NTP
National Toxicology Program

Occupational and Inhalation Exposures Program

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Division of the NTP
National Institute of Environmental Health Sciences

NTP Board of Scientific Counselors Meeting
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Occupational and Inhalation Exposures (OIE) Team

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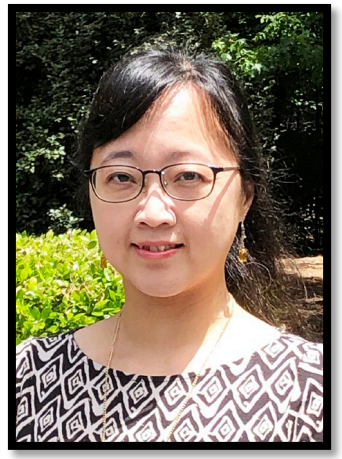

Pei-Li Yao
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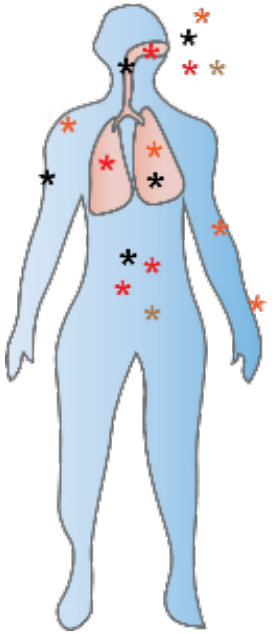
Photos: Steve McCaw

Occupational and Inhalation Exposures

Problem Statement

Chronic respiratory diseases were reported as the 3rd leading cause of deaths in 2017

