Opportunities for Waiving Inhalation Studies for Pesticides

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Guiding Principles for Data Needs for Pesticides

- Guiding Principles for Data Requirements
  - Purpose: provide consistency in the identification of data needs, promote and optimize full use of existing knowledge, and focus on the critical data needed for risk assessment.
  - https://www.epa.gov/sites/production/files/2016-01/documents/data-require-guide-principle.pdf
- "…ensure there is sufficient information to reliably support registration decisions that are protective of public health and the environment while avoiding the generation and evaluation of data that does not materially influence the scientific certainty of a regulatory decision…."
- "…avoid unnecessary use of time and resources, data generation costs, and animal testing."

Guiding Principles for Data Needs for Pesticides

- Promotes the full use of existing knowledge to focus on the data needed
- Provide consistency in the determination of toxicology data needs across OPP divisions
- Data needs decisions are typically case-by-case and consider all existing knowledge including the pesticide's physical–chemical properties, metabolism/pharmacokinetics, toxicological profile, exposure, available human information, as well as information on structural analogues.

Data Needs for Pesticides

- EPA data requirements listed under 40 CFR Part 158
  - Includes requirements for conventional, biochemical, and antimicrobial pesticides
- Flexibility in implementing Part 158 data requirements (§158.30):
  - Waivers may be granted as permitted by 40 CFR Part 158.45
  - Additional data beyond the 158 data requirements may be important to the risk management decision (§158.75), alternative approaches can be accepted, and other data can be used.

Hazard & Science Policy Council (HASPOC)

- Develop overarching guidance and policies to allow OPP to accomplish its scientific and regulatory goals
- Achieve harmonization and develop consistent use of toxicity and other data in human health assessment across the divisions
- Build efficiencies into the risk assessment process
  - Fewer studies submitted = Less resources spent
  - Better focus on most important issues
- Implement the 3R's of animal testing: Replace, Reduce, Refine:
  - Reduce: Waivers for inhalation, dermal, neurotoxicity, immunotoxicity
  - Refine: Special protocol studies instead of standard guideline protocols (e.g., shorter duration, fewer animals, single gender, etc)
  - Replace: Pharmacokinetic studies in lieu of toxicity study

Part 158 Toxicology Data Requirements: Guidance for Neurotoxicity Battery, Subchronic Inhalation, Subchronic Dermal and Immunotoxicity Studies

- Document covers:
  - Subchronic Inhalation (870.3465),
  - Subchronic Dermal (870.3250),
  - Neurotoxicity screening batteries (870.6200; acute and subchronic neurotoxicity),
  - Immunotoxicity (870.7800)
- If a waiver cannot be granted, the document provides guidance on retaining a database uncertainty factor (UF_{DB}) is needed until the study is conducted and/or other information is used to fill the data gap.

https://www.epa.gov/sites/production/files/2014-02/documents/part158-tox-data-requirement.pdf

WOE Approach Used by HASPOC

- Risk-based decision making
  - Consider both hazard and exposure
- Committee is comprised of senior toxicologists & exposure scientists across various divisions
- Considerations for waivers:
  - Physical chemical properties
  - Use & exposure pattern
  - Hazard characterization:
    - Toxicity profile, information on mode of action (MOA)/adverse outcome pathway (AOP), other pesticides in the class
  - Risk assessment implications

Exposure is important!

- Why exposure information is important:
  - Use pattern - how the chemical is used reflects:
    - The food the pesticide is used on and how we will be exposed in our diets,
    - How a worker will be exposed when using the product,
    - How a worker will be exposed after using the product (post-application exposure),
    - How a residential handler will be exposed when using the product around a home, and
    - How someone will be exposed after a product is used around a home.
- Qualitative vs. quantitative evaluation considered
- Risk estimates represent the risk after considering the hazard and exposure of the active ingredient.
- It is important for HASPOC to understand BOTH hazard and exposure when considering whether to waive or require a study.

