Regulatory Needs and Decision Contexts for Acute Oral Systemic Toxicity Data

Emily Reinke, PhD, D.A.B.T.; DoD, Co-chair, ICCVAM
Judy Strickland, PhD, D.A.B.T; ILS/NICEATM

Predictive Models for Acute Oral Systemic Toxicity Workshop
April 11-12, 2018

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

Acute Toxicity Workgroup

- *Grace Patlewicz (EPA)
- *Donald Cronce (DoD)
- Kent Carlson (CPSC)
- Xinrong Chen (CPSC)
- John Gordon (CPSC)
- Joanna Matheson (CPSC)
- Lyle Burgoon (DoD)
- Natalia Garcia-Reyero (DoD)
- Jeffery Gearhart (DoD)
- David Mattie (DoD)
- Ronald Meris (DoD)
- Heather Pangburn (DoD)
- Brain Pate (DoD)
- Michael Phillips (DoD)
- Emily N. Reinke (DoD)
- Mark Williams (DoD)
- Aiguo Wu (DoD)
- Ryan Vierling (DOT)
- Anna Lowit (EPA)
- Tracy Keigwin (EPA)
- Edward Odenkirchen (EPA)
- Thao (Tina) Pham (EPA)
- Elissa Reaves (EPA)
- Christopher Schlosser (EPA)
- P. V. Shah (EPA)
- Jenny Tao (EPA)
- Garland Waleko (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
- Kamel Mansouri

*co-chairs

A Strategic Roadmap for Establishing New Approaches to Evaluate the Safety of Chemicals and Medical Products in the United States

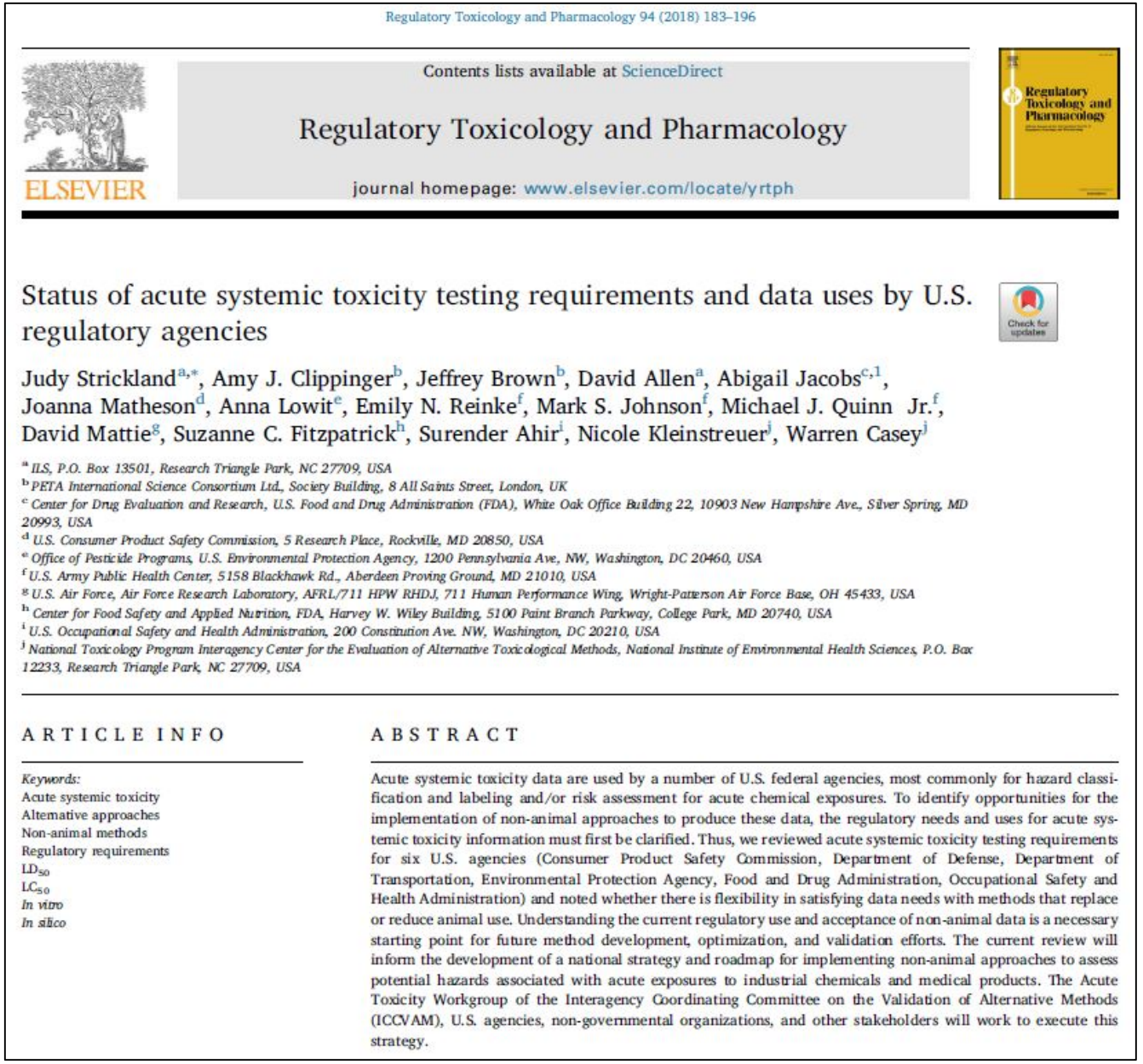
Method Development → Validation → Regulatory Acceptance

