EPA Activities on New Approach Methods:

Update from the Office of Pesticide Programs

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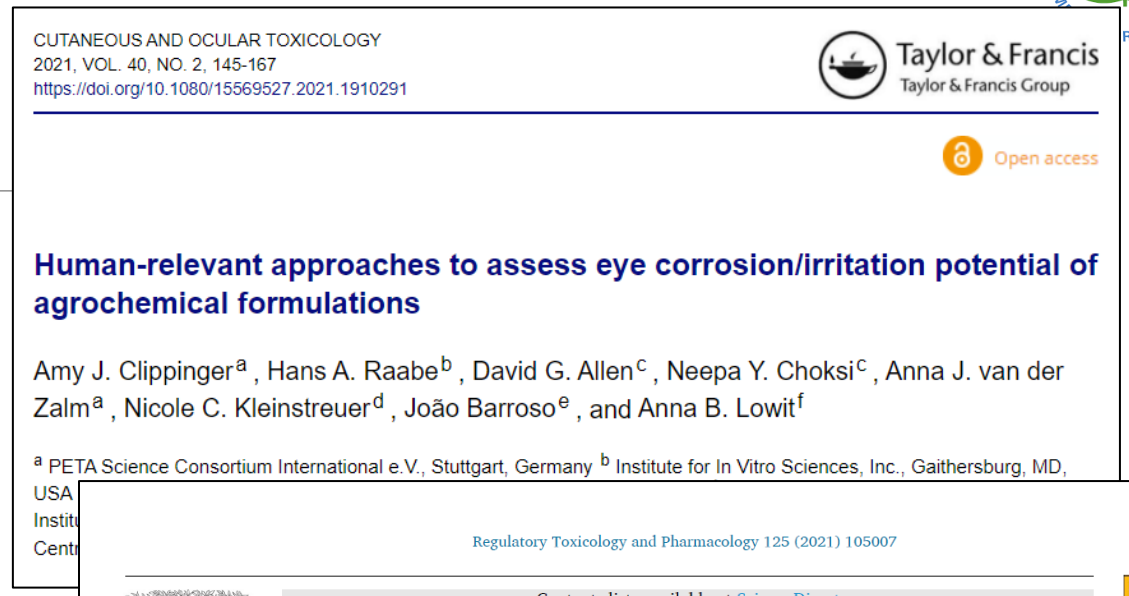
Acute Toxicity

- Eye irritation (Clippinger et al., 2021)
  - Provides evaluation of human relevance, strengths, and uncertainties of *in vivo* and *in vitro* studies
  - Comparison of corneas across species
  - Proposes adverse outcome pathway for eye irritation
  - Concludes many *in vitro/ex vivo* methods are equivalent or scientifically superior to *in vivo* rabbit study
- Acute Oral (Hamm et al., 2021)
  - Pilot program to evaluate mathematical tool (GHS Mixtures Equation) as alternative to acute testing in animals
  - Worked with NICEATM to conduct retrospective analyses, which demonstrated the utility of the GHS Mixtures Equation to predict oral toxicity, particularly for formulations with lower toxicity



CUTANEOUS AND OCULAR TOXICOLOGY
2021, VOL. 40, NO. 2, 145-167
https://doi.org/10.1080/15569527.2021.1910291

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Human-relevant approaches to assess eye corrosion/irritation potential of agrochemical formulations

Amy J. Clippinger[a], Hans A. Raabe[b], David G. Allen[c], Neepa Y. Choksi[c], Anna J. van der Zalm[a], Nicole C. Kleinstreuer[d], João Barroso[e], and Anna B. Lowit[f]

