NIOSH Research on Peracetic Acid (PAA)

NIOSH Board of Scientific Counselors
April 28, 2020

Peracetic Acid (PAA)

- Colorless liquid with a pungent odor primarily used as a bactericide and fungicide, sterilizing and bleaching agent
- Used in commercial solutions with hydrogen peroxide, and acetic acid
- Use as a sterilant is projected to be the fastest growing market segment due to its high biocidal effectiveness, short dwell time, and no rinse requirement (for food applications)
- Highly corrosive and extremely irritating to the eyes, skin, and upper respiratory tract

How PAA is used in Industry

- Food and Beverage
  - Food Tissue treatment (poultry, red meat)
  - Hard surface sanitizer
- Healthcare
  - Surface disinfection—terminal cleaning of patient rooms, surgical suites
  - High level disinfection—endoscopes
- Water treatment
  - Process water treatment
  - Clean in place (CIP) of process lines

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Exposure Limits

- ACGIH 15 minute STEL- 0.4 ppm
- CAL-OSHA HEAC Proposed 15 min STEL 0.4 ppm, 8-hr PEL 0.15 ppm
- NRC AEGL-1 (10 min-8 hr): 0.17 ppm, AEGL-2: 0.5 ppm
- NIOSH Immediately Dangerous to Life and Health (IDLH)
  - Proposed 1.7 mg/m^3 (0.55 ppm) in 2015
  - Stakeholders had concerns including: accurate measurement, quality of data and use of uncertainty factor, distance from STEL to IDLH

Peracetic Acid Project

Purposes:

1. Address the gaps in PAA research including measurement issues, lack of irritation data, and minimal workplace exposure data.
2. Develop an IDLH and risk management guidance to protect workers from occupational exposures to peracetic acid

Approach:

1. Cross-divisional research agenda
2. Includes basic, applied, and field studies

PAA Project Team

- Risk Assessment (DSI)
  - Christine Whittaker, Todd Niemeier
- Analytical Studies (HELD)
  - Amos Doepke, Angela Stastny, Bob Streicher, Jason Ham, John Snawder, Surendra Devarakonda, Juliana Meadows, Stephen Jackson (former NIOSH)
- Animal Studies (HELD)
  - Jeff Reynolds, Walter McKinney, Marlene Orandle, Ann Hubbs
- In Vitro Studies (HELD)
  - Steve Leonard, Nicole Olgun, Marlene Orandle
- Field Studies (DFSE)
  - Mike Grant, Barb Alexander, Kevin Dunn, Martha Waters (former NIOSH), Brie Blackley (RHD)
- Project Management
  - Paul Schulte, Sam Glover, TJ Lentz, Kevin Dunn

Peracetic Acid – NIOSH Activities

- Health Hazard Evaluation (HHE) Report - Assessment of peracetic acid exposure among federal poultry inspectors [Report No. 2014-0196-3254]
- Health Hazard Evaluation (HHE) Report - Evaluation of peracetic acid exposure among federal poultry inspectors [Report No. 2015-0130-3290]
- Health Hazard Evaluation (HHE) Report - Evaluation of exposure to a new cleaning and disinfection product and symptoms in hospital employees [Report No. 2015-0053-3269]
- Health Hazard Evaluation (HHE) Report - Evaluation of exposure to a hydrogen peroxide, peracetic acid, and acetic acid containing cleaning and disinfection product and symptoms in hospital employees [Report No. 2017-0114-3357]

Developing an IDLH

- For chemicals under consideration, an IDLH can be based on:
  - Lethality
  - Severe, irreversible health effects
  - Safety considerations (>10% LEL or O2 displacement)
  - **Escape-impairing irritation**
- Peracetic acid is highly irritating but does not seem to persist in air
  - Best data we have indicates irritation is a key health effect