Socioeconomic status



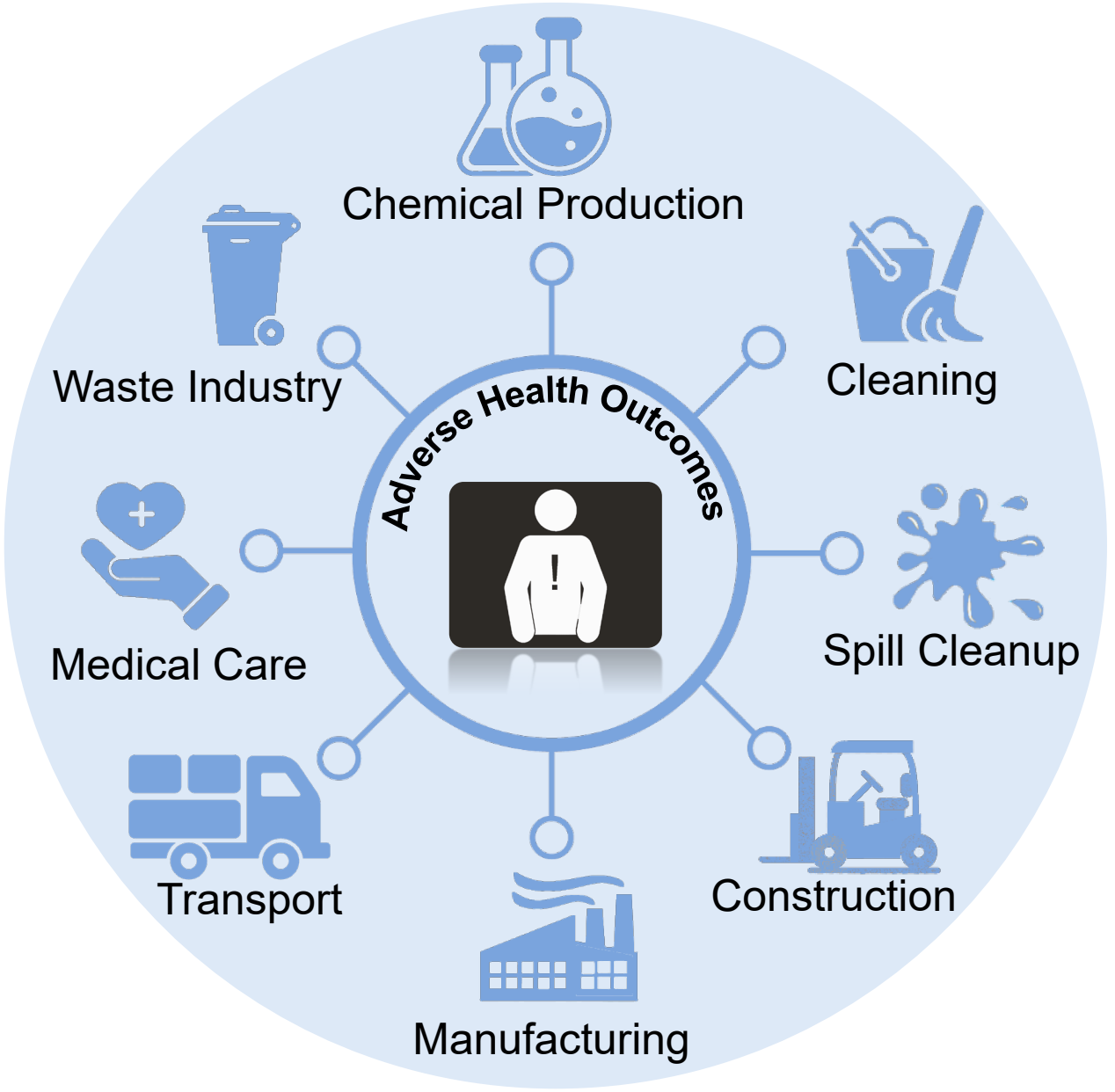
Occupation

Climate

Genetics

Environmental exposures increase the risk of respiratory disease

(e.g., COPD, asthma, airway/lung fibrosis, and cancer)

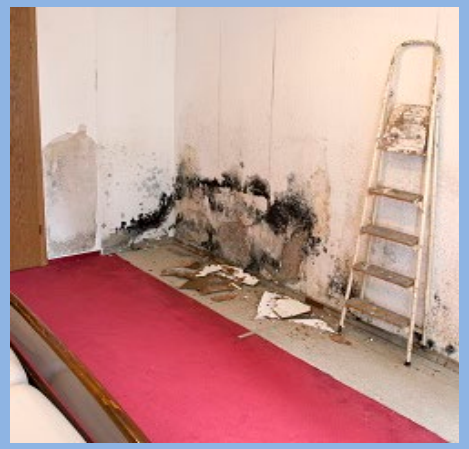


Problem Statement

Hazard characterization is critical to creating a safe living/working environment and reducing disease burden following inhalation exposures

Mimicking Inhalation Exposures is a Challenge!





DNTP Experience Evaluating Complex Exposures


Whole-Body Exposure


Nose-Only Exposure


Exposure systems for gases, vapors, particles


Complex Exposures (e.g. fibers)

> 100 Studies Reported

Methods Development

Prechronic Toxicity

Carcinogenicity

Human Cancer Hazard Assessment

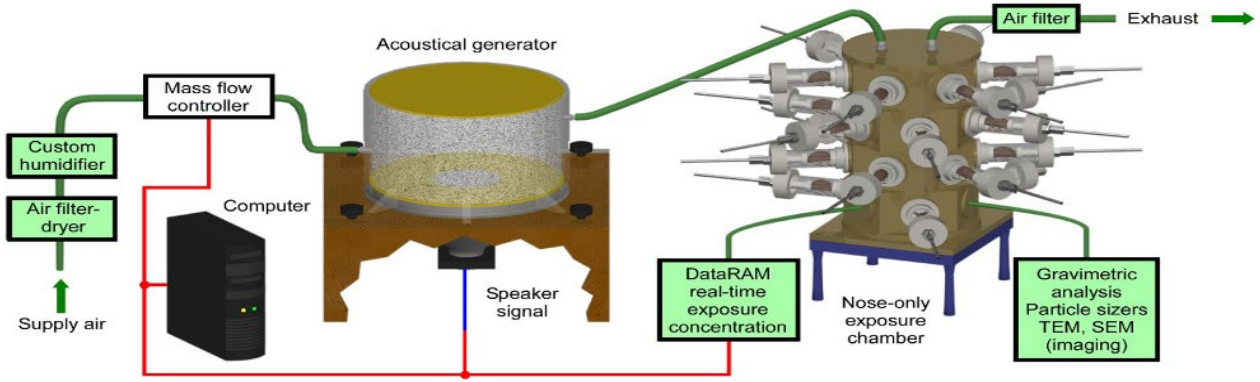
Technical Capabilities = Established, Unique, and Robust

