Inhalation Studies Required Under 40CFR Part 158

- 870.1300 – Acute inhalation toxicity study
  - Technical active ingredient and formulations/end-use products
- 870.3465 – 90-day inhalation toxicity study
  - Technical active ingredient
  - Required if there is the likelihood of significant repeated inhalation exposure to the pesticide as a gas, vapor, or aerosol.
  - Based on estimates of the magnitude and duration of human exposure, studies of shorter duration, e.g., 21- or 28-days, may be sufficient to satisfy this requirement. Registrants should consult with the Agency to determine whether studies of shorter duration would meet this requirement.

Part 158 Flexibility

- 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.

USEPA Administrator Memo Prioritizing Efforts to Reduce Animal Testing, September 10, 2019

- EPA will reduce its requests for, and our funding of, mammal studies by 30 percent by 2025
- EPA will eliminate all mammal study requests and funding by 2035. Any mammal studies requested or funded by the EPA after 2035 will require Administrator approval on a case-by-case basis.
- Form a working group of agency experts in this field who will provide a work plan within six months.
- EPA held the *First Annual Conference on the State of the Science on Development and Use of New Approach Methods (NAMs) for Chemical Safety Testing* on December 17, 2019

Refined Inhalation Risk Assessment for Contact Irritants

- Proposal for refining inhalation risk assessment using a 3D human airway epithelia reconstituted in vitro model initially presented to EPA in 2014 by Syngenta Crop Protection
- Agency recognized the value of the proposal for chlorothalonil, as well as other respiratory contact irritants and encouraged further development
- Collaborated with National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM), Office of Pollution Prevention (OPPT), and Office of Research and Development (ORD) for review
- Convened FIFRA SAP meeting in December 4-7, 2018 to evaluate the proposed approach
  - First time a point of departure for risk assessment will be derived using in vitro data for a pesticide
  - Potential use for other contact irritants, as well as other chemicals that cause portal of entry effects in the respiratory tract

Refined Inhalation Risk Assessment for Contact Irritants

- SAP Report released in April 2019
  - https://www.epa.gov/sap/fifra-scientific-advisory-panel-meetings
- No panelists supported using laboratory animal study
- In general, panel recommended:
  - Use of most sensitive endpoint
  - Repeat dosing with *in vitro* assay
  - Consideration of several parameter assumptions for CFD model
  - Particle size distributions based on empirical data
  - Additional clarifications and/or request for supporting information

Systemic vs. Portal of Entry Effects

- Analysis in 2018 indicated 127 chemicals used effects observed in inhalation toxicity studies to evaluate inhalation exposures
  - Approximately 50% chemicals used portal of entry (POE) effects
  - For chemicals using systemic effects, majority (>60%) have known neurotoxic mode of action (e.g., OPs, pyrethroids, carbamates)