Must start here!!

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

ICCVAM Acute Toxicity Workgroup Scoping Document

- Identifies requirements, needs, and decision contexts for acute systemic toxicity data



Regulatory Toxicology and Pharmacology 94 (2018) 183–196

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

Status of acute systemic toxicity testing requirements and data uses by U.S. regulatory agencies

Judy Strickland[a,*], Amy J. Clippinger[b], Jeffrey Brown[b], David Allen[a], Abigail Jacobs[c,1], Joanna Matheson[d], Anna Lowit[e], Emily N. Reinke[f], Mark S. Johnson[f], Michael J. Quinn Jr.[f], David Mattie[g], Suzanne C. Fitzpatrick[h], Surender Ahir[i], Nicole Kleinstreuer[j], Warren Casey[j]

[a] ILS, P.O. Box 13501, Research Triangle Park, NC 27709, USA
[b] PETA International Science Consortium Ltd., Society Building, 8 All Saints Street, London, UK
[c] Center for Drug Evaluation and Research, U.S. Food and Drug Administration (FDA), White Oak Office Building 22, 10903 New Hampshire Ave., Silver Spring, MD 20993, USA
[d] U.S. Consumer Product Safety Commission, 5 Research Place, Rockville, MD 20850, USA
[e] Office of Pesticide Programs, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460, USA
[f] U.S. Army Public Health Center, 5158 Blackhawk Rd., Aberdeen Proving Ground, MD 21010, USA
[g] U.S. Air Force, Air Force Research Laboratory, AFRL/711 HPW RHDJ, 711 Human Performance Wing, Wright-Patterson Air Force Base, OH 45433, USA
[h] Center for Food Safety and Applied Nutrition, FDA, Harvey W. Wiley Building, 5100 Paint Branch Parkway, College Park, MD 20740, USA
[i] U.S. Occupational Safety and Health Administration, 200 Constitution Ave. NW, Washington, DC 20210, USA
[j] National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods, National Institute of Environmental Health Sciences, P.O. Box 12233, Research Triangle Park, NC 27709, USA

ARTICLE INFO

Keywords:
Acute systemic toxicity
Alternative approaches
Non-animal methods
Regulatory requirements
LD_{50}
LC_{50}
In vitro
In silico

