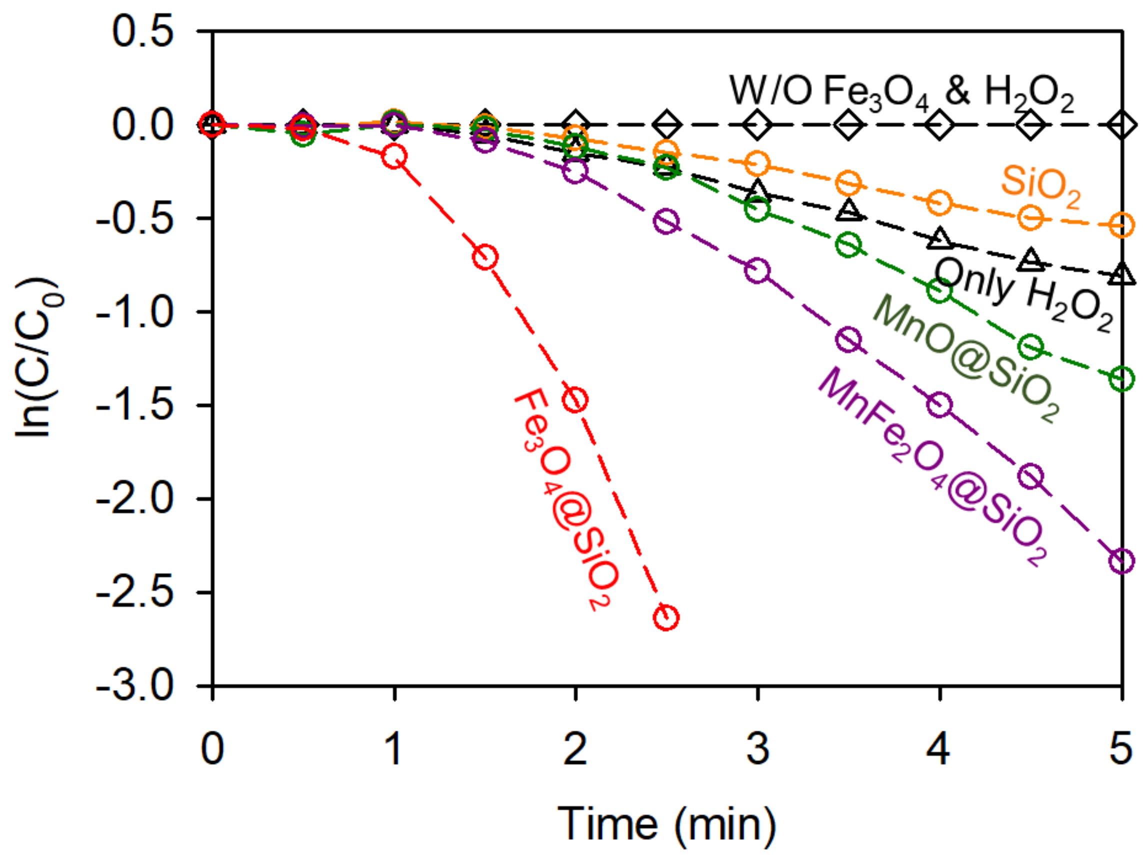


Benign reaction products
(CO, CO_2, H_2O, etc.)

