UNITED STATES ICCVAM
Advancing Alternatives to Animal Testing

Interagency Coordinating Committee on the Validation of Alternative Methods

Agencies' Implementation of Strategic Roadmap

Nicole C. Kleinstreuer, PhD
NICEATM Deputy Director

NTP BSC Meeting
Dec 7-8, 2017

Agency for Toxic Substances and Disease Registry • Consumer Product Safety Commission • Department of Agriculture
Department of Defense • Department of Energy • Department of the Interior • Department of Transportation
Environmental Protection Agency • Food and Drug Administration • National Institute for Occupational Safety and Health
National Institutes of Health • National Cancer Institute • National Institute of Environmental Health Sciences
National Library of Medicine • Occupational Safety and Health Administration

Implementation Plan Outline

Roadmap implementation plans will provide the strategy for the reduction and replacement of animal use for toxicity testing, specific to each endpoint, via six key endeavors:

- Coordinate activities via ICCVAM Workgroups
- Draft a scoping document to identify U.S. agency requirements, needs, and decision contexts
- Coordinate efforts with stakeholders
- Identify, acquire, and curate high quality data from reference test methods
- Identify and evaluate non-animal alternative approaches
- Gain regulatory acceptance and facilitate use of non-animal approaches

ICCVAM Agency-Driven

- Prioritize endpoints to focus on based on:
  - agency needs
  - expected impact on animal usage
  - mechanistic understanding
  - ability to mitigate obstacles
  - available resources
- Coordinate efforts with international partners (e.g. ICATM, OECD)

Active ICCVAM Workgroups

- Acute Toxicity (ATWG)
- Skin Sensitization (SSWG)
- Ocular and Dermal Irritation (ODIWG)

Implementation Plans Underway

- Developmental and Reproductive Toxicity (DARTWG)
- Read-Across (RAWG)
- In Vitro to In Vivo Extrapolation (IVIVE-WG)

Acute Toxicity Implementation Plan:

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Acute Toxicity Workgroup

- *Don Cronce (DOD)
- *Grace Patlewicz (EPA)
- Kent Carlson (CPSC)
- Xinrong Chen (CPSC)
- John Gordon (CPSC)
- Joanna Matheson (CPSC)
- Lyle Burgoon (DOD)
- Natalia Vinas (DOD)
- Jeffery Gearhart (DOD)
- David Mattie (DOD)
- Ronald Meris (DOD)
- Heather Pangburn (DOD)
- Michael Phillips (DOD)
- Emily N. Reinke (DOD)
- Mark Williams (DOD)
- Aiguo Wu (DOD)
- Ryan Vierling (DOT)
- Anna Lowit (EPA)
- Thao (Tina) Pham (EPA)
- Christopher Schlosser (EPA)
- Warren Casey (NIEHS)
- Nicole Kleinstreuer (NIEHS)
- Elizabeth Maull (NIEHS)
- George Fonger (NLM)
- Pertti (Bert) Hakkinen (NLM)
- Surender Ahir (OSHA)
- Deana Holmes (OSHA)

ICATM Liaison Members

- Pilar Prieto Peraita (EURL ECVAM)
- Seung-Tae Chung (KoCVAM)

NICEATM Support Staff (ILS)

- Judy Strickland
- Agnes Karmaus
- David Allen

*co-chairs

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Agencies that Use Acute Oral Toxicity Data

Hazard

- I (≤ 50mg/kg)
- II (>50 ≤ 500mg/kg)
- III (>500 ≤ 5000mg/kg)
- IV (>5000mg/kg)

Hazard

- Highly toxic (≤50mg/kg)
- Toxic (>50-5000mg/kg)

Packing Group

GHS

- I (≤ 5mg/kg)
- II (>5 ≤ 50mg/kg)
- III (>50 ≤ 300mg/kg)
- IV (>300 ≤ 2000mg/kg)

Hazard

I (≤ 50mg/kg)
II (>50 ≤ 500mg/kg)
III (>500 ≤ 5000mg/kg)
IV (>5000mg/kg)

Label Review Manual

Chapter 10: Worker Protection Label

~300 formulation submissions/year

~10 active ingredient submissions/year

Acute Systemic Toxicity: U.S. Statutes and Regulations

Statute/Regulations	Agency
Federal Hazardous Substances Act (FHSA) (1964): 16 CFR 1500.3: **Consumer Products**	CPSC
Poison Prevention Packaging Act (1970): 16 CFR 1700: **Hazardous Household Substances**	CPSC
Federal Hazardous Material Transportation Act (1975): 49 CFR 173.132: **Transported Substances**	DOT
Federal Insecticide, Fungicide, and Rodenticide Act (U.S.C. Title 7, Chapter 6): 40 CFR 156, 40 CFR 158.500, 40 CFR 158.2140, 40 CFR 158.2230: **Pesticides**	EPA
Toxic Substances Control Act (TSCA; 1976): 40 CFR 700-799: **New or Imported Chemicals**	EPA
Occupational Safety and Health Act (1970): 29 CFR 1910.1200: **Workplace Chemicals**	OSHA