HASPOC Results

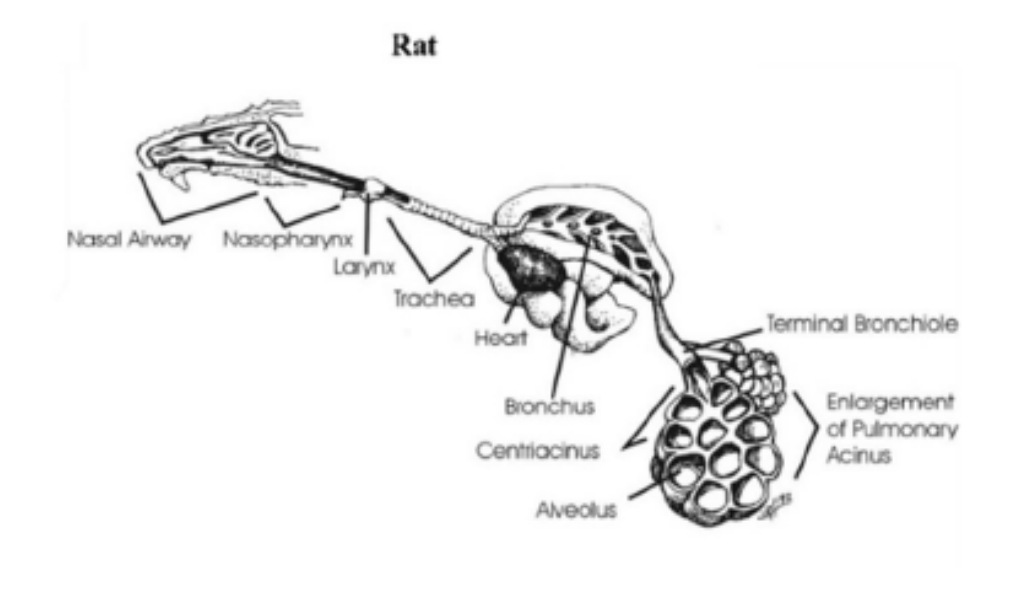
- Out of 296 requests for inhalation waivers, 233 have been granted
  - From December 2011 through August 2018
- In FY'16, waivers were granted for 153 of 180 requests resulting in savings of about 44,000 animals and over $16 million in the cost of conducting the studies.
- In FY'17, waivers were granted for 70 of 78 requests resulting in savings of about 41,000 animals and approximately $10.4 million in the cost of conducting the studies.
- https://www.epa.gov/pria-fees/annual-reports-pria-implementation

