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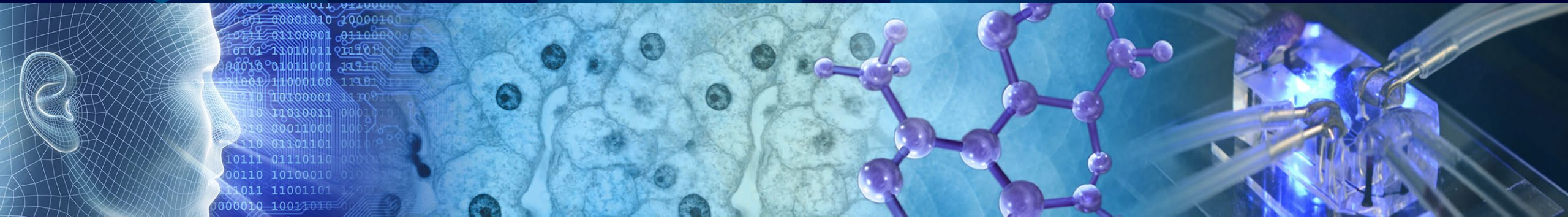

Beyond the 6-pack: Strategic Roadmap Future Priorities

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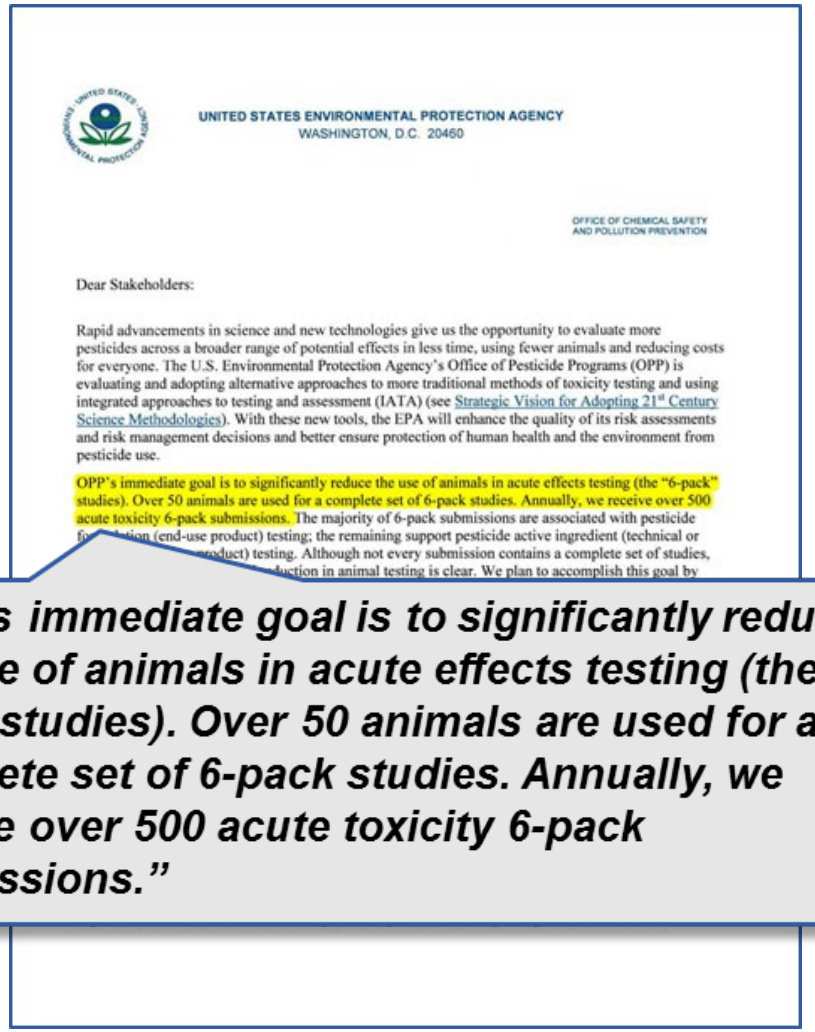
National Institutes of Health • U.S. Department of Health and Human Services