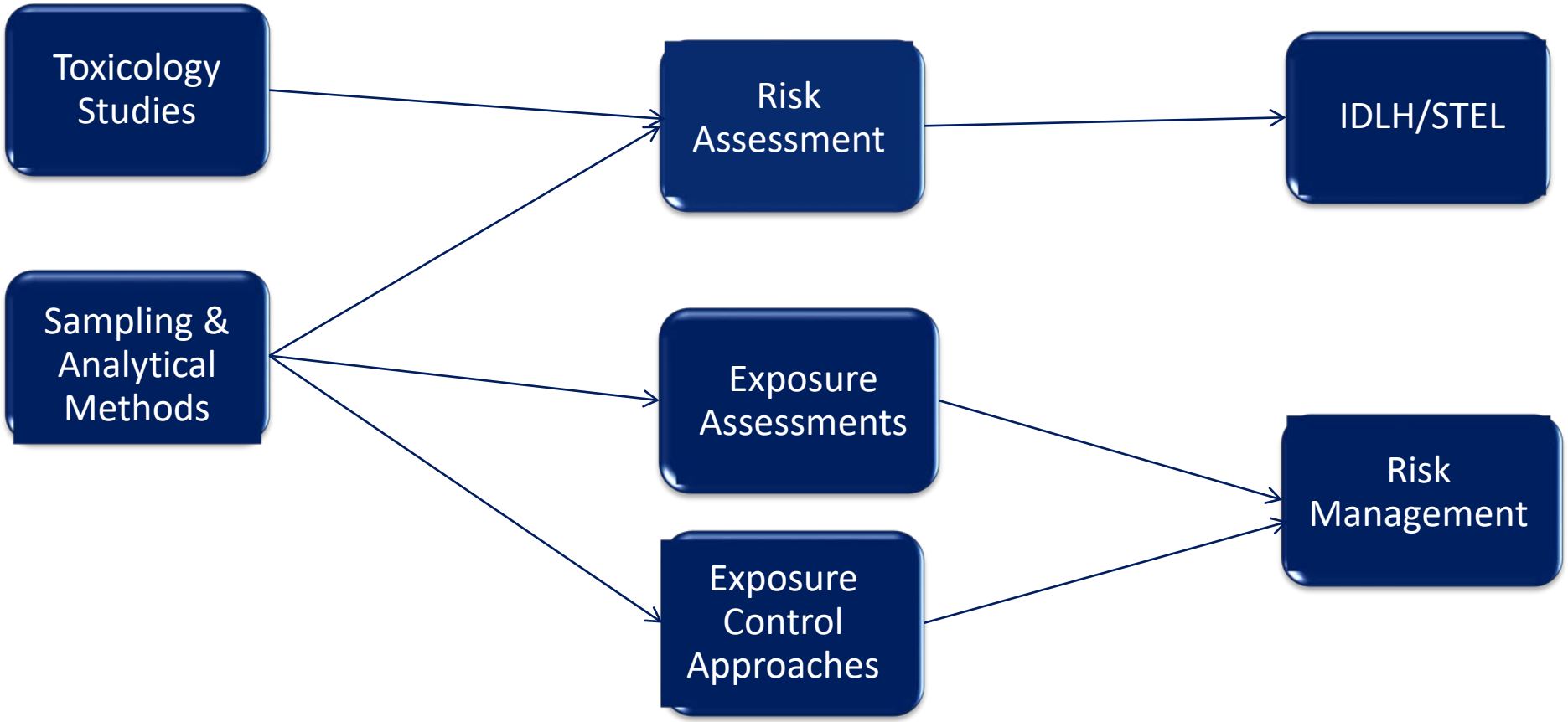
Developing an IDLH

- Data needed to develop an IDLH
  - **Animal toxicology data:**
    - Short-duration exposures
    - Respiratory effects (RD_{50})
    - Histopathological damage
    - Recovery after exposure
    - Separate assessment of peracetic acid and mixture

Developing an IDLH

- Data needed to develop an IDLH
  - Field study data:
    - Workplace exposures
    - Workplace environmental conditions
  - Analytical method:
    - Confidently measure exposures for animal studies
    - Confidently measure exposures in field studies, subject to variable temperatures, humidity, etc.

IDLH/Risk Management development process



Analytical Studies Objectives

- **Evaluate Existing Laboratory Methods and Direct Reading Methods**
  - Confidence is needed in measurements and generation of controlled atmospheres.
  - Do they pass NIOSH criteria for measurement methods?
  - Interferences?
- **Modify and Improve Existing Methods**
- **Explore New Chemical Assays That May Have Advantages Over Existing Methods**
- **Support Field, In Vivo, and In Vitro Studies:**
  - Large concentration range 0-50 ppm.
  - Comparison of detection methods (emerging and traditional) for use in given conditions.

