A National Strategy to Modernize Safety Testing

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SRP e-Learning Webinar Series
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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 Institute of Standards and Technology • National Library of Medicine • Occupational Safety and Health Administration

National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM), organized as an office under the NTP Division, part of NIEHS

National Toxicology Program
NTP

UNITED STATES
ICCVAM
Advancing Alternatives to Animal Testing

ICCVAM

- Interagency Coordinating Committee for the Validation of Alternative Methods
- H.R. 4281 (106th): ICCVAM Authorization Act of 2000
- To establish, wherever feasible, guidelines, recommendations, and regulations that promote the regulatory acceptance of new and revised toxicological tests that protect human and animal health and the environment while reducing, refining, or replacing animal tests and ensuring human safety and product effectiveness.

7 Regulatory Agencies

Consumer Product Safety Commission
Department of Agriculture
Department of the Interior
Department of Transportation
Environmental Protection Agency
Food and Drug Administration
Occupational Safety and Health Administration

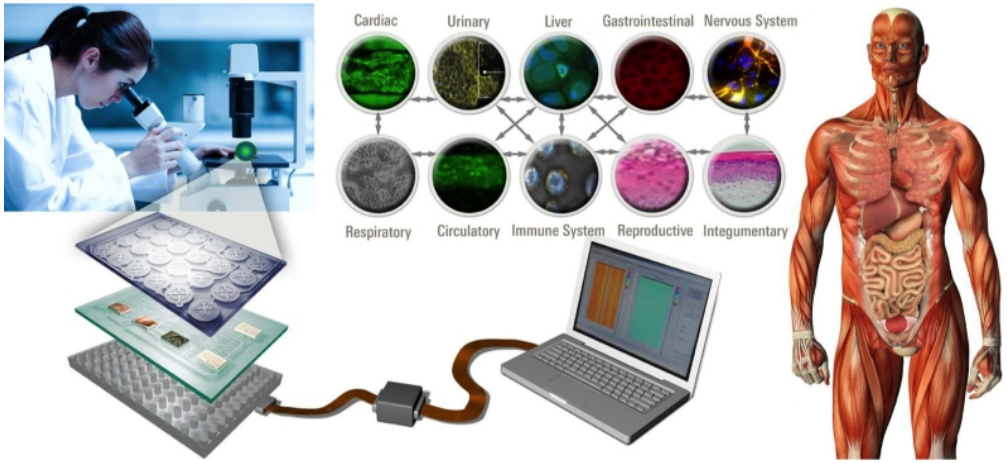
9 Research Agencies

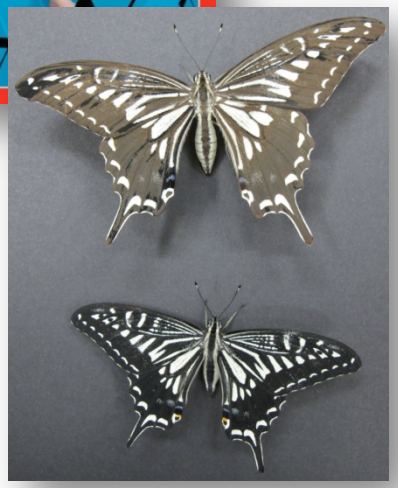
Agency for Toxic Substances and Disease Registry
National Institute for Occupational Safety and Health
National Cancer Institute
National Institute of Environmental Health Sciences
National Library of Medicine
National Institutes of Health
Department of Defense
Department of Energy
National Institute of Standards and Technology

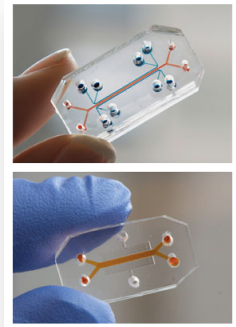
- Other participants include: NCATS , Tox21 Representatives

1928	2018
	
	
	

It is difficult for evolving institutional practices to keep pace with revolutionary advances in science and technology







Wyss Institute researchers and a multidisciplinary team of collaborators seek to build and link 10 human organs-on-chips to mimic whole body physiology. The system will incorporate the Institute's Human Lung-on-a-Chip (top) and Human Gut-on-a-Chip (bottom).