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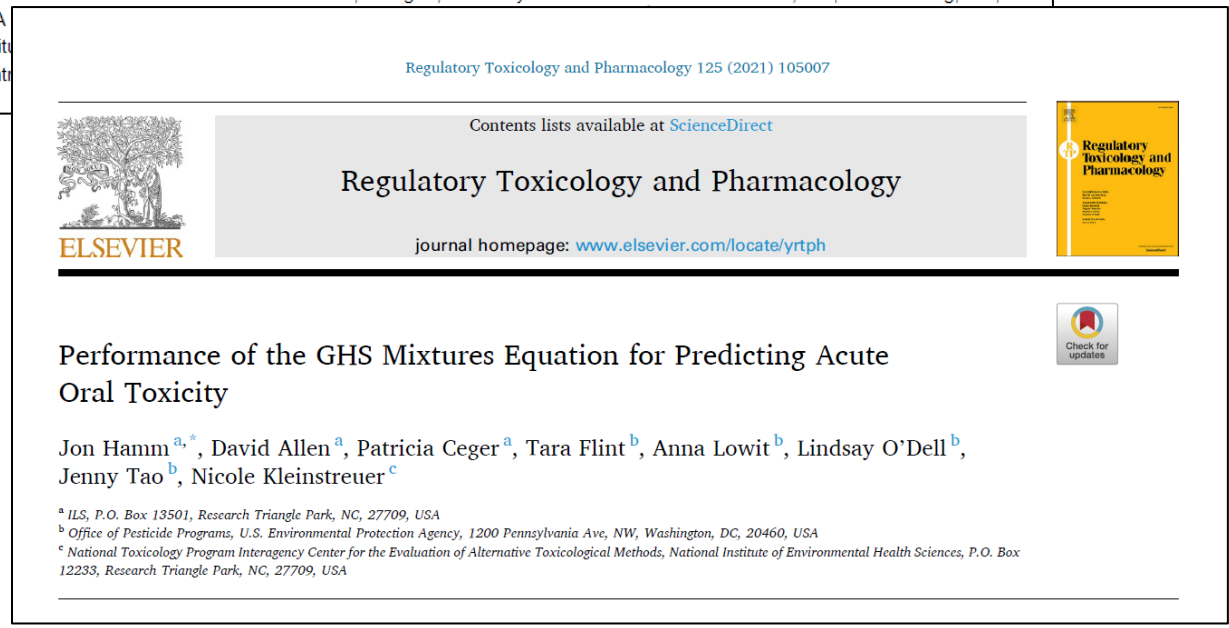

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Performance of the GHS Mixtures Equation for Predicting Acute Oral Toxicity

Jon Hamm[a,*], David Allen[a], Patricia Ceger[a], Tara Flint[b], Anna Lowit[b], Lindsay O'Dell[b], Jenny Tao[b], Nicole Kleinstreuer[c]

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Dermal Absorption "Triple Pack"

ALTEX preprint
published March 12, 2021
doi:10.14573/altex.2101121

Research Article

Retrospective Analysis of Dermal Absorption Triple Pack Data

David G. Allen[1], John Rooney[1], Nicole Kleinstreuer[2], Anna Lowit[3], Monique Perron[3]
[1]Integrated Laboratory Systems LLC, Research Triangle Park, NC, USA; [2]National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods, National Institute of Environmental Health Sciences, Research Triangle Park, NC, USA; [3]Office of Pesticide Programs, U.S. Environmental Protection Agency, Washington, DC, USA

- Retrospective analysis of human *in vitro*, rat *in vitro*, and rat *in vivo* studies using similar protocols (e.g., same test material, doses)
- Industry partners provided >30 triple pack studies
- Demonstrates *in vitro* studies alone provide similar or more protective estimates of dermal absorption, with limited exceptions
- Incorporating shift in use of *in vitro* studies into updated OECD Guidance Notes on Dermal Absorption