DNTP Experience Evaluating Complex Exposures

Partner and Collaborator Capabilities: Fit-for-Purpose

Reverberation Chamber for Radiofrequency Radiation Studies

Acoustical Generating System for Mold Studies (NIOSH)



Active Air Sampling (charcoal tube)

Exhaled breath collection

Sampling for Human Exposure Assessments (NIOSH)

Images courtesy Battelle

Images courtesy NIOSH

Current Projects Monitored by OIE Program

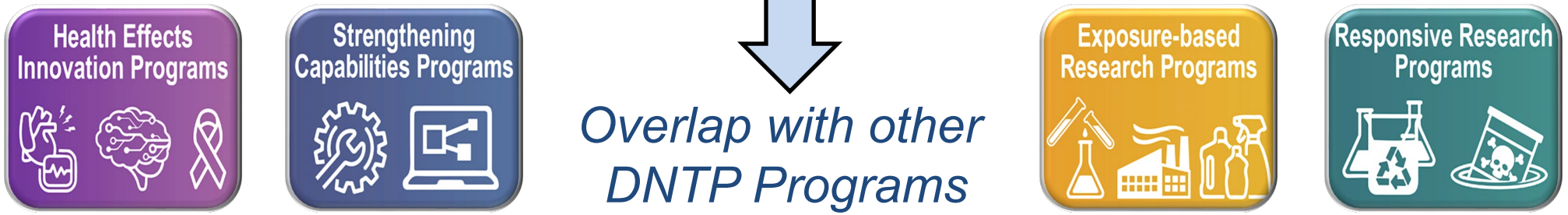
Design & Conduct

- Asbestos fibers
- Mold (*Aspergillus versicolor*)
- Alkylbenzenes (xylene)
- Occupational exposures (2D nanomaterials, Per- and polyfluorinated substances)
- Radiofrequency radiation
- *In vitro* airway models

Reporting

- Monoterpenes (α-pinene)
- Mold (*Aspergillus fumigatus*)
- Alkylbenzenes (trimethylbenzene)
- Nanomaterials (multi-wall carbon nanotubes)
- Chemical reagents (trimethylsilyldiazomethane)
- Butter-flavoring agents (2,3-pentanedione)