Strickland et al. 2017, under review

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Stakeholder Coordination

- Establish public/private partnerships
- Organize workshops to discuss state of the science and implementation progress
- Work with ICATM partners and the OECD TG program

Cosmetics Europe
the personal care association

CropLife AMERICA

PETA INTERNATIONAL SCIENCE CONSORTIUM LTD.
Advancing 21st Century Toxicology

Physicians Committee for Responsible Medicine

EURL ECVAM
European Union Reference Laboratory for Alternatives to Animal Testing

OECD
BETTER POLICIES FOR BETTER LIVES

Interagency Coordinating Committee on the Validation of Alternative Methods

Workshop on Acute Toxicity Testing (2017)

NC 3Rs

~50 international participants

ICATM Regional Updates:

- Europe, Japan, Korea, Brazil

U.S. National Strategy and Roadmap

Industry Perspectives:

- Current regulatory climate
- GHS additivity calculations

International Harmonization:

- OECD coordination
- ECVAM perspectives on credibility and validation
- Cosmetics Europe skin sensitization collaboration

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EPA: Data Extraction from Pesticide Formulations

816	Product Names
437	Products with 1 a.i.
227	Products with 2 a.i.
152	Products with ≥3 a.i.

- NICEATM CBI-cleared to extract data from FIFRA DERs
- Data from all "6-pack" endpoints have been extracted for 816 products
  - Acute Oral Lethality
  - Acute Dermal Lethality
  - Acute Inhalation Lethality
  - Skin Sensitization
  - Skin Irritation/Corrosion
  - Eye Irritation/Corrosion
- Final database entry (ICE): October 2017

Rat oral acute toxicity LD50 Database

- Multiple existing resources containing rat oral acute toxicity LD50 data were mined and merged

Data source	Number of LD50 values	Number of unique chemicals
ECHA ChemProp	5,533	2,136
NLM HSDB	3,981	2,205
JRC AcutoxBase	637	138
NLM ChemIDplus	13,072	12,977
NICEATM PAI	364	293
OECD eChemPortal	10,119	2,290

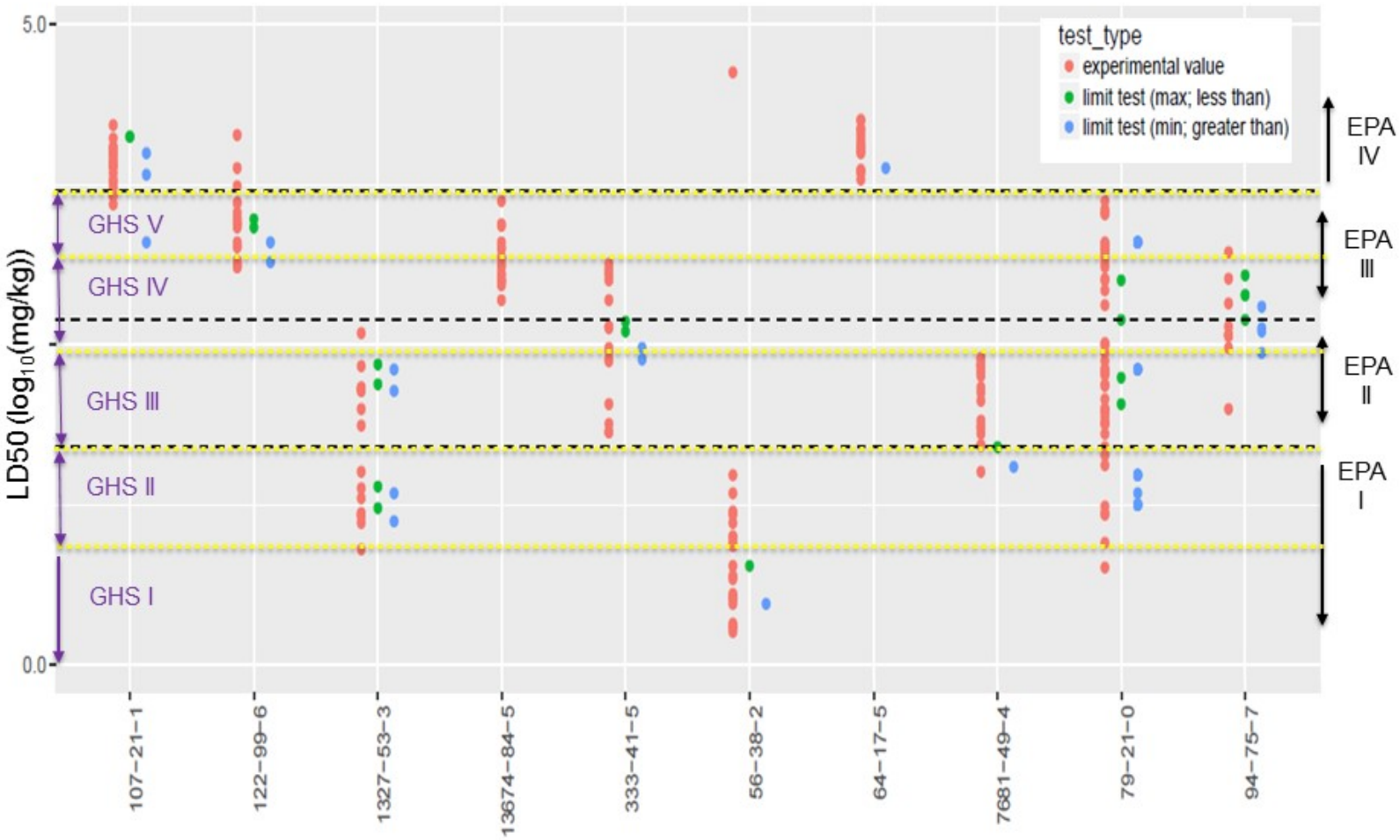
Total:
34,511 LD50 values
16,307 chemicals

