Recent Progress Towards Reducing Animal Use & Adopting New Approach Methods at EPA's Office of Pesticide Programs

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SACATM
September 28-29, 2021

Progress on Metrics: EPA - Office of Pesticide Program's (OPP) Webpage

Strategic Vision for Adopting New Approach Methodologies
Quick Resources

Overview

To better protect human health and the environment, EPA's Office of Pesticide Programs (OPP) is developing and evaluating new approach methodologies (NAMs) in molecular, cellular and computational sciences to supplement or replace more traditional methods of testing chemicals — such as animal testing — for potential hazards. OPP is enhancing its ability to use these new methods such as integrated approaches to testing and assessment (IATA). IATA promotes a hypothesis-based, systematic, integrative use of exposure and hazard information.
Adopting 21st Century Methodologies for risk assessment and toxicology review purposes is built upon the "three Rs": reduction, replacement and refinement.
Reduction of unnecessary animal testing is primarily addressed via EPA waiver policies and guidance documents, many of which have already been released to the public, with others still under development.
Replacement pertains to the substitution of animal studies with alternate methods such as predictive modeling and biochemical or cellular assays.
Refinement a test method that modifies procedures to enhance animal well-being, and lessen or avoid pain and distress in animals.
OPP has focused on the need to measure successes of these strategies with metrics and active quantitative tracking of progress in reducing animal testing.

Webpages, updated Oct 2020:

- Main page: https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/strategic-vision-adopting-new-approach-methodologies
- Metrics: https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/adopting-21st-century-science-methodologies-metrics

3Rs: Reduction, Refinement, Replacement

- Reduction
  - Retrospective studies: fewer tests (avian acute, fish acute, fish chronic incl. early life stage & acute-to-chronic ratio)
- Replacement
  - In-vitro or in-silico (CATMoS rat oral, fish acute QSAR)
- Refinement
  - Modify test guideline (fish bioconcentration, fewer dose levels)

Retrospective Studies: Focus on Reduction

- OPP receives data for multiple species for some study types
  - Fish LC50 – 3 species
  - Avian single-dose oral LD50 and 5-day dietary LC50 (2 -3 species)
  - Avian reproduction (2 species)
  - Fish early life stage & acute-to-chronic ratio
- Question: Can we perform a protective risk assessment with data on fewer species? How can we tell which 1 or 2 species is most consistently more sensitive? Are chronic tests always needed?

Quantitative structure-activity relationship (QSAR) studies: Focus on Replacement

- OPP has toxicity test results for hundreds to thousands of pesticide active ingredients for terrestrial and aquatic, vertebrate and invertebrate, for both acute and chronic endpoints
    - Question: Can we use these data to build models to predict toxicity within relevant chemical categories and with knowable uncertainty limits?
    - Collaborative Acute Toxicity Modeling Suite (CATMoS) Rat Oral project
    - EPA-Office of Research and Development (ORD) fish acute QSAR model – improvement to Ecological Structure Activity Relationship (ECOSAR)

Avian subacute/acute risk retrospective

- EPA-OPP ecological risk assessments use both acute oral and sub-acute dietary studies to assess acute risks to birds (the endpoint that results in the highest risk quotient drives the risk conclusion)
- Question: 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?
- Partnership with People for the Ethical Treatment of Animals Science Consortium International (PSCI)
- Bottom line results are that 99% (118 of 119) of all subacute dietary studies for new use assessments did not change risk conclusions already reached using oral dose-based RQ's.
  - In most cases (there are some exceptions) a robust avian acute risk assessment can be conducted without the sub-acute dietary studies.
- Hilton, G.M., Odenkirchen, E., Panger, M., Waleko, G., Lowit, A., Clippinger, A.J. 2019, Regulatory Toxicology and Pharmacology, 105: 30-35, https://doi.org/10.1016/j.yrtph.2019.03.013
- *Policy finalized in February 2020*
  - https://www.epa.gov/sites/production/files/2020-02/documents/final-waiver-guidance-avian-sub-acute-dietary.pdf