Barrangou & Doudna, Nat. Biotech 933–941 (2016)

Why Do We Need a National Roadmap?

- Helps federal agencies identify consensus goals and coordinate key activities required to achieve them
- Provides a framework to support the planning and coordination of technology development
- Facilitates communication and collaboration within and between government agencies, stakeholders, and international partners

Agencies Strategic Plans are aligned…

https://ntp.niehs.nih.gov/go/natl-strategy

"The 3Cs"

Communication

Collaboration

Commitment

Traditional Validation

Method Development → Validation → Regulatory Acceptance → Industry Adoption

OECD GD34

New Approach to Validation: Creating Fit-for-Purpose Methods

Encourage the adoption and use of new methods and approaches by federal agencies and regulated industries

Help end-users guide the development of the new tools needed to support their needs

Foster the use of efficient, flexible, and robust practices to establish confidence in new methods

Protecting health of public/ecosystems and improving relevance are key drivers

Driven by the priorities of agencies

Paired with implementation plans that will be tracked and publically reported

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

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)
- Ed Odenkirchen (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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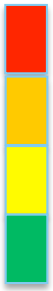
Agencies that Use Acute Oral Toxicity Data

Hazard



I (≤ 50mg/kg)

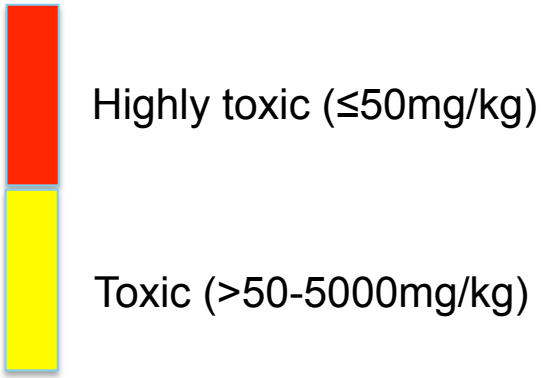
II (>50 ≤ 500mg/kg)

III (>500 ≤ 5000mg/kg)

IV (>5000mg/kg)

EPA

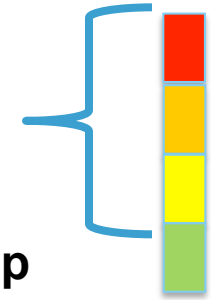
Hazard



Highly toxic (≤50mg/kg)

Toxic (>50-5000mg/kg)

Packing Group



I (≤ 5mg/kg)

II (>5 ≤ 50mg/kg)

III (>50 ≤ 300mg/kg)

IV (>300 ≤ 2000mg/kg)

GHS

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

U.S. Statutes and Regulations

US 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
Hazardous Materials Transportation Act (1970); 49 CFR 173.132: **Transported Hazardous Substances**	DOT
Federal Insecticide, Fungicide, and Rodenticide Act (U.S.C. Title 7, Chapter 6): 40 CFR 156; 40 CFR 158.500**: Pesticides**; CFR 158.2230: **Antimicrobials**	EPA
Toxic Substances Control Act (TSCA; 1976, amended 2016): 40 CFR 720.50: **Industrial Chemicals**	EPA
Federal Food, Drug, and Cosmetic Act (1938): **Biologicals**	FDA
Federal Food, Drug, and Cosmetic Act (1938): **Food Ingredients**	FDA
Occupational Safety and Health Act (1970): 29 CFR 1910.1200: **Workplace Chemicals**	OSHA