Identify unique data in mg/kg

21,210 LD50 values
15,698 chemicals

- LD50 data comprised point estimates as well as limit tests

Impact of Variability on Hazard Classification



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Development of Predictive Models for Acute Oral Toxicity

- International modeling community invited to build models to predict acute oral systemic toxicity
- Agency input on model output has been solicited
  - Quantitative and categorical endpoints requested
- Training and test data derived from the dataset used to analyze LD50 variability
  - QSARs, hybrid approaches, mechanistic models, etc.

https://ntp.niehs.nih.gov/go/tox-models

Timeline

- **November 17, 2017:** Release of Training Data to the public.
- **December 15, 2017:** Release of Prediction Data to the public.
- **February 9, 2018:** Deadline for submission of model results and documentation to NICEATM.
- **March 9, 2018:** Organizing Committee finalizes selection of models to be invited for platform presentations and notifications are sent to presenters.
- **April 11-12, 2018:** Predictive Models for Acute Oral Systemic Toxicity Workshop, NIH Natcher Conference Center, Bethesda, MA.

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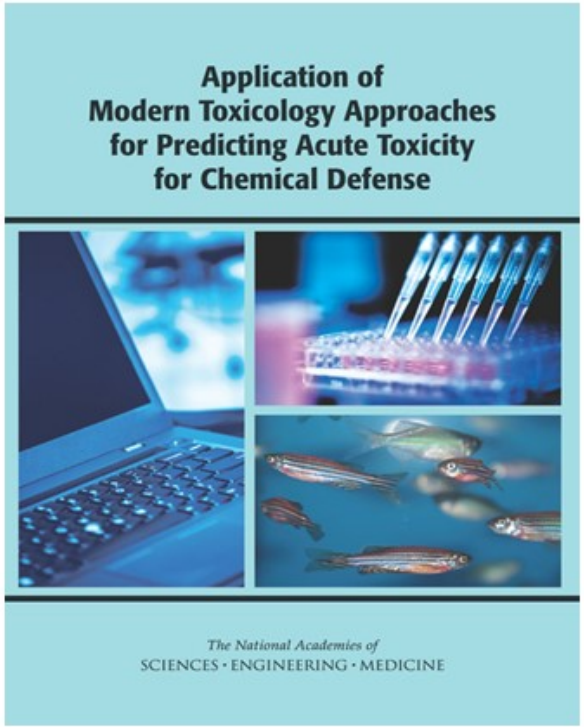
Commitment from Federal Agencies

DOD Funded NRC Report



Reducing Animal Use for the "6-Pack"

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

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

Stakeholder Engagement

- ICCVAM SACATM Meeting: Sept 18-19 2017, Natcher Center, NIH, Bethesda MD
  - Received public comments and scientific advisory feedback
- U.S. Strategic Roadmap Implementation: New Approach Methodologies for Acute Systemic Toxicity Testing, Nov 3 2017, Porter Neuroscience, NIH, Bethesda MD
  - U.S. agency reps, international partners, industry, NGO, modelers
- Society of Toxicology Annual Meeting: March 11-15 2018, San Antonio, TX
  - Session on "Implementing new approaches to evaluate the safety of chemicals and medical products in the United States"

Challenges

- Animal methods currently provide the reference data for evaluating alternatives
  - Results are variable
  - Need to identify appropriate summary metrics & characterize uncertainty
- Data requirements vary across U.S. and global regulatory authorities and are often ambiguous
- Overcoming regulatory and institutional inertia
  - Education and training, communication with method/model developers

Acknowledgments

- ILS/NICEATM staff
- NTP collaborators
- ICCVAM members
- ICATM members
- Industry partners
- NGO partners

Thank you!

Questions?