ABSTRACT

Acute systemic toxicity data are used by a number of U.S. federal agencies, most commonly for hazard classification and labeling and/or risk assessment for acute chemical exposures. To identify opportunities for the implementation of non-animal approaches to produce these data, the regulatory needs and uses for acute systemic toxicity information must first be clarified. Thus, we reviewed acute systemic toxicity testing requirements for six U.S. agencies (Consumer Product Safety Commission, Department of Defense, Department of Transportation, Environmental Protection Agency, Food and Drug Administration, Occupational Safety and Health Administration) and noted whether there is flexibility in satisfying data needs with methods that replace or reduce animal use. Understanding the current regulatory use and acceptance of non-animal data is a necessary starting point for future method development, optimization, and validation efforts. The current review will inform the development of a national strategy and roadmap for implementing non-animal approaches to assess potential hazards associated with acute exposures to industrial chemicals and medical products. The Acute Toxicity Workgroup of the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM), U.S. agencies, non-governmental organizations, and other stakeholders will work to execute this strategy.

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

Current Acute Oral Toxicity Test Guidelines

- Up-and-down Procedure (UDP)
  - U.S. EPA Health Effects Test Guidelines OPPTS 870.1100 Acute Oral Toxicity (2002)
  - OECD Test Guideline 425 Acute Oral Toxicity - Up-and-Down Procedure (2008)
- Acute Toxic Class method (ATC)
  - OECD Test Guideline 423 Acute Oral Toxicity - Acute Toxic Class Method (2001)
- Fixed Dose Procedure (FDP)
  - OECD Test Guideline 420 Acute Oral Toxicity - Fixed Dose Procedure (2001)

Comparison of In Vivo Methods

Feature	UDP	ATC	FDP
Endpoint	Lethality	Lethality	Evident toxicity
Starting dose	Below expected LD50	Likely to be lethal	Nonlethal
Doses	Factor of 3.2	Fixed	Fixed
Animals/dose	1	3	5
Time between doses	At least 48 h	Depends on survival	At least 24 h
Total animals	6-9	7	5-7
Animals for limit test	≤5	≤6	≤5
Outcome	LD50 value	LD50 range	Inferred LD50 range

Hazard Classification Systems

EPA Category	Oral LD_{50}
I	≤50 mg/kg
II	>50 to 500 mg/kg
III	>500 to 5000 mg/kg
IV	>5000 mg/kg

GHS Category	Oral LD_{50}
1	≤5 mg/kg
2	>5 to 50 mg/kg
3	>50 to 300 mg/kg
4	>300 to 2000 mg/kg
5 (optional)	>2000 to 5000 mg/kg
Unclassified	>5000 mg/kg

Agencies Included in the Scoping Document

- Office of Pesticide Programs
- Office of Pollution Prevention and Toxic Substances

- Center for Biologics Evaluation and Research
- Center for Food Safety and Applied Nutrition

Consumer Product Safety Commission

- Federal Hazardous Substances Act
  - Requires cautionary labeling on hazardous (i.e., toxic or highly toxic) household substances to help consumers safely store and use and apply first aid for accidents
  - Also considers acute dermal and inhalation toxicity
  - Data submission not required

Category	Oral LD_{50}
Highly Toxic	≤50 mg/kg
Toxic	>50 to 5000 mg/kg

- Poison Prevention Packaging Act
  - Child-resistant packaging must be applied to hazardous household substances such as aspirin, furniture polish, and oral prescription drugs
  - Data submission required for exemptions

Department of Defense

- Acute oral toxicity data used to protect human health and the environment
  - During the development of new substances and the evaluation of new substances entering the supply chain
  - Required during the testing and demonstration phase of new substance development and new weapon systems
    - Also considers acute dermal and inhalation toxicity
  - Used to develop exposure limits

Department of Transportation

- Federal Hazardous Material Transportation Act
  - Requires hazard labeling and special packaging for “poisonous materials,” substances known or presumed to be sufficiently toxic to humans so as to produce a health hazard during transportation
    - Also considers acute dermal and inhalation toxicity
  - Data submission not required