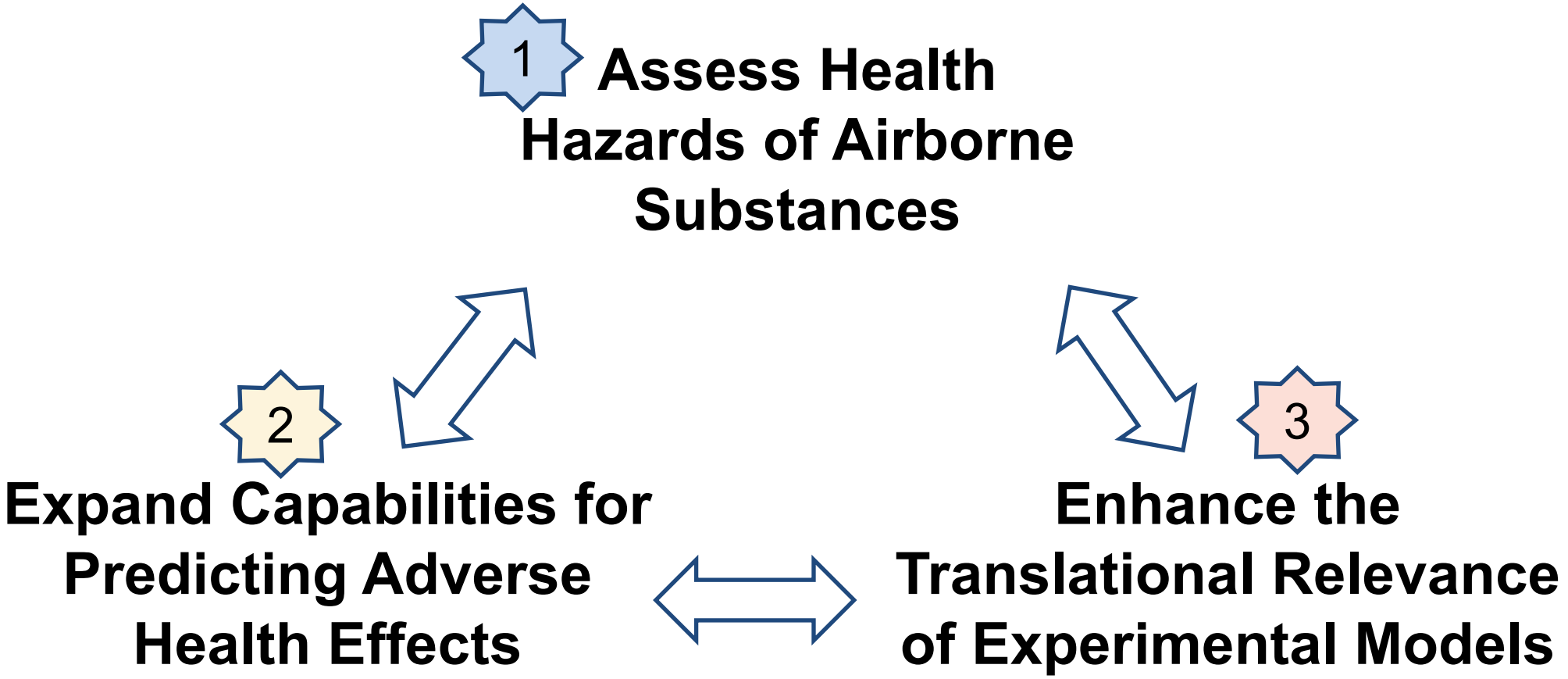
Projects include chemical toxicity assessments or establishment of capabilities



Why Should DNTP Continue to Focus on OIE?

The OIE program can focus research efforts to generate and communicate trusted scientific information to support decision making on environmental hazards of public interest.
- *DNTP Mission*

OIE Objectives



OIE Program Objectives

Examples & Integration

Assess Health Hazards of Airborne Chemicals

α-Pinene 1

- Common flavor and fragrance ingredient and major component in turpentine
- Ubiquitous low level indoor air pollutant with high levels in various occupations (e.g., lumber industry)
- No U.S. exposure limits specific to α-pinene and no available chronic toxicity data
- NTP conducted studies to address data gaps and provide hazard characterization data with exposure concentrations that overlap occupational exposures
  - Shorter-term studies reported in Toxicity Report 81 identified male reproductive effects and non-neoplastic lesions
  - Carcinogenicity studies currently being reported

Assess Health Hazards of Airborne Chemicals

α-Pinene 1 3

- Studies to compare animal data to human context
  - Toxicokinetic studies for animal to human dose extrapolation
  - *In vitro* metabolism in human and rodent hepatocytes
- Collaboration with NIOSH on human exposure context
  - Synthesis of available exposure literature
  - Identification of industries with high exposure potential
  - Measurement of α-pinene in workers
- Early stakeholder engagement
  - Presentation of pre-report findings to NTP executive committee
  - Explore regulatory implications
  - Facilitate communication to public