PAA Measurement Methods

Chemical Measurement	Manufacturer	Measurement Range	LOD	Measurement Method
PortaSens II	Analytical Technology Inc.	0-2 ppm[a], 0-20 ppm[a]	0.05 ppm[a] 0.1 ppm[a]	Direct Reading Method
SafeCide Portable Monitoring	ChemDAQ Inc.	0-3 ppm[a]	0.04 ppm[a]	
4000 Series Compact Portable Analyzer	Interscan Corporation	0-5 ppm[a], 0-50 ppm[a]	0.05 ppm[a] 0.5 ppm[a]	
Impinger (colorimetric)	CHEMetrics Inc.	0-1.6 ppm per 15 L[a]	0.016 ppm[a]	Lab-based Method
Impinger (Hecht liquid analysis)	Reagents purchased directly	0.02 – 16.2 ppm per 15 L[b]	0.003 ppm[b] 0.013 ppm[d]	
Sorbent tubes (Hecht solid phase analysis)	SKC Inc.	at least 0.47 ppm per 15 L[b]	0.005 ppm[c]	

[a] Criteria from manufacturer's documents [b] Nordling, Ecolab – Sampling and Analysis – unpublished – 2017. [c] Burton and Gibbins, Health Hazard Evaluation Report 2015-0130-3290, 2017. [d] Nordling *et. al.* 2017

Analytical Studies—Accomplishments

Evaluate Direct Reading Methods for PAA

- Confidence is needed in measurements and generation of controlled atmospheres

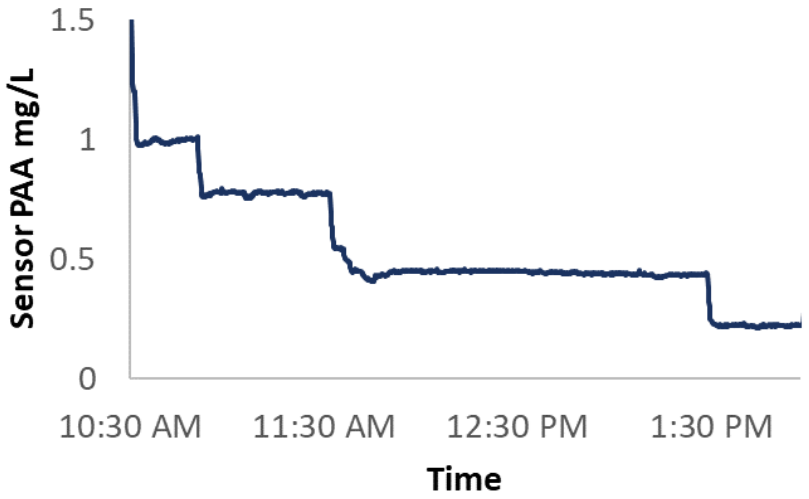
- **Key Accomplishments**
  - Completed development of a stable PAA atmosphere generator
  - Evaluated 3 different PAA real-time monitors (ChemDAQ, Interscan, Portasens) and multiple sensor ranges
    - Completed approx. 5000 test conditions across a wide range of concentrations, temperatures and humidities
    - Assessed recovery time, response time, span drift, zero drift, temperature range, humidity range

PAA Direct Reading Monitor Assessment

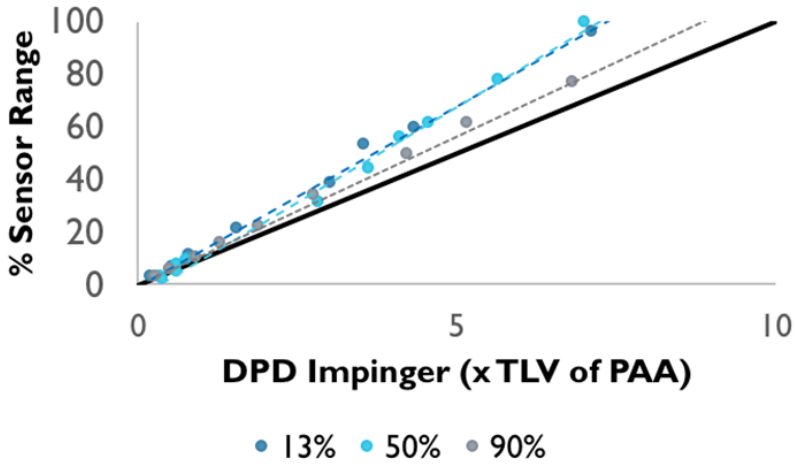
Photo by NIOSH

Electrochemical PAA sensors attached to sampling column

Stability



Relative Humidity Range



Analytical Studies-Accomplishments

Evaluate and improve existing laboratory-based methods

Assessing commercially available sampler/analysis methods

- **Key Accomplishments**
  - Improved existing sorbent tube (Hecht) method with revised sample prep to increase recovery
  - Developed a new impinger (colorimetric) method for potential workplace measurements (low cost/low uncertainty)
  - Developed a new PAA sorbent tube method (Prilezhaev Reaction) which allows longer sampling durations, is less subject to interference from other oxidants/disinfectants, decreases cost/sample and allows for a smaller/lightweight sample train