Fish Bioconcentration Single Dose Study Data Evaluation Guidance

Refinement of required studies

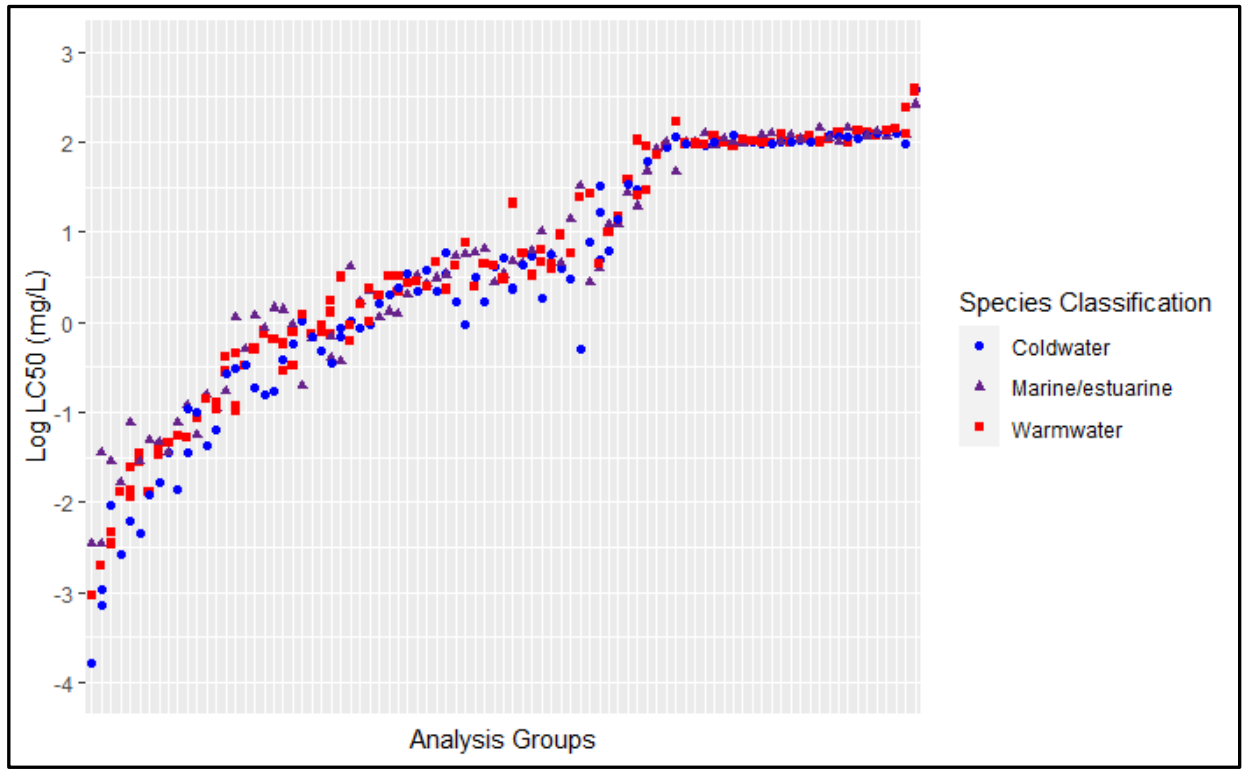
- Existing Office of Chemical Safety and Pollution Prevention (OCSPP) guideline specifies using at least two test concentrations to establish bioconcentration factor (BCF)
- Question: Can we reduce the number of concentrations and still obtain data acceptable to characterize a fish BCF?
- Bottom line results are that conditions were identified under which a single concentration test can be used in lieu of multiple concentrations
- Policy finalized in July 2020: **https://www.epa.gov/sites/production/files/2020-07/documents/bcf-study-july-15-2020.pdf**

Fish Acute Retrospective

- Pesticide registration data requirement (40 CFR Section 158) for an acute LC50 test on 3 species (commonly rainbow trout, bluegill sunfish, and sheepshead minnow)
  - Acute toxicity testing for a single chemical can use 200 or more fish
- Question: Is there a consistently more sensitive fish across all compounds and can we reduce data sets to two or even one fish study?
    - Focus on conventional pesticide active ingredients newly registered by EPA for the years 1998-2016
- Collaboration with National Toxicology Program (NTP) Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM)

Fish Acute Retrospective

- Almost 800 studies representing tests initially collected (active ingredients, formulations, and degradation products)
- Exclusion criteria: unacceptable studies; multiple active ingredient formulations; isomeric mixes; chemicals without a study with at least one each of a cold freshwater fish, warm freshwater fish, and estuarine/marine fish
- Final Dataset: 87 chemicals/formulations with at least one each of a cold freshwater, warm freshwater, and estuarine-marine fish
- Manuscript under development



QSAR for Rat Acute Oral LD_{50}

Replacement of required studies

- Collaborative Acute Toxicity Modeling Suite (CATMoS)
  - Being developed by NIEHS-NICEATM and the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM)
  - 35 Participants/Groups from around the globe representing academia, industry, and government contributed to the development
- Goal
  - OPP is working with NICEATM & Humane Society to evaluate applicability for pesticides as a potential replacement of the rat acute single oral dose study for establishing the effects endpoint in ecological risk assessment
- Products (Ongoing)
  - Peer–reviewed publication anticipated 2022

Up and Coming Efforts (Retrospective, Reduction)

- Fish Acute to Chronic Ratio (ACR)
  - Partner with NICEATM
  - Beginning data extraction on chronic studies
  - *Question*: Evaluate if an ACR can be used in place of chronic studies
- Fish Early Life Stage (Retrospective)
  - Is Full Life Stage test needed?

Up and Coming Efforts

- Avian Reproduction Retrospective Analysis (Reduction)
  - Partner with PETA-US
  - Data set undergoing QA
  - Similar to acute fish retrospective in scope
  - *Question*: Can we confidently assess chronic risk for birds using a reduced number of species tested?
- Aquatic Organism QSAR (Replacement)
  - Updates to ECOSAR model using measured pesticide data