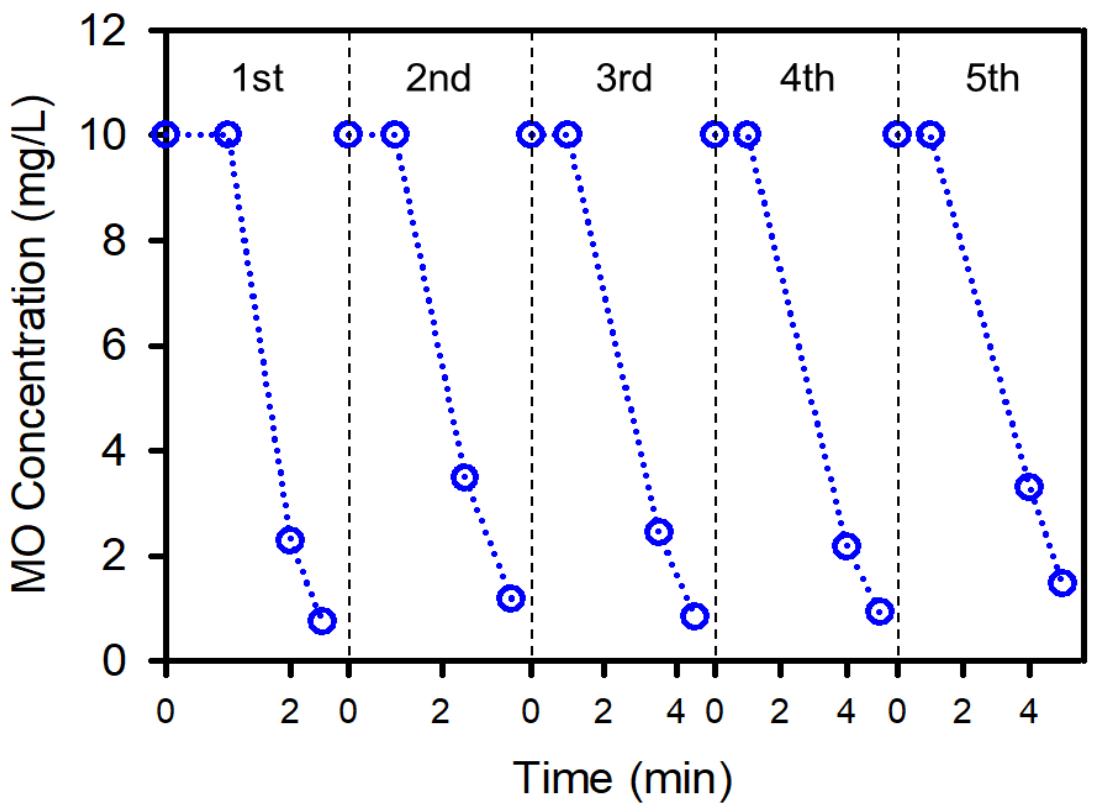


TEM images for metal oxide and ferrite nanocrystals with silica coating (SiO_2, $MnO@SiO_2$, $MnFe_2O_4@SiO_2$, and $Fe_3O_4@SiO_2$).

Project 4
Aim 1: Development of Thermocatalytic Materials for VOC Degradation

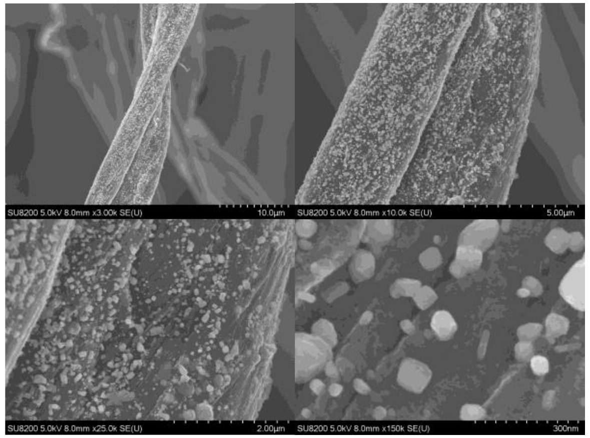


Organic dye (10 mg/L) degradation under microwave (MW) irradiation with (A) various catalysts.