Analytical Studies-Future Plans

- **Direct Reading Methods**
  - Assess chemical interferents which are commonly used such as chlorine and bromine
  - Evaluate monitor performance in mixed aerosol environments (vapor and mist)
- **Laboratory-based Methods**
  - Assess humidity effects and increased sample duration on Hecht sorbent tube method
  - Conduct storage study and determine LOD/LOQ of hydrogen peroxide using Hecht impinger method
  - Evaluate (Prilezhaev Reaction) sorbent tube method sample duration, humidity effects and determine method criteria (LOD/LOQ, bias, accuracy and environmental effects)

Animal Studies Objectives

- **Assess the respiratory irritation response of mice exposed to vapor of commercially available peracetic acid solution**
  - Perform acute inhalation exposures at several concentrations
  - Develop a system capable of measuring breathing rates during exposure in unrestrained mice to assess sensory irritation

- **Assess the respiratory histopathological response of mice exposed to vapor of commercially available peracetic acid solution**
  - Assess nasal histopathology from samples collected immediately following acute exposure and at 24 hours post exposure
  - Emphasis on nasal histopathology, but also look at the trachea and the lung

Animal Studies-Accomplishments

Assess sensory irritation and nasal histopathology of mice exposed to commercial PAA solution

- **Key Accomplishments**
  - Completed construction of inhalation exposure system with integrated unrestrained plethysmography
  - Completed animal exposures to commercially available PAA mixture
    - 2 exposures for 0, 3, 6, 12, and 24 ppm concentrations
    - Respiratory rates collected
    - Histology samples collected at 7 sites, distal to proximal, across the nares (0 and 24 hours post exposure)