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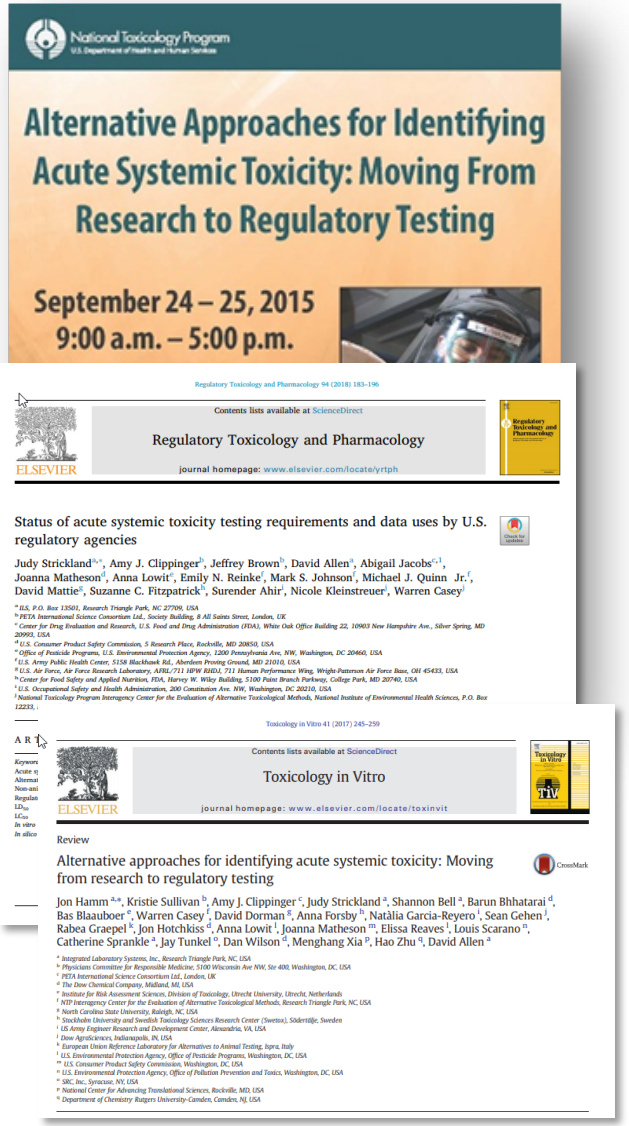
Workshop on Acute Toxicity Testing (2015)

- > 60 participants from industry, academia, and ICCVAM agencies
- Recommendations:
  - Clear understanding of agency requirements
    - *Strickland et al., Reg Tox Pharm, 2018*
  - Emphasize training and education
    - NICEATM and PISC outreach/reviewer training
  - International harmonization of existing approaches
    - ICATM and OECD coordination, NC3Rs satellite
  - Use of existing data (curation and sharing efforts) for development of new *in vitro* and *in silico* approaches
    - ICE, CLA stakeholder discussions, inhalation tox workgroups
    - *Hamm et al., Tox In Vitro, 2017*



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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Rat oral acute toxicity LD50 Database

- Mined and merged multiple existing resources containing rat oral acute toxicity LD50 data (collaboration with NCCT)