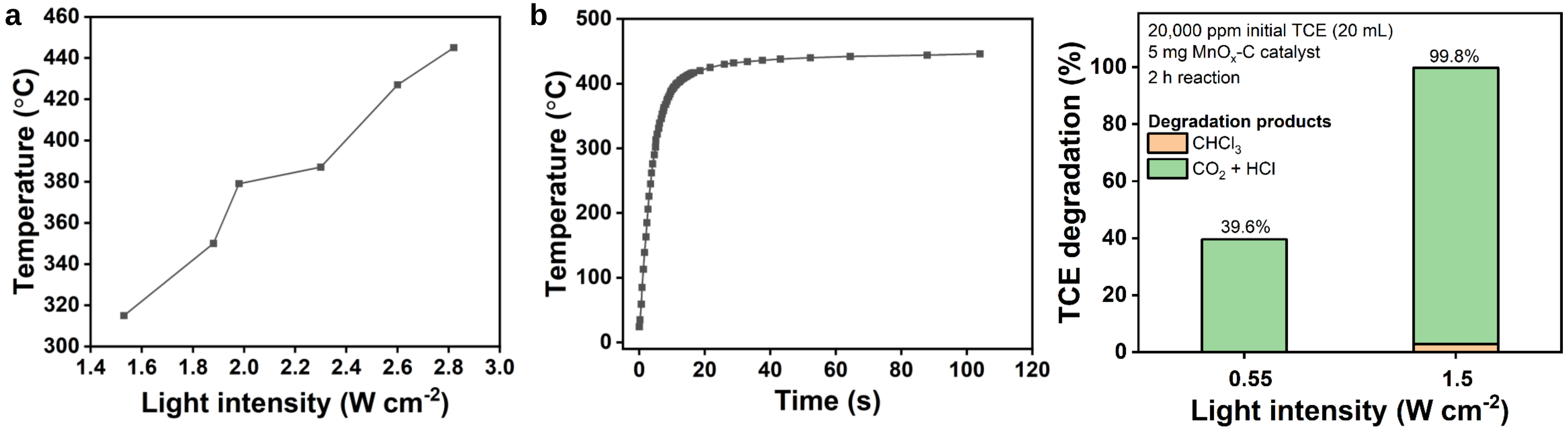


Organic dye (10 mg/L) degradation cycling with $Fe_3O_4@SiO_2$

Project 4
Aim 2: Development of Photothermal Materials for VOC Degradation

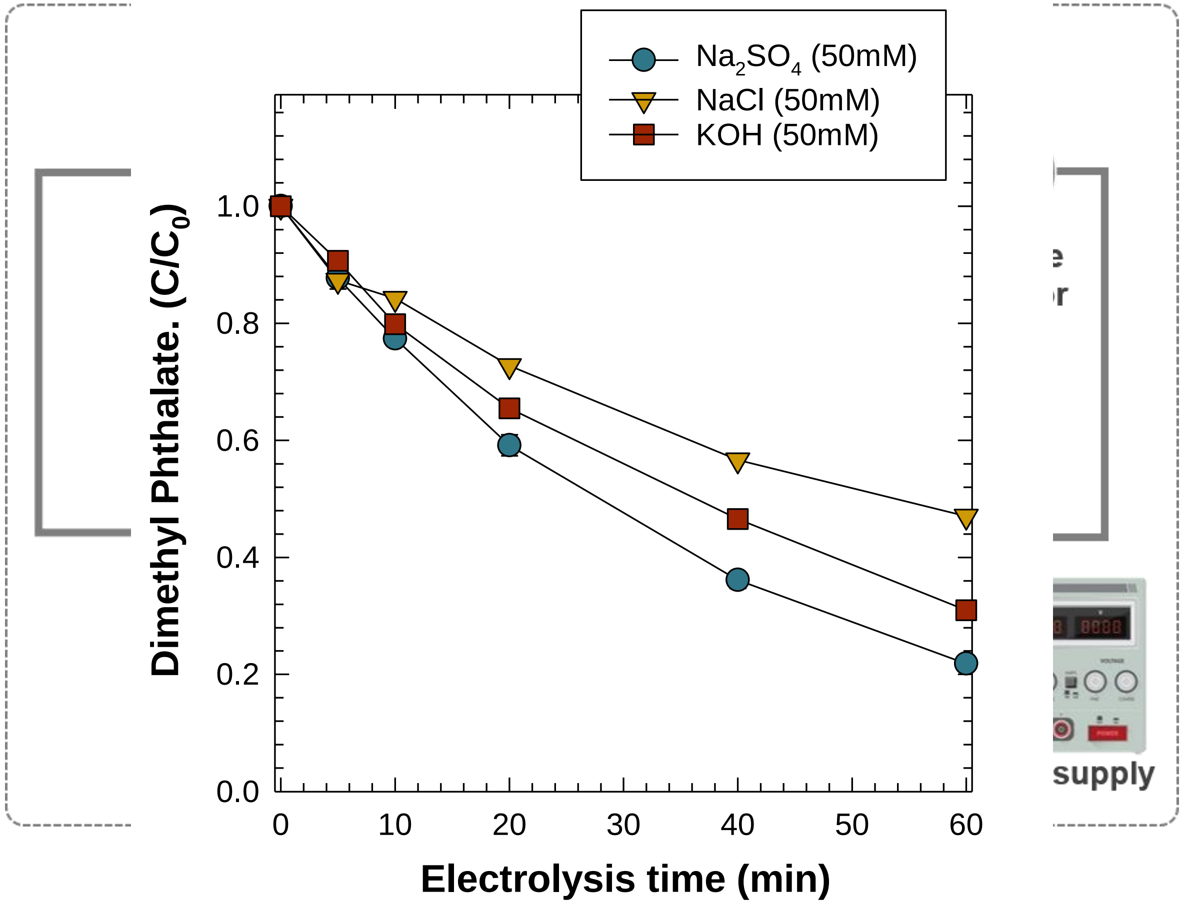


SEM images of MnO_x- on natural fibers.



(a) Stable temperature of cotton-derived composite materials reached under illumination of varying light intensity. (b) Time response of temperature increase for cotton-derived C upon 2.8 W cm^{-2} illumination. (c) Photothermal TCE degradation by MnO_x-C catalyst under varying light intensities.

Project 4
Aim 3: Development of Novel Flow Through Membrane Approach(es) for VOC Treatment



Project 4….Progress!

Project Tasks (defined in each section above)	Year 1	Year 2	Year 3	Yea
Specific Aim 1.1 Hyperthermic NP Library Synthesis/Development				
Specific Aim 1.2. Hyperthermic NP Library Characterization				
Specific Aim 1.3. Optimize Reactions/Materials for VOC Treatment				
Specific Aim 2.1 Catalyst Development and Reaction Studies				
Specific Aim 2.2 Mechanistic Studies				
Specific Aim 2.3 Mechanism-Guided Optimization				
Specific Aim 3.1 CGO Composite Development / Membrane Fabrication				
Specific Aim 3.2 Membrane Performance/Optimization for VOC Treat.				