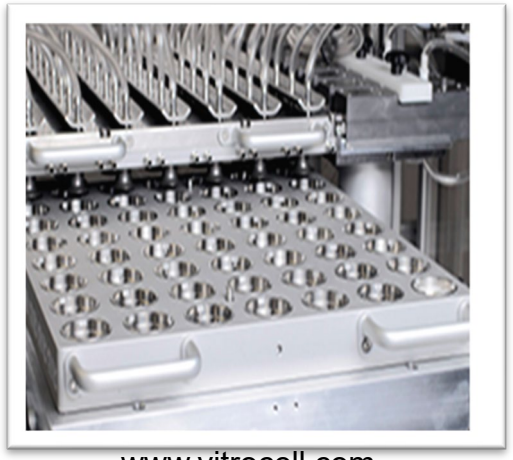
Expand Capabilities for Predicting Adverse Health Effects 2

- Novel/alternative technologies (i.e., *in vitro* models and microphysiological systems) have emerged for investigating inhalation toxicity to human airways
  - Screening level assessments to predict toxicity
  - Guide additional study design
  - Mechanistic evaluations of mode of action
  - Provide support (i.e., weight-of-evidence) for human risk assessment

Assess Health Hazards of Airborne Chemicals

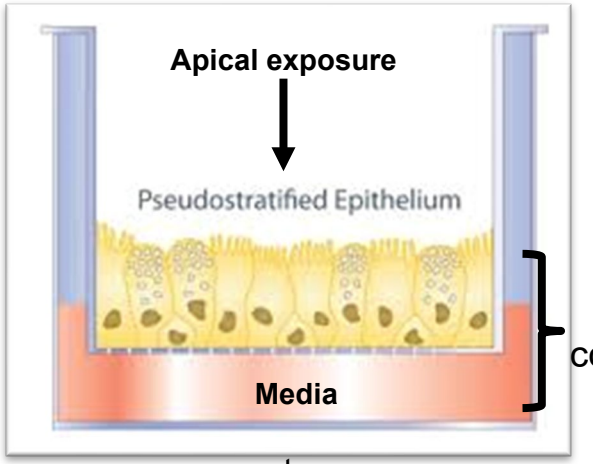
Expand Capabilities for Predicting Adverse Health Effects 2

Air-liquid interface (ALI) in vitro airway cultures



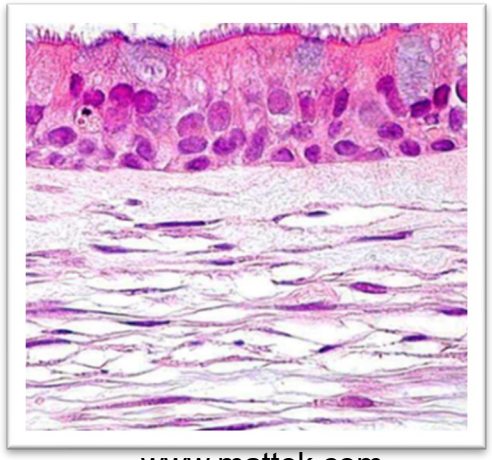
www.vitrocell.com

Exposures to vapors, gases, aerosols, or particles
↑ doses & throughput



www.atcc.org

Human- or rodent-derived primary cells
(tracheobronchial, bronchial, or alveolar compartment)