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

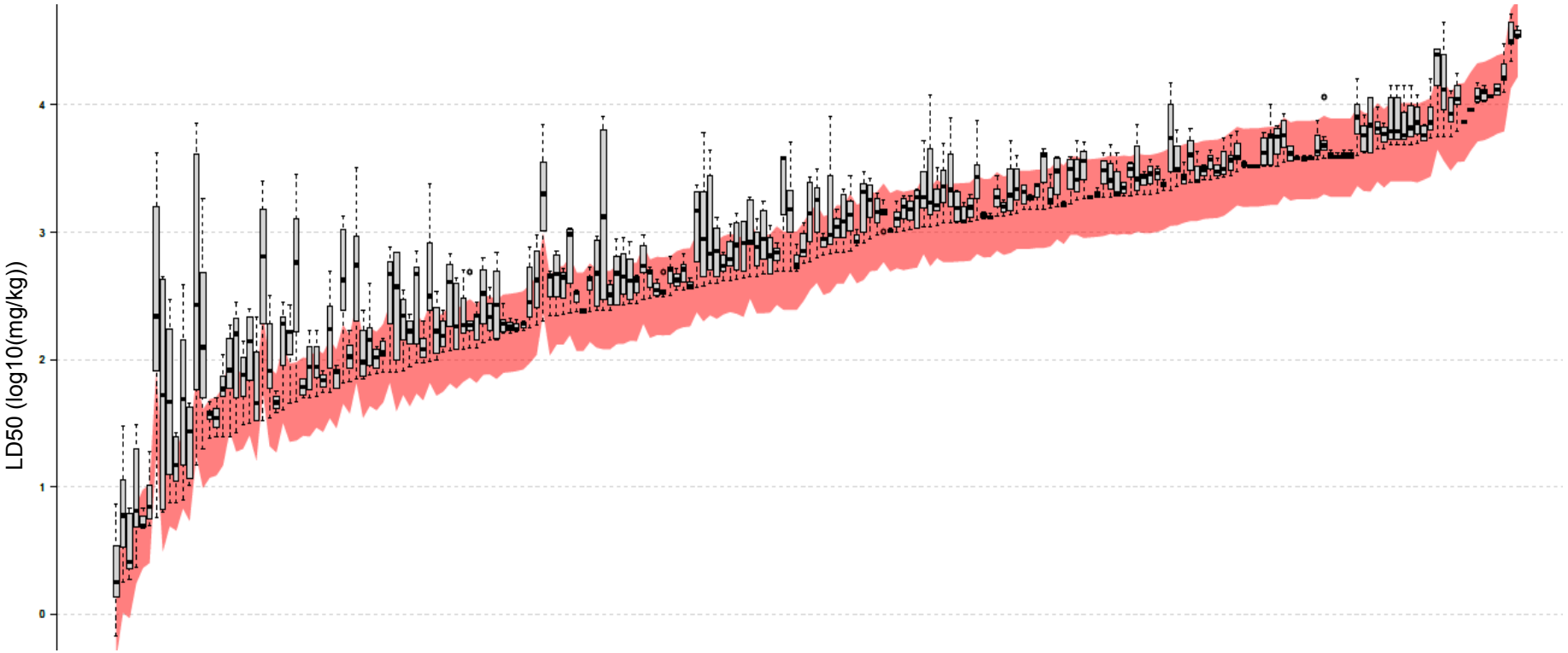
Total:
34,511 LD50 values
16,307 chemicals

↓ Identify unique data in mg/kg

21,210 LD50 values
15,698 chemicals

Defining a Confidence Range

Bootstrapping of the standard deviations for repeat test chemicals identified a 95% confidence interval for LD50 values of ±0.31 $\log_{10}$(mg/kg)



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
- NICEATM database release: March 2018

https://ice.ntp.niehs.nih.gov/

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Development of Predictive Models for Acute Oral Toxicity

- International QSAR modeling groups tasked with building models to predict acute oral systemic toxicity
- Model outputs (quantitative and categorical) based on agency input - coordinated by ICCVAM ATWG
- 32 groups from the US, Europe, and Asia responded with 135 models for LD50, EPA and GHS categories, and binary nontoxic vs all others and very toxic vs all others.
- Models were qualitatively and quantitatively assessed and combined into consensus models.

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

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Recent Workshop: Modelers + Regulators

Predictive Models for Acute Oral Systemic Toxicity

William H. Natcher Conference Center
National Institutes of Health, Bethesda, Maryland
April 11 – 12, 2018

Attendees in-person: 89; webcast: 215

Predictive Models for Acute Toxicity:

Performance vs Animal Data

Rat Oral LD50: Reproducibility | Consensus Model Performance (Tr/Ts Avg)

	Sensitivity	Specificity	BA	Sensitivity	Specificity	BA
VT	63%	99%	81%	77%	95%	86%
NT	96%	82%	89%	82%	92%	87%
EPA	74%	91%	82%	62%	94%	78%
GHS	66%	92%	79%	54%	92%	73%

	R2	RMSE	R2	RMSE
LD50	0.8	0.42	0.74	0.42

Stakeholder Engagement

- Strategic Roadmap public webpage:

https://ntp.niehs.nih.gov/pubhealth/evalatm/natl-strategy/index.html

- ICCVAM Public Forum, May 24, 2018
- Scientific Advisory Committee on Alternative Toxicological Methods (SACATM), Sept. 5-6, 2018

https://ntp.niehs.nih.gov/pubhealth/evalatm/3rs-meetings/

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Thank you!

Questions?