Animal Studies

- Inhalation exposure system with integrated unrestrained plethysmography

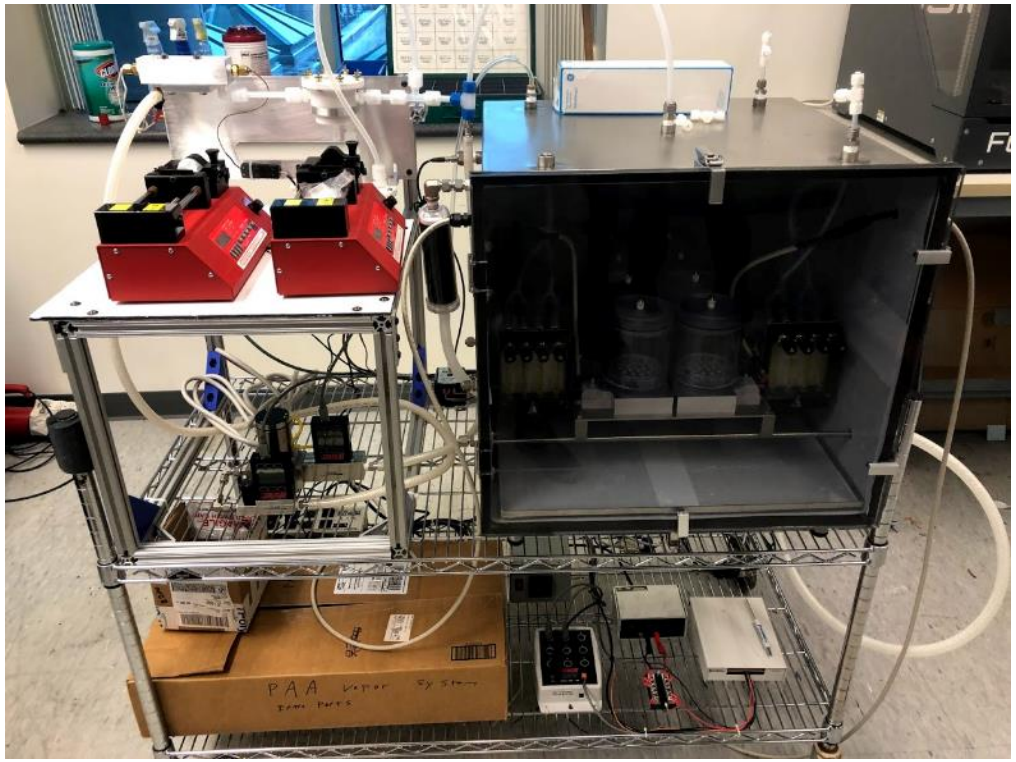
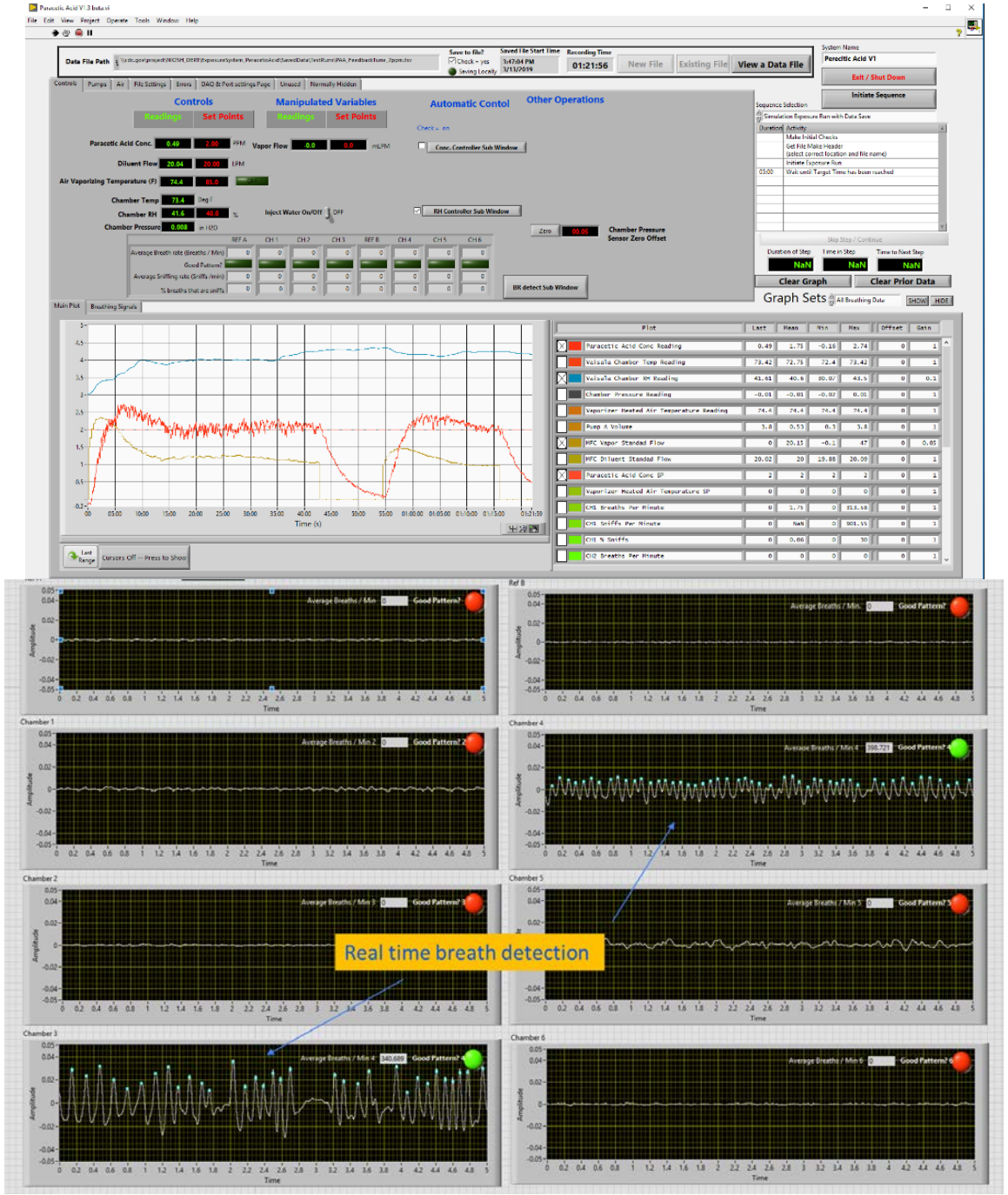


