21st Century Toxicology: OPP's Efforts on Reduced Animal Testing for Ecological Risk Assessment
New Approach Methodologies and Retrospective Analyses

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Today's Discussion

- Guiding principles
- Avian subacute/acute risk retrospective comparison project
  - Question asked
  - Methods used
  - Next steps
- Fish acute lethal endpoint retrospective project
  - Question asked
  - Achievements to date
- ICCVAM Organizing Committee Predictive Modeling of Rat Oral Acute Systemic Toxicity
- ICCVAM Ecotoxicity Working Group
- Participation in Toxicology Forum Summer Meeting
- Feedback

Guiding Principles

- Identification, Development of New Approach Methodologies (NAMs)*
  - Defining tasks that are fit for purpose
  - Establishing Scientific Relevance, Reliability and Confidence
  - Staff Training, Education and Collaboration
  - Leveraging partner resources
- Implementation of NAMs for Ecological Risk Assessment (ERA) Under FIFRA
  - Commitment of time and resources through the completion of specific NAMS tasks
  - Establishment of OPP guidance and policy in a publicly transparent manner

* EPA views the term New Approach Methodologies as equivalent to alternative test methods and strategies

Use of NAMs for ERA-FIFRA –Decision Context

- EPA has been using NAMs for years
  - ECOSAR, EPISuite, SAR/QSAR/Read-Across
- EPA has considered NAMs for:
  - Screening degradates for effects testing prioritization
  - Screening degradates for toxicity equivalency bridging with tested parent compound
  - Addressing data gaps for parent compounds in risk assessment
- Potential for use in risk assessment in place of whole animal testing
  - Use will be fit-for-purpose having established
    - Scientific Relevance,
    - Reliability, and
    - Confidence

Avian Subacute/Acute Risk Retrospective Comparison Project (Background and Questions Asked)

- Background
  - 40 *CFR* Section 158 outlines two requirements for avian acute effects testing
    - Two single oral dose LD50 studies (commonly quail or mallard and a songbird)
    - Two subacute dietary LC50 studies (commonly quail and mallard)
  - Pesticide risk assessments conduct estimation of risk quotients using BOTH lethal effects study types using the most sensitive endpoint from each type of study
  - EPA and PETA collaborated on a retrospective analysis of avian risk assessments
- Questions Asked: **Can we confidently assess acute risk for birds using a reduced suite of effects studies focusing on the single oral dose protocol?**
  - How often have subacute dietary risk quotients (RQs) quantitatively driven risk assessment conclusions?
  - How often have subacute dietary risks qualitatively altered the risk conclusions?

Avian Subacute/Acute Risk Retrospective Comparison Project (Methods)

- Focus on risk assessment outcomes not effects data
  - Integrates the effects of both toxic potency and exposure assessment
  - Allow for a differentiation (if any) in conclusions relative to surrogate bird size and exposure media (food type)
- Establishment of evaluation data set
  - Focused on pesticide actives newly registered through RD for the years 1998-2016
  - Most recent classes of pesticides
    - Reflect evolution of new chemistries to avoid broad spectrum acute toxicity
    - Most likely the newest pesticide mechanism of action classes with greatest potential for analog development going forward
  - Review most recent publicly available risk assessment
  - Determine mode of action for each pesticide (publicly available sites)

Avian Subacute/Acute Risk Retrospective Comparison Project (Methods cont.)

- From each risk assessment:
  - Extract and compare the single oral dose- and dietary-based risk quotients
  - Summarize any risk characterization qualitative discussion of dietary-based risk estimates

Avian Subacute/Acute Risk Retrospective Comparison Project (Results)

- EPA identified **181** pesticides new to the Agency from the annual reports from 1998 to 2016.
- **119** chemicals had ecological risks assessments available to PETA for analysis.
  - **79** of the chemicals did not have RQ values calculated so a difference between dietary and oral RQs was moot (**dietary RQ had no impact**)
    - **70** of these were Limit test results for both diet and oral endpoints (**there was no difference in risk prediction for dietary or oral**),
    - **9** were non-standard assessments (indoor, greenhouse, or piggy back assessments)
  - **40** of the chemicals had RQ values presented for comparison
    - **37** cases **oral RQ dominated dietary and drove the assessment,**
    - **2** cases **RQs for dietary only as oral was at limit, but no concern for risk in any case**
    - **1** case dietary RQ> Oral RQ, it was a anticoagulant rodenticide
- **Bottom Line: In 99% of cases (118 of 119) the subacute dietary approach did not change risk conclusions already reached using oral, dose-based RQs**

Avian Subacute/Acute Risk Retrospective Comparison Project (Results cont.)

But what about those 62 cases not evaluated?