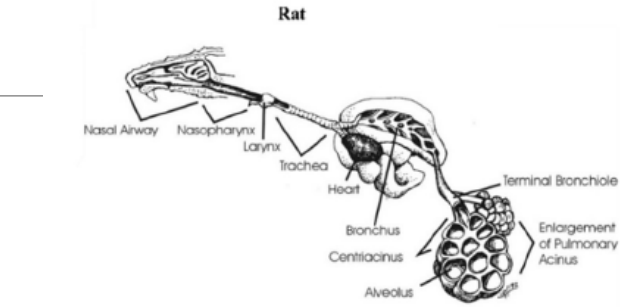
Inhalation Risk Assessment

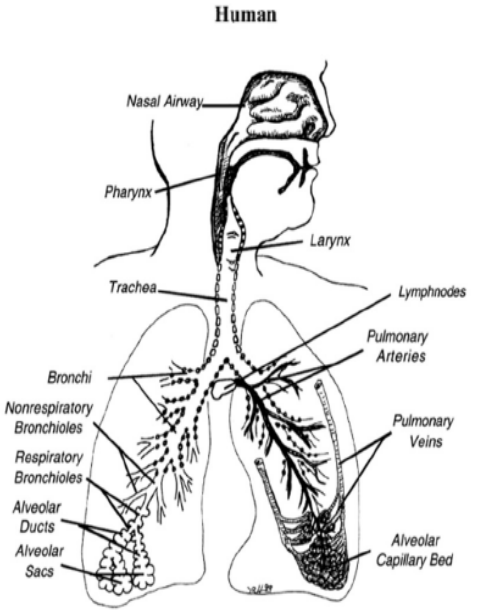
- Refined approach using *in vitro* point of departure and human dosimetry modeling incorporated into chlorothalonil risk assessment for Registration Review

  https://www.regulations.gov/document/EPA-HQ-OPP-2011-0840-0080

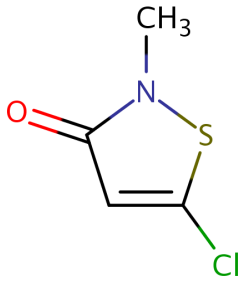
  - Evaluating available *in vitro* data for other contact irritants
  - Investigating potential to apply similar approach for other pesticides

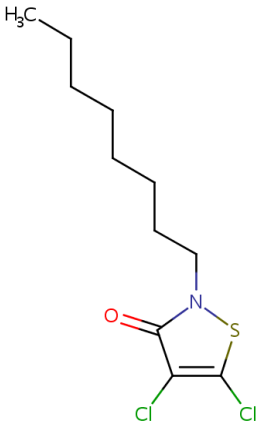
- Additional projects/discussions to evaluate and compare across *in vitro* assays





Images taken from Clippinger et al. (2018)



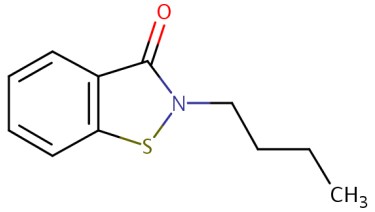


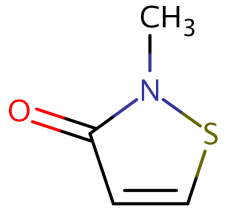
HAZARD CHARACTERIZATION OF ISOTHIAZOLINONES IN SUPPORT OF FIFRA REGISTRATION REVIEW

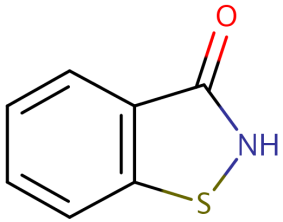
April 6, 2020

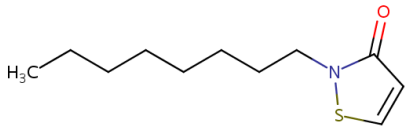
US Environmental Protection Agency, Office of Pesticide Programs, Antimicrobials Division

In Collaboration with the National Toxicology Program's Interagency Coordinating Committee for the Evaluation of Alternative Toxicological Methods









Isothiazolinone biocides are used as material preservatives to prevent the growth of microbial organisms and are used in industrial processes and consumer products

https://www.federalregister.gov/documents/2020/05/14/2020-10376/pesticide-registration-review-draft-human-health-and-ecological-risk-assessments-for-several

Rethinking Carcinogenicity Assessment for Agrochemicals Project (ReCAAP)

- Collaborative project to develop a waiver framework for pesticides
  - Project led by PETA-ISC
  - Retrospective & prospective case studies were developed as part of the weight of evidence (WOE) development
  - Framework provides structure to organize existing critical information, including NAM data, that can be considered by a regulatory authority when making a waiver decision
  - Review by 2020 Scientific Advisory Board (SAB)
  - Manuscript published in June 2022