Photo by NIOSH



Animal Studies-Future Plans

- **Future Plans**
  - Vapor inhalation exposures
    - Fill in at least one lower dose (1.5 ppm)
    - Repeat exposures with head-out plethysmography
  - Other potential activities (FY 21 and beyond)
    - Repeated (multi-day) exposures
    - Vapor exposures to component parts: AA, HP, pure PAA
    - Aerosol exposures

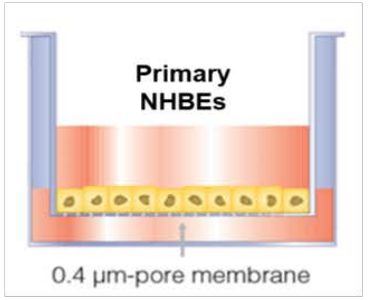
In vitro studies - Objectives

- Assess the cytotoxicity of PAA vapor exposures on primary, normal human bronchial epithelial (NHBE) cells using an air-liquid interface (ALI) system
- Acute exposure response (3, 12, 22 ppm)
- Repeated exposure response (low dose PAA)

A

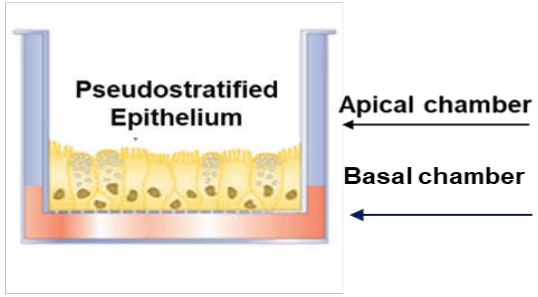
- Cells taken out of liquid nitrogen
- Placed in T25 flasks
- 5 days

B



- 1.5 x 10^5 cells/membrane
- Media in both apical & basal chamber
- 80% confluency
- 6 days

C



- Media in basal chamber only
- "ALI Day 1"
- Differentiation of cells
- Expose to PAA vapors on ALI Day 28.

In vitro studies – Endpoints

- Cellular viability
- Lactate dehydrogenase (LDH)
- Reactive Oxygen Species (ROS)
- Pro-Inflammatory cytokines (IL-6, IL-8)
- Endothelin-1 (pro-inflammatory mediator and vasoconstrictor)
- Histological changes – H&E, PAS, and Immunofluorescence
- Transepithelial/ Transendothelial electrical resistance (TEER)
- Scanning Electron Microscopy
- Transmission Electron Microscopy

Completed for 22 ppm PAA and 12 ppm PAA (4 hr exposure + 4h and 24h recovery period