- Reviewed the MOAs posted for each case chemical to determine whether the mechanism of action was covered by another pesticide for which the comparison of RQs was completed
- An unevaluated chemical was reasoned important if its MOA was not represented by an analog's risk assessment comparison

Results

- Only 8 chemicals and their associated MOAs were not represented by analogs
- These 8 were all unique mechanisms
- **Bottom Line: In the majority of unevaluated cases, the subacute dietary approach was represented by chemical analogs; unique modes of action may be a category for establishing a base set of studies (and RQ comparisons) for future use.**

Avian Subacute/Acute Risk Retrospective Comparison Project (Next Steps)

- Peer-reviewed scientific journal publication (PETA lead, Agency coauthors)
- Developing policy/guidance
  - Outlining comparison effort and its results by citation to journal article
  - Recommend, for new chemicals with mechanisms of action covered, a reliance on acute oral dose protocols, with dietary protocols held in reserve
  - Recommend an evidence-driven consideration of dietary testing for:
    - Unique modes of action
    - Cases where data on MOA suggest a mechanism for accumulative damage (e.g., anticoagulant rodenticides)
    - A high potential for bioaccumulation or a facilitated transport mechanism of absorption
      - High octanol-water partition coefficient and high molecular weight
      - High bioconcentration factor
      - Mammalian toxicity and animal residue studies
- Outreach to international and other partners
- Release draft policy for public comment

Fish Acute Lethal Endpoint Retrospective Project
(Background and Questions Asked)

- Background
  - 40*CFR* Section 158 outlines three requirements for fish acute effects testing
    - One study with a warm freshwater fish (e.g., bluegill sunfish)
    - One study with a cold freshwater fish (e.g., rainbow trout)
    - One study with an estuarine/marine fish (e.g., sheepshead minnow)
  - Pesticide risk assessments conduct estimation of risk quotients using the most sensitive freshwater fish and the estuarine/marine fish
  - Exposure estimates for each fish RQ calculation are identical, whether freshwater or estuarine marine
- Questions Asked: **Can we confidently assess acute risk for fish using a reduced suite of effects studies focusing on a consistently most sensitive fish?**
  - Is there a consistently most sensitive fish across all compounds?
  - Are there patterns of most sensitive fish based on chemical properties, chemical class, or mechanism of action?
  - Can we reduce data sets to two or even one fish study?

Fish Acute Lethal Endpoint Retrospective Project (Methods)

- Focus of this effort is comparative toxicity
  - NICEATM* Federal Partner
  - Exposure is not a confounding factor; only relative toxicity matters

- Evaluation data set: same as avian effects studies
  - Extraction of the data evaluation records
  - Submission to a shared drive
  - NICEATM review of the quality of information
  - Cross walk with available structure and mechanism data

*NICEATM: NTP Interagency Center for the Evaluation of Alternative Toxicological Methods

Fish Acute Lethal Endpoint Retrospective Project
(Progress to Date)

- Initial suite of 250+ individual fish toxicity records have been shared with NICEATM

- NICEATM feedback on whether this information is fit for purpose is imminent within a few weeks

ICCVAM Organizing Committee Predictive Modeling of Rat Oral Acute Systemic Toxicity

- EPA representation on the Organizing Committee for April workshop.
- Objective: integrate the collective expertise of the international modeling community to develop predictive models for acute oral toxicity based on regulatory needs put forward by ICCVAM
- EPA Role: provide EPA ecological risk assessment perspective on prioritization of candidate alternative methods for presentation at the workshop
  - Focus on methods most suitable for application in a quantitative manner for ecological risk assessment
    - Transparency of mechanistic considerations
    - High degree of documentation of the method
    - Accuracy in predicting an LD50
  - EPA selection criteria lead to a proposed methods selection that was highly consistent with other Agency priority selections

ICCVAM Ecotoxicity Working Group

- EPA representative is a co-chair of the newly formed Working Group
- Draft Charter has been developed
- Charges:
  - Identify agency requirements for ecotoxicology testing
  - Identify endpoints needed by each federal agency and commonalities and differences between agencies
  - Define the current approaches to ecotoxicology testing and create a catalog of existing and emerging technologies to assess their potential to fulfill regulatory testing requirements without using animals.
  - Work with ICATM* partners to identify international regulatory requirements for ecotoxicology testing
  - Establish a stakeholder group comprised of both government and non-government scientists to coordinate efforts towards developing and implementing alternative approaches for ecotoxicology testing

*ICATM: International Cooperation on Alternative Test Methods

Toxicology Forum Summer Meeting
July 9-11 2018

- Objective:
  - International, nonprofit organization devoted to conducting open dialogues among various segments of society concerned with problems in toxicology.
  - Meeting intended to provide a venue for experts from domestic and international government regulatory and health agencies to exchange perspectives on issues of mutual interest.
- Session Topics:
  - Building on the Science: Possible Opportunities to Reduce Toxicity Testing and Better Allocate Resources for Evaluating Ecological Risk
  - Integration of Toxicokinetics and the Kinetically-Derived Maximum Dose into Toxicity Testing and Risk Assessment
  - US FDA's Predictive Toxicology Road Map—A Six-Part Framework for Integrating Predictive Toxicology Methods into Safety and Risk Assessments.

In Closing….

EPA is:

- Committed to reduced animal testing burden without compromising the quality of the risk assessment process
- Considering ideas for additional projects
- Operating under a set of principles to achieve streamlined testing or alternative methods endpoints fit for quantitative ecological risk assessment purposes
- Considering mechanisms for policy/guidance (waiver guidance?)
- Intends to partner with government and private stakeholders (thoughts/suggestions on entities to include?)
- Open to other ideas and opportunities for collaboration in future retrospective studies