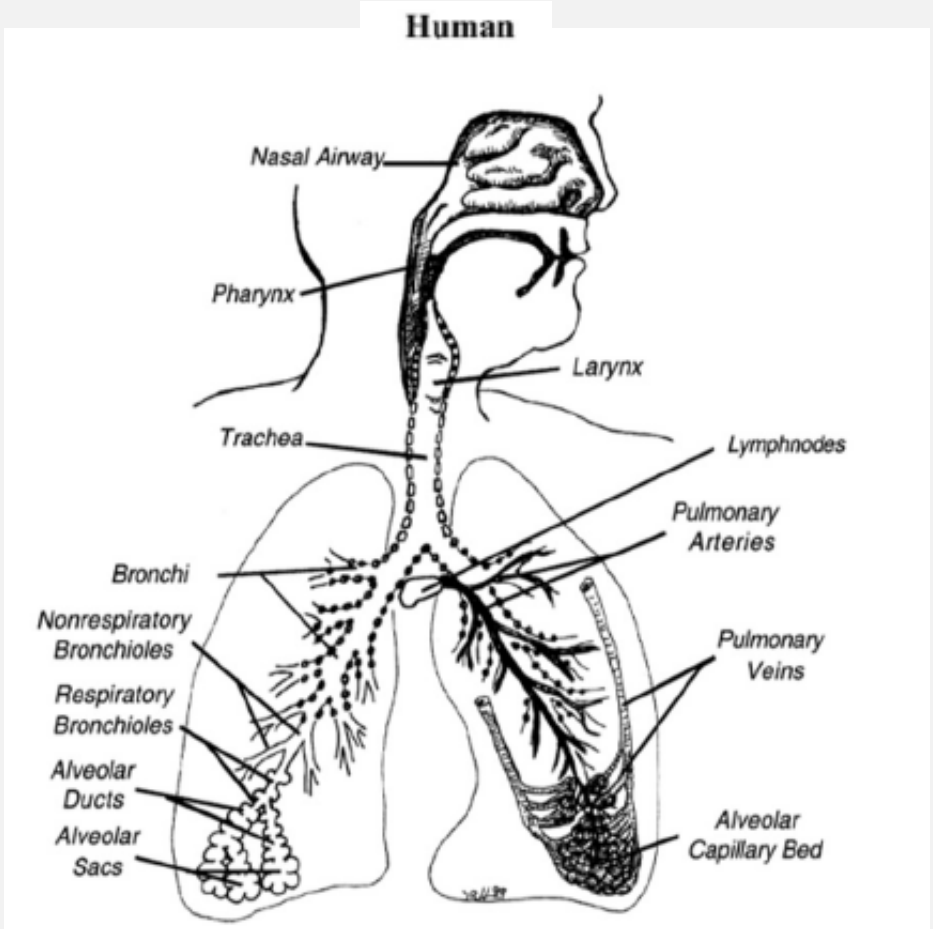
Alternative Approaches

Rat vs Human Respiratory Tract

Differences lead to changes in airflow and deposition of inhaled substances

- Airway size and surface area
- Nasal turbinate systems
- Branching patterns
- Cell composition/distribution of surface epithelium
- Anatomy of larynx





Images taken from Clippinger et al. (2018)

Challenges associated with irritants

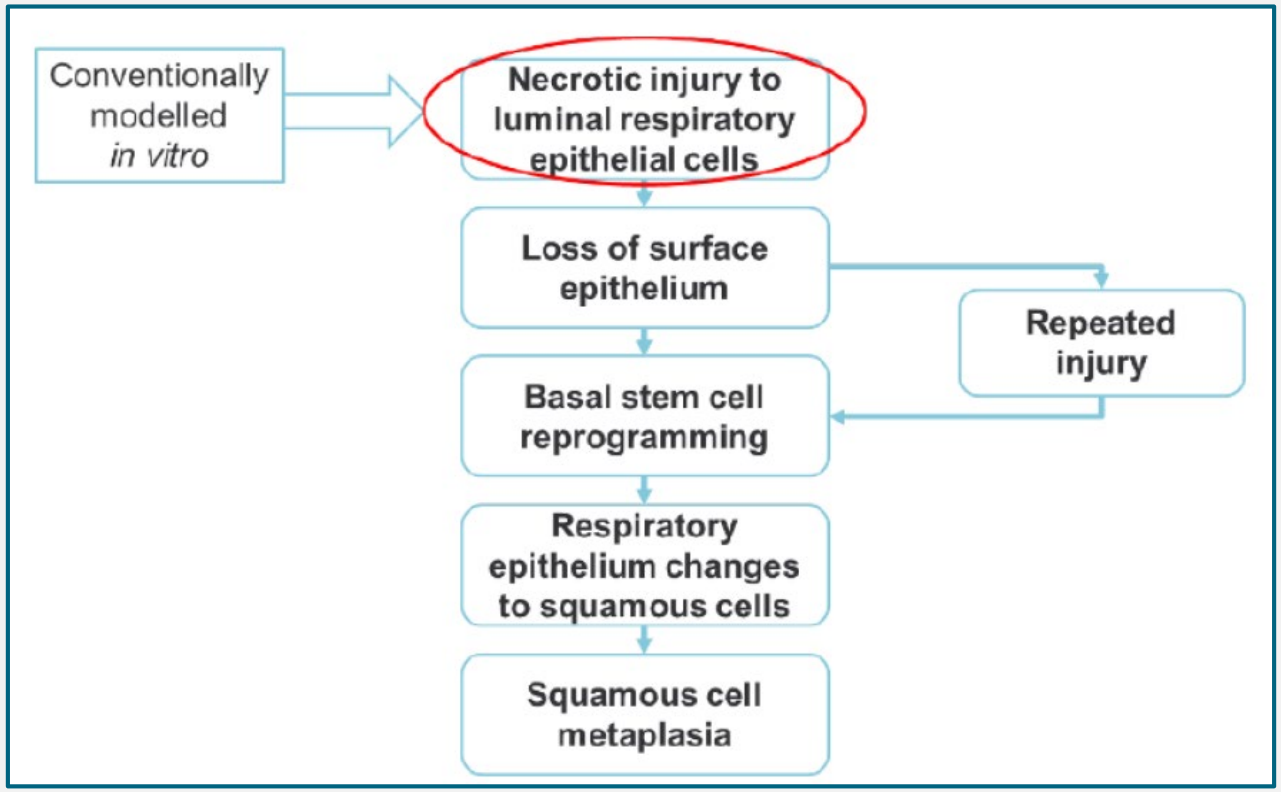
- Traditional *in vivo* inhalation studies are resource intensive in terms of animal use, expense, and time
- Respiratory irritants can elicit damage at very low doses
  - Clear no observed adverse effect concentration (NOAEC) may not be established
  - Animal welfare concerns
- Efforts to develop new approach methodologies (NAMs)