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Regulatory Toxicology and Pharmacology

Volume 131, June 2022, 105160

Rethinking chronic toxicity and carcinogenicity assessment for agrochemicals project (ReCAAP): A reporting framework to support a weight of evidence safety assessment without long-term rodent bioassays

Gina M. Hilton [a], Catherine Adcock [b], Gregory Akerman [c], James Baldassari [d], Michael Battalora [d], Warren Casey [e], Amy J. Clippinger [a], Rhian Cope [f], Amber Goetz [g], A. Wallace Hayes [h], Sabitha Papineni [i], Richard C. Peffer [j], Deborah Ramsingh [b], Brandy Williamson Riffle [k], Mitscheli Sanches da Rocha [k], Natalia Ryan [g], Edward Scollon [l], Nicolo Visconti [m] ... Anna Lowit [c]

Developmental Neurotoxicity (DNT)

- International effort to develop DNT NAM battery to assess critical processes of neurodevelopment
- Convened FIFRA Scientific Advisory Panel (SAP) soliciting comment on currently available battery of assays
  - Report published in December 2020: https://www.epa.gov/sap/use-new-approach-methodologies-nams-derive-extrapolation-factors-and-evaluate-developmental
- Provide chemical nominations to NTP for additional testing
- OECD DNT NAM Expert Group drafting guidance document on integration of DNT NAMs into regulatory decision-making
- Release of data evaluation records (DERs) and memos to aid in NAM evaluation
  - Docket on reguations.gov: EPA-HQ-OPP-2016-0093

Regulatory Toxicology and Pharmacology
Volume 131, June 2022, 105167

Integration of toxicodynamic and toxicokinetic new approach methods into a weight-of-evidence analysis for pesticide developmental neurotoxicity assessment: A case-study with DL- and L-glufosinate ☆

Sarah Dobreniecki [a], Elizabeth Mendez [a], Anna Lowit [a], Theresa M. Freudenrich [b], Kathleen Wallace [b], Amy Carpenter [c], Barbara A. Wetmore [b], Anna Kreutz [c], Evgenia Korol-Bexell [c], Katie Paul Friedman [b], Timothy J. Shafer [b]

Use of DNT assays in WOE

- DNT study exists for DL-glufosinate; however, L-glufosinate isomers lack *in vivo* DNT study
- Data from *in vitro* DNT assays and toxicokinetics of DL- and L-glufosinate evaluated
- Incorporated data into a WOE assessment to support waiving *in vivo* DNT study for L-glufosinate

Eco Retrospective Analyses

- Fish acute retrospective
  - OPP uses cold freshwater fish, warm freshwater fish, and saltwater fish to assess acute risks (200 fish or more used)
  - Is there a consistently more sensitive fish across all compounds and can we reduce data sets to two or even one fish study?
  - Manuscript in preparation
- Avian reproductive retrospective
  - Currently 2 species are required: Mallard Duck and Bobwhite Quail
  - How could a protective risk assessment be done with only one species?
  - Currently in data curation and exploration stage

QSAR Evaluation for Acute Lethality

- QSAR for Fish LC_{50}
  - Data submitted to EPA by registrants
  - Much larger database than main current tool (ECOSAR) and with pesticide-specific data
  - Working on peer-reviewed publication and web-based GUI
- Collaborative Acute Toxicity Modeling Suite (CATMoS)
  - 35 participants/groups from around the globe representing academia, industry, and government contributed to the development
  - Evaluate potential replacement of rat acute oral toxicity study with LD_{50} predictions
  - Manuscript in preparation

