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)
• 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 an 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
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
  • 40CFR 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