6pack Implementation

- Guidance/policy docs within and across agencies
  - Public/Private partnerships
- International harmonization
  - OECD guidelines and/or IATA case studies
- Education/training
  - Role of NGOs and industry consortiums



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION

Dear Stakeholders:

Rapid advancements in science and new technologies give us the opportunity to evaluate more pesticides across a broader range of potential effects in less time, using fewer animals and reducing costs for everyone. The U.S. Environmental Protection Agency's Office of Pesticide Programs (OPP) is evaluating and adopting alternative approaches to more traditional methods of toxicity testing and using integrated approaches to testing and assessment (IATA) (see Strategic Vision for Adopting 21st Century Science Methodologies). With these new tools, the EPA will enhance the quality of its risk assessments and risk management decisions and better ensure protection of human health and the environment from pesticide use.

OPP's immediate goal is to significantly reduce the use of animals in acute effects testing (the "6-pack" studies). Over 50 animals are used for a complete set of 6-pack studies. Annually, we receive over 500 acute toxicity 6-pack submissions. The majority of 6-pack submissions are associated with pesticide

"OPP's immediate goal is to significantly reduce the use of animals in acute effects testing (the "6-pack" studies). Over 50 animals are used for a complete set of 6-pack studies. Annually, we receive over 500 acute toxicity 6-pack submissions."

March 2016 letter to Stakeholders from Jack Housenger on the goal to reduce animal testing

Extending beyond single chemicals

- Application to mixtures (e.g. pesticide formulations, medical device extracts)
  - Data sharing across industry
  - Generating data with Defined Approaches
  - GHS Additivity Approach

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Performance of the GHS Mixtures Equation for Predicting Acute Oral Toxicity

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ABSTRACT

Acute oral toxicity classifications are based on the estimated chemical dose causing lethality ratory animals tested (LD_{50}). Given the large number of pesticide registration applications t toxicity data, an alternative to the *in vivo* test could greatly reduce animal testing. The United Harmonized System of Classification and Labelling of Chemicals (GHS) Mixtures Equation es toxicity of mixtures using the toxicities of mixture components. The goal of this study wa concordance of LD_{50}s predicted using the GHS Mixtures Equation and LD_{50}s from the *in vivo* t the EPA classification system, concordance was 55 % for the full dataset (N = 671), 52 % formulations (N = 620), and 84 % for antimicrobial cleaning products (N = 51). Most discor from substances LD_{50} > 2000 mg/kg (limit test) or 2000 < LD_{50} < 5000 mg/kg that were pre 5000 mg/kg. A supplementary analysis combining all formulations with an LD_{50} > 500 m concordance of 82 %. The lack of more toxic formulations in this dataset prevented a thorough GHS equation for such substances. Accordingly, our results suggest the GHS equation is helpf toxicity of mixtures, particularly those with lower toxicity.

Chemical Research in Toxicology

pubs.acs.org/crt Article

In Silico Assessment of Acute Oral Toxicity for Mixtures

Yaroslav Chushak,* Jeffery M. Gearhart, and Darrin Ott

Cite This: https://dx.doi.org/10.1021/acs.chemrestox.0c00256 Read Online

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ABSTRACT: While exposure of humans to environmental hazards often occurs with complex chemical mixtures, the majority of existing toxicity data are for single compounds. The Globally Harmonized System of chemical classification (GHS) developed by the Organization for Economic Cooperation and Development uses the additivity formula for acute oral toxicity classification of mixtures, which is based on the acute toxicity estimate of individual ingredients. We evaluated the prediction of GHS category classifications for mixtures using toxicological data collected in the Integrated Chemical Environment (ICE) developed by the National Toxicology Program (United States Department of Health and Human Services). The ICE database contains *in vivo* acute oral toxicity data for ~10,000 chemicals and for 582 mixtures with one or multiple active ingredients. By using the available experimental data for individual ingredients, we were able to calculate a GHS category for only half of the mixtures. To expand a set of components with acute oral toxicity data, we used the Collaborative Acute Toxicity Modeling Suite (CATMoS) implemented in the Open Structure−Activity/Property Relationship App to make predictions for active ingredients without available experimental data. As a result, we were able to make predictions for 503 mixtures/formulations with 72% accuracy for the GHS classification. For 186 mixtures with two or more active ingredients, the accuracy rate was 76%. The structure-based analysis of the misclassified mixtures did not reveal any specific structural features associated with the mispredictions. Our results demonstrate that CATMoS together with an additivity formula can be used to predict the GHS category for chemical mixtures.