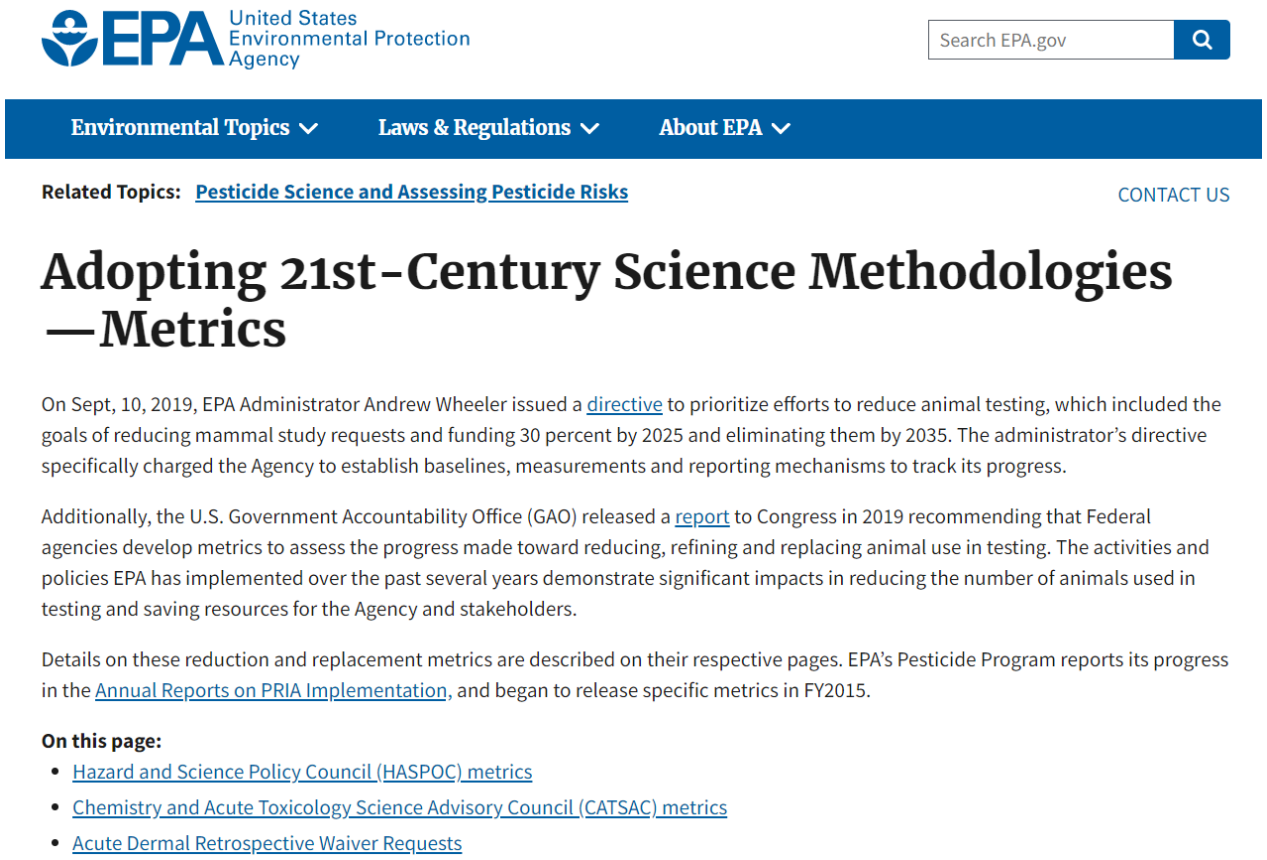
Honeybees

- Five tests (adult acute contact, adult acute oral, larval acute, adult chronic, and larval chronic toxicity) currently required
  - Examining EFED data holdings to determine whether all 5 tests are needed to do risk assessment
  - Manuscript published in PLOS One, April 7, 2022: “A retrospective analysis of honey bee (Apis mellifera) pesticide toxicity data”
- SeqAPASS (Sequence Alignment to Predict Across Species Sensitivity) model being evaluated to extrapolate honeybee data to non-Apis bees
- Colony models (e.g., VarroaPOP)

Updated OPP Webpage

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



EPA NAM Workplan

- Original EPA NAMs Work Plan released in June 2020, which laid out the Agency's objectives and strategies
- Committed to regularly reviewing the work plan and acknowledge the work plan will evolve as EPA's knowledge and experience grows, and as outside experts offer their perspectives and contributions
- Work plan recently updated in December 2021
  - Main objectives and strategies were left unmodified

https://www.epa.gov/chemical-research/epa-new-approach-methods-work-plan-reducing-use-vertebrate-animals-chemical

Thank You!