U.S. EPA/OPPT Regulatory Perspective on Acute Inhalation Toxicity Testing

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Risk Assessment Paradigm under the Toxic Substances Control Act (TSCA)

• Under TSCA, OPPT evaluates and regulates, as appropriate, the full life cycle of industrial chemicals (i.e., manufacture (import), distribution in U.S. commerce, use and disposal)
  – Safety evaluation for a wide array of industrial chemicals
  – Existing and new industrial chemicals
  – Data availability/quality varies but generally limited/incomplete
  – New risk assessment/risk management challenges continually arise as new chemistries and new uses emerge
Data for Assessment Under TSCA

• **New chemicals**
  – Computational approaches used extensively
    • QSAR and Expert Systems
    • Read-across from analogs/Categories
  – Tiered-testing approach: requests for higher tiered testing contingent on screening results
    • May request acute inhalation toxicity testing, OECD test guideline 403, to characterize inhalation hazards related to acute exposure scenarios in humans (lethal and non-lethal endpoints)

• **Existing chemicals**
  – To date, have mostly used *in vivo* toxicity testing conducted with established test guidelines
    • Acute inhalation toxicity tests (may or may not follow OECD test guideline 403)
    • Used to characterize inhalation hazards related to acute exposure scenarios in humans
  – Categories and read-across from analogs used extensively in screening programs (e.g., HPV)
  – Categories/clusters used in some TSCA Work Plan assessments
Data for AEGL Assessments

• Acute Exposure Guideline Levels (AEGLs), [www.epa.gov/aegl](http://www.epa.gov/aegl)
  – Short-term exposure limits (10 min to 8 hrs)
  – For a single exposure
  – Three defined health effect threshold levels (discomfort, disability, death)-disability is an action level
    • Use acute inhalation toxicity tests to set thresholds (OECD TG 403 and non-OECD tests)
    • Examples of toxic endpoints: eye irritation, respiratory effects, nervous system effects, effects in kidneys, liver and heart, lethality
  – Intended for airborne releases of acutely toxic chemicals
  – Use in emergency preparedness and response activities
    • Applicable to accidental chemical releases
    • Applicable to chemical terrorist activities
The New TSCA

• The “Frank R. Lautenberg Chemical Safety for the 21st Century Act” was signed by the President and went into effect on June 22, 2016

• Amends and updates TSCA (1976)
The New TSCA: New Requirements for New Chemicals

- EPA must make an affirmative finding on the safety of a new chemical or significant new use of an existing chemical before it is allowed into the marketplace.
- EPA can still take a range of actions to address potential concerns including ban, limitations, and additional testing on the chemical.
  - Acute inhalation toxicity testing may be requested when warranted (i.e., OECD test guideline 403)
The New TSCA: Major Improvements Related to Existing Chemicals

- Mandatory duty on EPA to evaluate existing chemicals with clear and enforceable deadlines
- Chemicals assessed against a risk-based safety standard
- Unreasonable risks identified in the risk evaluation must be eliminated
- Expanded authority to more quickly require development of chemical information when needed
The New TSCA: Prioritization Requirements

• EPA must establish a risk-based process to identify whether a substance is a “high” or “low” priority for risk evaluation
  – *High-Priority*: The chemical may present an unreasonable risk of injury to health or the environment due to potential hazard and potential route of exposure, including susceptible subpopulations/subject to risk evaluation
  – *Low-Priority*: The chemical does not meet the standard for High-Priority
The New TSCA: Prioritization Requirements

- Criteria and Considerations
  - 50% of High-Priority chemicals must come from Work Plan
  - Preference for those with persistence and bioaccumulation scores of 3 and known human carcinogens with high acute/chronic toxicity
  - Hazard, exposure, persistence, bioaccumulation, storage near drinking water, conditions of use and volume, and significant changes in condition of use and volume

- Bottom line: EPA is required to consider acute toxicity data (when available) during the prioritization process to determine if chemical substance has high acute toxicity. This includes the inhalation route.
New TSCA and Alternative Testing

• Requires development of strategic plan for promoting the development and implementation of scientifically valid, alternative testing methodologies and protocols

• Main goal is to reduce, refine, or replace vertebrate animal testing and provide scientifically reliable information of equivalent or better scientific quality and relevance for assessing risks of injury to health or the environment of chemical substances

• Examples of methodologies/protocols:
  – Computational toxicology and bioinformatics
  – High-throughput screening methods
  – Testing of categories of chemical substances
  – Tiered testing methods
  – In vitro studies
  – System biology
  – New or revised methods (ICCVAM, OECD)
Thank you!

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