www.mattek.com

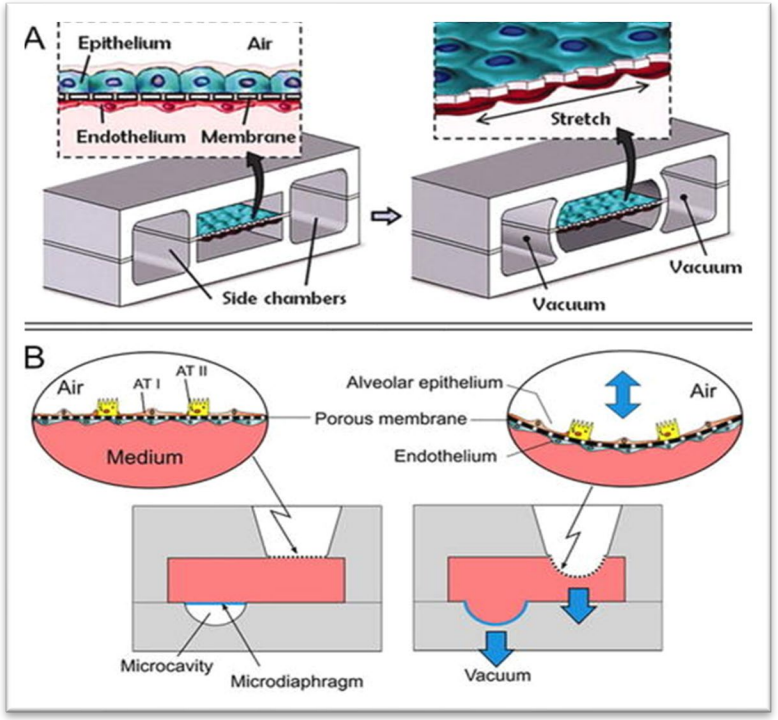
Replicates cell types and architecture of the human airway

Extensively used for the evaluation of inhalation/respiratory toxicity

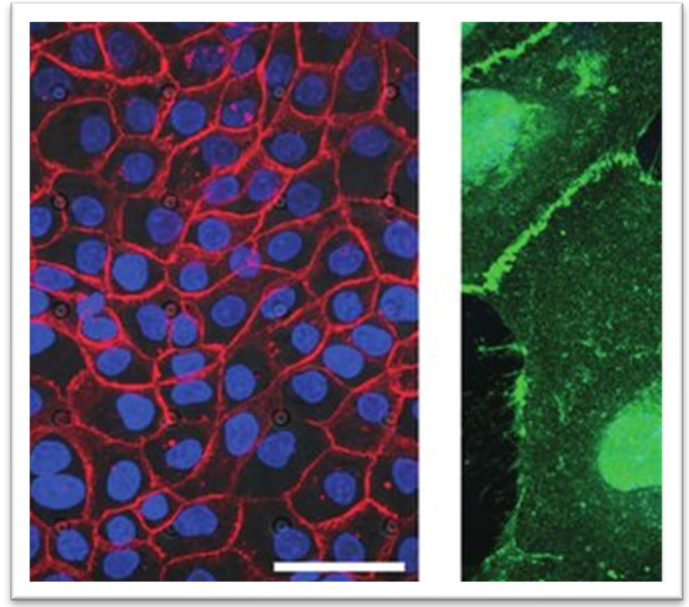
Expand Capabilities for Predicting Adverse Health Effects 2

Lung-on-chip (LOC) microphysiological system

www.alveolix.com



Guenat and Berthiaume 2018

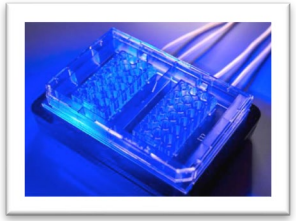


Stucki et al. 2014

More studies for application to pulmonary toxicity testing and mechanistic evaluations are needed

Assess Health Hazards of Airborne Chemicals

Expand Capabilities for Predicting Adverse Health Effects 2



Evaluate known respiratory toxicants
(defined by rodent studies)

Acquire* → **Optimize** → **Utilize** → **Expand tools for responding to specific stakeholder needs**

- Provide guidance regarding the value/application of these tools
- Make our evaluations and data publicly available

