Occupational and Inhalation Exposures Program

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Photos: Steve McCaw
Chronic respiratory diseases were reported as the 3rd leading cause of deaths in 2017.

Environmental exposures increase the risk of respiratory disease (e.g., COPD, asthma, airway/lung fibrosis, and cancer).
Hazard characterization is critical to creating a safe living/working environment and reducing disease burden following inhalation exposures.
DNTP Experience Evaluating Complex Exposures

> 100 Studies Reported

Methods Development
Prechronic Toxicity
Carcinogenicity
Human Cancer Hazard Assessment

Technical Capabilities = Established, Unique, and Robust
Partner and Collaborator Capabilities: Fit-for-Purpose

Reverberation Chamber for Radiofrequency Radiation Studies

Acoustical Generating System for Mold Studies (NIOSH)

Sampling for Human Exposure Assessments (NIOSH)

Active Air Sampling (charcoal tube)

Exhaled breath collection

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*

Overlap with other DNTP Programs
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

1. Assess Health Hazards of Airborne Substances

2. Expand Capabilities for Predicting Adverse Health Effects

3. Enhance the Translational Relevance of Experimental Models
OIE Program Objectives

Examples & Integration
• 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

- 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 \( \alpha \)-pinene in workers

- Early stakeholder engagement
  - Presentation of pre-report findings to NTP executive committee
  - Explore regulatory implications
  - Facilitate communication to public
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

Air-liquid interface (ALI) in vitro airway cultures

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

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

- Replicates cell types and architecture of the human airway

Extensively used for the evaluation of inhalation/respiratory toxicity
Assess Health Hazards of Airborne Chemicals

Expand Capabilities for Predicting Adverse Health Effects

Lung-on-chip (LOC) microphysiological system

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

- Acquire*
- Optimize
- Utilize

Evaluate known respiratory toxicants (defined by rodent studies)

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

Expand tools for responding to specific stakeholder needs

* Complete
Enhance the Translational Relevance of Experimental Models

**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

- 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**
   - Short-term 1-2 years:
     - Project closeout
     - Reporting
     - System validation
   - Medium-term 2-4 years:
     - Evaluation
   - Long-term 4-5 years:
     - Chronic studies

2. **Expand Capabilities**
   - Acquire *in vitro* technologies and perform pilot studies

3. **Enhance Translational Relevance**
   - Implement new methods
   - Establish baseline data
   - Human exposure assessment
   - Cancer evaluation
   - Human exposure assessment
   - Evaluation & Communication

- Acquire *in vitro* technologies and perform pilot studies
- Optimize & establish scientific confidence in technologies
- Utilize technologies in hazard characterization
- Implement new methods
- Establish baseline data
- Human exposure assessment
- Cancer evaluation
• 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)
Thank You!