1-3 ppm PAA exposures- Spring 2020

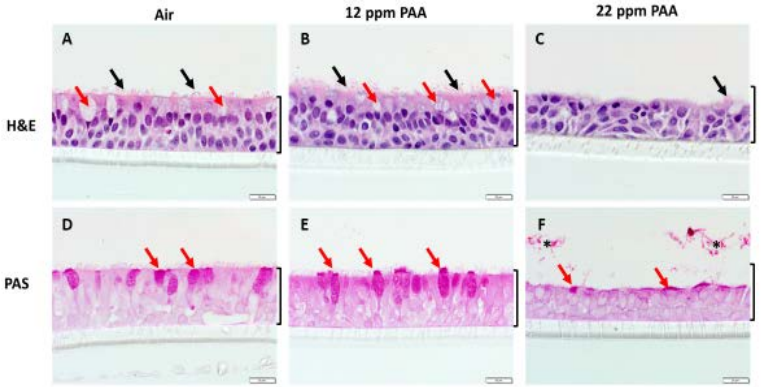
In Vitro Studies-Accomplishments

Key Accomplishments

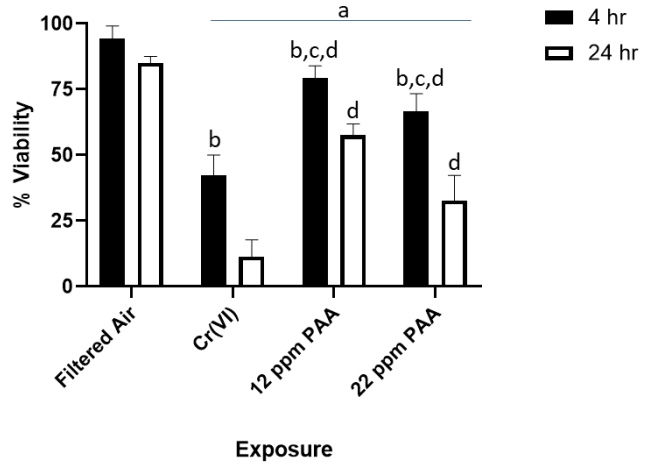
- Confirmed that NHBE cells could be exposed to filtered air for 4 hrs with minimal loss of viability, despite differences in temperature, $\%CO_2$ and relative humidity when compared to the cell culture incubator
- Completed NHBE cell exposures to commercially available PAA mixtures at the mid and high dose (12 and 22 ppm).
- Currently working on lower doses (1-3 ppm)
- Assessment of viability, LDH release, production of pro-inflammatory mediators (IL-8, IL-6, ET-1) and TEER at 4 and 24 hr post exposure
- Histopathology also evaluated at 4 and 24 hr post exposure

In Vitro Studies-Initial Findings and Future Plans

- **Key Findings**
  - Dose response effect observed in cellular viability and cytotoxicity
  - 12 ppm PAA – “injury response”, mucus cell hyperplasia, loss of cilia
  - 22 ppm PAA- “cell death”, epithelial blunting, cell debris, loss of apical layer



- **Future Plans**
  - Complete SEM, TEM, IF, H&E and PAS staining for all exposures and timepoints
  - Finish exposures of NHBE cells to 3 ppm PAA vapors (FY20; in progress)
  - Repeated exposures of NHBE cells to low-dose PAA (FY21 and beyond)



Field Studies-Objectives

- To assess exposures to PAA, HP, and AA and evaluate the use and design of engineering controls in facilities using PAA
  - Conduct personal sampling to assess short term worker exposures to PAA, HP, and AA
  - Assess sources of emission, control effectiveness and plant ventilation schemes
  - Develop guidance on reducing employee exposures to PAA mixtures

Photo by NIOSH

Field Studies-Objectives

- To assess the accuracy and response of direct reading PAA monitors in the field against the filter/sorbent tube and impinger methods
  - Conduct area sampling to evaluate accuracy and response of real time monitors in field applications
  - Co-locate filter/sorbent tube sampler (Hecht method), impinger, and real time monitors for field-based method evaluation

Photo by NIOSH

Field Studies-Accomplishments

Assess exposures to PAA, HP, and AA and evaluate the use and design of engineering controls in a variety of workplaces

Key Accomplishments

- Drafted study protocol and completed peer and tripartite reviews
  - Protocol approved by NIOSH IRB February 2020
- Conducted walkthroughs at 4 sites, including:
  - Pharmaceutical, hospital, food production plants
  - Have had discussions with additional partners including: hospitals, pharmacy, food production

Summary and Accomplishments

Analytical Activities

- Assessment of PAA real time monitors have completed and shown the effects of temperature and humidity across a wide range of concentrations for the three commercially available monitors
- New impinger method for analyzing PAA in air has been developed and evaluated and compared to a second impinger method (Hecht)
- New (Prilazhaev) sorbent tube method developed allowing for cheaper analysis and extended sample times
- Improvements to the existing commercially available sorbent tube/treated filter sampling method (Hecht et al) has increased recovery

Animal Studies

- Initial mice exposures have been completed and RD50 for irritation is being analyzed
- Additional exposures planned for lower concentrations (below 3 ppm)

Summary and Accomplishments

In Vitro Studies

- Initial exposures at concentrations of 12 and 22 ppm concentrations completed
- PAA decreases cellular viability and TEER, while increasing cytotoxicity and inflammation
- Histopathology shows changes in mucus production and cilia in PAA exposed cells as compared to filtered air controls

Field Studies

- Study protocol completed peer, tripartite, and IRB review and is approved for use
- Recruiting of potential facilities is ongoing with 8 sites identified at this point and more likely in the near future
- Walkthrough of sites started in 2019 and will continue in 2020. Site surveys will start in 2020

Questions/Discussion

- Do we have the critical pieces of the project adequately covered?
  - Do all of the individual projects adequately address the goal of developing the basis for an IDLH?
  - Are there other areas/research needs that we should be focusing on?