ICE GHS Category \ Predicted GHS Category	1	2	3	4	5
1	0	0	0	0	0
2	1	0	1	0	0
3	0	0	22	6	2
4	0	1	8	85	47
5	0	0	7	67	256

Future Planning

- Defining agency- and endpoint- specific contexts of use
  - Prioritizing NAM development/validation accordingly
- Focus on more complex endpoints
  - DTT partnerships: DNT, Cardiotoxicity, Carcinogenicity
  - Systemic toxicity
  - Others?
- Improving environmental health protection
  - Addressing population variability and susceptibility
  - Further developing protective, probabilistic NGRA approaches
  - Providing rapid response options

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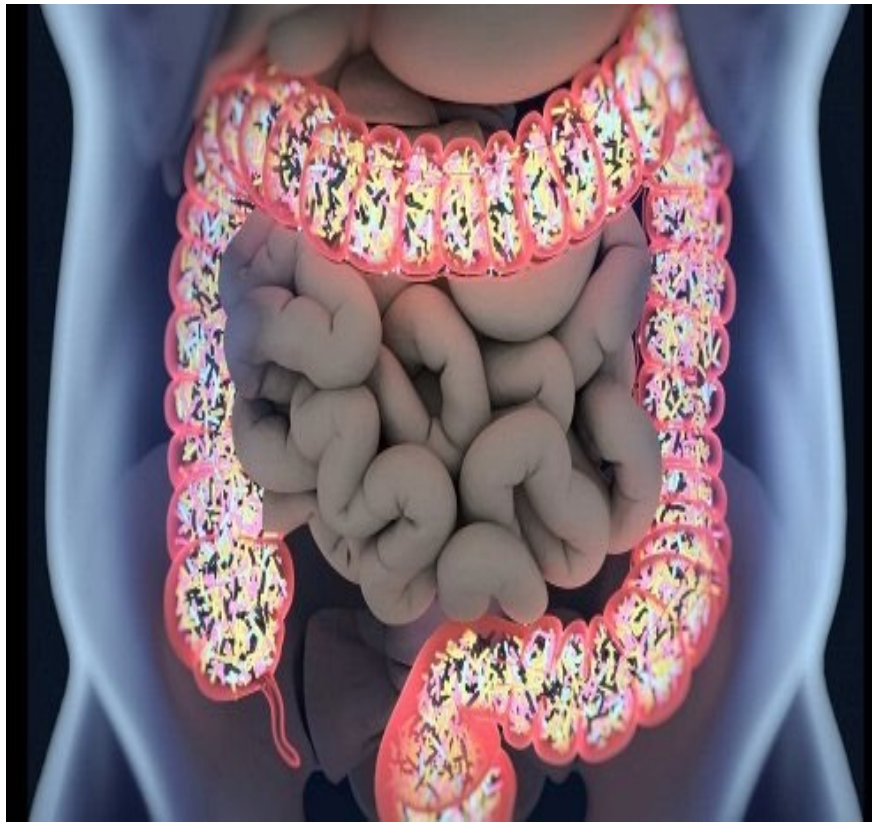
Workshop on NAMs for the Gastrointestinal Tract
October 11-12, 2023

An in-person workshop to examine the state of the science for NAMs modeling the gastrointestinal tract and their context for regulatory consideration.

- **Focal Areas:**
  - General “state of the science” for NAM gut models
  - Models for de-risking chemicals for systemic toxicity (regulatory relevance and application)
  - Gastrointestinal toxicity
  - Systemic absorption and distribution
  - Gut allergenicity
  - Breakout groups covering the following themes:
    - Establishing confidence in existing models
    - Strengths and limitations of different model systems
- **Webinar series to provide background information**
  - September 18, 9:00 am – 10:00 am EDT
  - September 20, 9:00 am – 10:00 am EDT
  - October 6, 9:00 am – 10:00 am EDT



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Acknowledgments

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