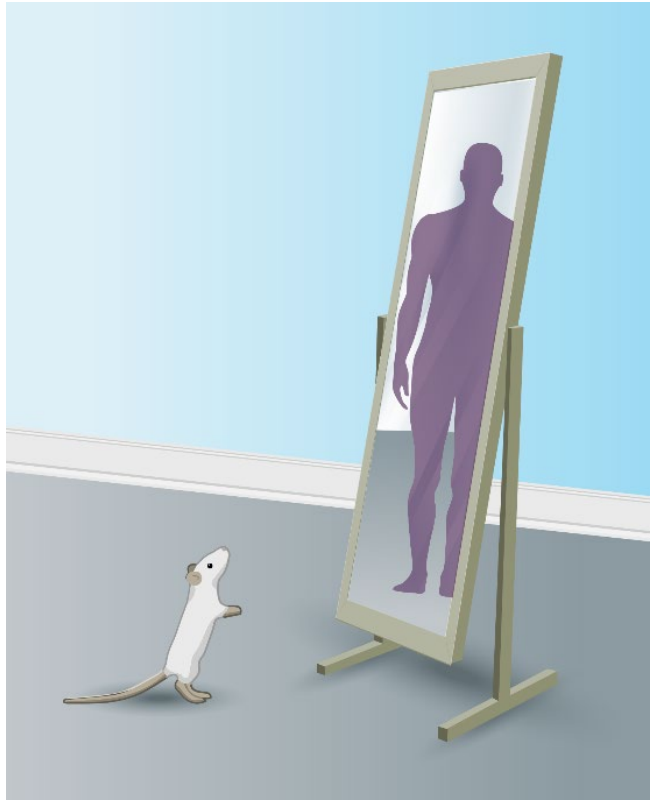
* Complete

Assess Health Hazards of Airborne Chemicals

Enhance the Translational Relevance of Experimental Models 3

Observation

Continued desire to understand how translatable rodent and/or *in vitro* models are for predicting human responses to chemical exposures