Case Study Using a NAM to Refine Inhalation Risk Assessment for Point of Contact Toxicity

- Submitted by Syngenta Crop Protection, one of the registrants for products containing the contact irritant chlorothalonil
- Proposal for refining inhalation risk assessment using a three-dimensional *in vitro* model to derive a point of departure
  - Initially presented to EPA in 2014
- Agency recognized the value of the proposal for chlorothalonil, as well as other respiratory contact irritants and encouraged further development
- Collaborated with NICEATM early in the process for review of the proposed approach

Outcome

- Epithelial cell damage occurs from initial inhalation exposure to chlorothalonil and causes cell death
- Following repeated exposure, cell death results in metaplastic response and transformation of respiratory epithelium into stratified squamous epithelium
- Sufficient amount of chlorothalonil is needed at the cell surface to result in cell death in pathway



Extracted from MRID 50610402 (Flack et al. 2018)

Dosimetry

- Site-specific deposition in human upper respiratory tract predicted by computational fluid dynamic (CFD) modeling
- CFD models for upper respiratory tract developed for several species including rats, monkeys, and humans
- Utilize computational mesh based on species-specific anatomical data to develop airflow patterns that are used with boundary conditions, chemical-specific diffusivity, and mass transfer coefficients to predict localized deposition of inhaled material
- Incorporate human relevant particle size distributions

Proposed Inhalation Risk Assessment Utilizing Refined Approach

- Site-specific HECs calculated by integrating dosimetry and outcome results
  - Benchmark dose modeling of *in vitro* data
  - Total Daily deposition calculated from CFD model results
    - Includes calculations to generate polydisperse particle distributions and incorporate relevant exposure duration

Peer Review: FIFRA Scientific Advisory Panel

- December 4-7, 2018
- Charge questions regarding:
  - How the biological understanding informs the applicability of the *in vitro* testing
  - Use of *in vitro* system (study design, methods, selected measurements, robustness of data, data reporting)
  - Assumptions and calculations using CFD model to calculate cumulative deposition
  - Calculation of human equivalent concentrations
  - Strengths and limitations of using approach for other contact irritants, as well as potential for use with other chemicals that cause portal of entry respiratory tract effects

https://www.epa.gov/sap/fifra-scientific-advisory-panel-meetings

Thank you!