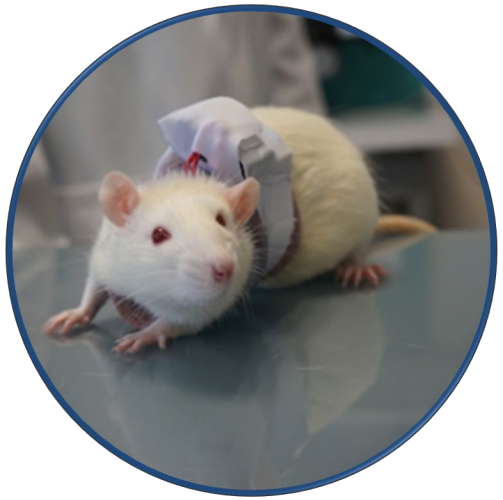


Aim

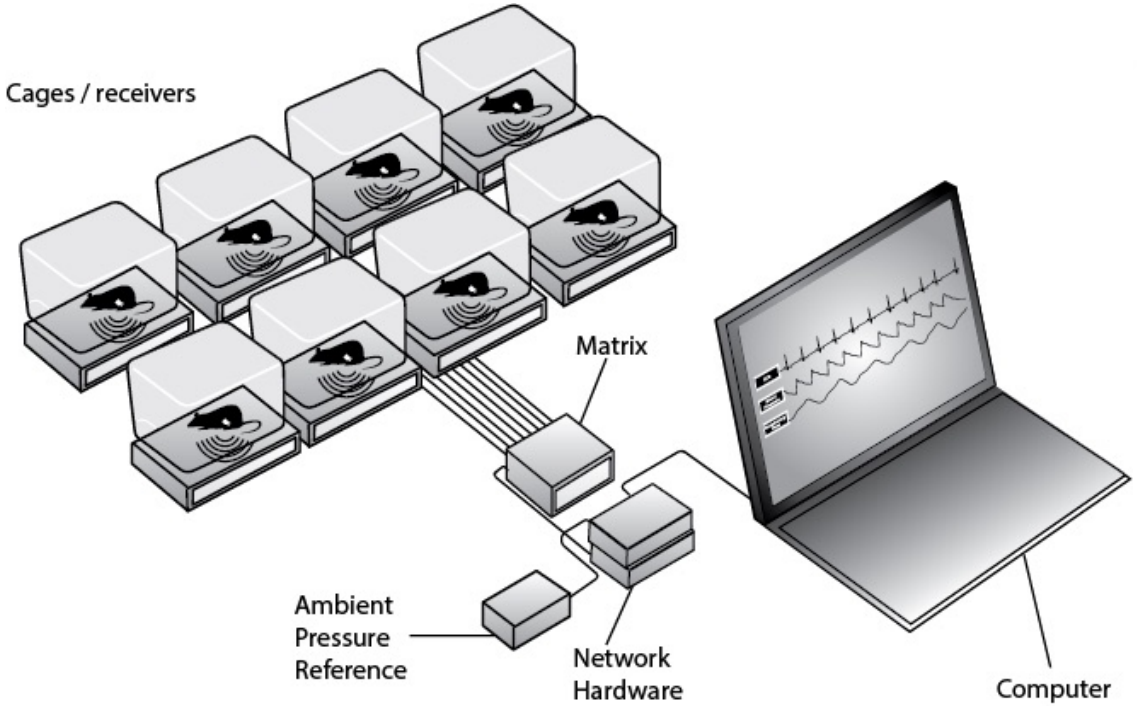
Improve upon existing technologies, identify more human-relevant endpoints, and gather human exposure data to support hazard characterization and risk assessment

Image from D. Germolec, DNTP

Physiological Monitoring 3



- The ability to monitor an animal's vital signs and other physiological parameters
  - Body temperature
  - Heart rate and rhythm (ECG)
  - Respiratory rate
  - Blood pressure
  - Blood glucose
  - Activity



https://www.datasci.com/products/implantable-telemetry/small-animal-telemetry

Physiological Monitoring

Why does the OIE Program want to move in this direction?

- Decrease the total number of animals required (i.e., animals serve as their own control)
- Provide critical information about the overall health status of the animal
- Detect clinical signs of toxicity at earlier time points or lower doses
- Obtain data without confounding factors such as stress due to handling
- Added value for inhalation studies – exposure chambers can cause stress

5-year Strategy

	1 Assess Health Hazards	2 Expand Capabilities	3 Enhance Translational Relevance
Short-term 1-2 years	• Project closeout • Reporting • System validation	• **Acquire** *in vitro* technologies and perform pilot studies	• Implement new methods
Medium-term 2-4 years	• Evaluation	• **Optimize** & establish scientific confidence in technologies	• Establish baseline data • Human exposure assessment • Cancer evaluation
Long-term 4-5 years	• Chronic studies	• **Utilize** technologies in hazard characterization	• Human exposure assessment • Evaluation & Communication

To Summarize……

- DNTP has established, robust, and unique capabilities to conduct assessments for inhalation/workplace exposures
  - Expertise from partnerships and contract capabilities

- The OIE Program was formed to:
  - Manage current projects and emerging public health problems related to inhalation exposures
  - Utilize resources and infrastructure to systematically and robustly build our capabilities (i.e., new tools and approaches)

Acknowledgements

Agency Partners

Contract Partners

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Thank You!

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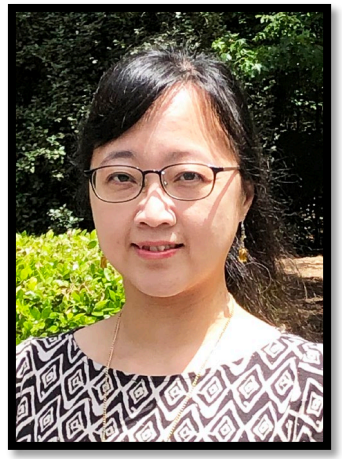

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