Packing Group	Oral LD_{50}
I	≤5 mg/kg
II	>5 to 50 mg/kg
III	>50 to 300 mg/kg

EPA Office of Pesticide Programs

- Federal Insecticide, Fungicide, and Rodenticide Act
  - Used for hazard labeling for consumer and worker protection
  - Used to determine whether child-resistant packaging should be applied (oral LD_{50} ≤ 1500 mg/kg)
  - Data submission required

EPA Category	Oral LD_{50}
I	≤50 mg/kg
II	>50 to 500 mg/kg
III	>500 to 5000 mg/kg
IV	>5000 mg/kg

Signal Word Requirements and Typical Label Statements

Toxicity Category	Signal Word	Statements
I	DANGER-POISON Skull & Crossbones required	Fatal if swallowed. Wash thoroughly with soap and water after handling and before eating, drinking, chewing gum, using tobacco or using the toilet.
II	WARNING	May be fatal if swallowed. Wash thoroughly with soap and water after handling and before eating, drinking, chewing gum, using tobacco or using the toilet.
III	CAUTION	Harmful if swallowed. Wash thoroughly with soap and water after handling and before eating, drinking, chewing gum, using tobacco or using the toilet.
IV	CAUTION (optional)	No statements are required. However, the registrant may choose to use category III labeling.

EPA Office of Pollution Prevention and Toxics

- Toxic Substances Control Act
  - OPPT must determine whether chemicals present an unreasonable risk to health or the environment
  - For new substances or new uses of existing substances, data submission is required only if existing data are available
  - EPA can request new information for existing substances if needed for prioritizing or conducting a risk evaluation
  - Used to suggest language on safety data sheets for occupational risk assessment and for determining appropriate protective equipment

2. HAZARDS IDENTIFICATION

2.1 Classification of the substance or mixture

GHS Classification in accordance with 29 CFR 1910 (OSHA HCS)
Acute toxicity, Oral (Category 4), H302
Serious eye damage (Category 1), H318

For the full text of the H-Statements mentioned in this Section, see Section 16.

2.2 GHS Label elements, including precautionary statements

Pictogram

Signal word	Danger
Hazard statement(s)	
H302	Harmful if swallowed.
H318	Causes serious eye damage.
Precautionary statement(s)	
P264	Wash skin thoroughly after handling.
P270	Do not eat, drink or smoke when using this product.
P280	Wear eye protection/ face protection.
P301 + P312 + P330	IF SWALLOWED: Call a POISON CENTER/doctor if you feel unwell. Rinse mouth.

Food and Drug Administration

- FDA is responsible for the safety of the nation's domestically produced and imported foods, cosmetics, drugs, biologics, medical devices, and radiological products
- FDA relies on guidances rather than testing standards or guidelines
  - FDA, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), and International Organization for Standardization (ISO)
  - Acute toxicity testing is typically not needed; lethality testing has been discouraged since 1988 (https://cdn.loc.gov/service/ll/fedreg/fr053/fr053196/fr053196.pdf)

FDA Center for Biologics Evaluation and Research

- CBER regulates biological products for human use, such as vaccines, blood and blood products, allergenics, cellular and tissue products, and gene therapies
- CBER's requirement is for sponsors to show that products are sufficiently safe to conduct the proposed clinical investigations
- Acute toxicity testing is not needed
  - FDA's 1996 "Guidance for Industry on Single Dose Acute Toxicity Testing for Pharmaceuticals" is no longer used
- Any needed acute toxicity information can typically be obtained from repeated-dose studies; single dose studies may not even be reviewed by FDA

FDA Center for Food Safety and Applied Nutrition

- CFSAN is mainly concerned with long-term repeated exposures to direct food additives and color additives
- Acute oral toxicity testing is not required or recommended
- If petitioners choose to perform acute oral toxicity tests, CFSAN recommends alternative protocols that reduce the use of animals, such as the up-and-down procedure
  - Acute toxicity information could be used for selecting doses for short-term (14 or 28 day) studies or subchronic (90-day) studies; and (2) provide insight on safety evaluations of accidental ingestions of contaminants in food (i.e., information on potential target organs and rapidity of effects)

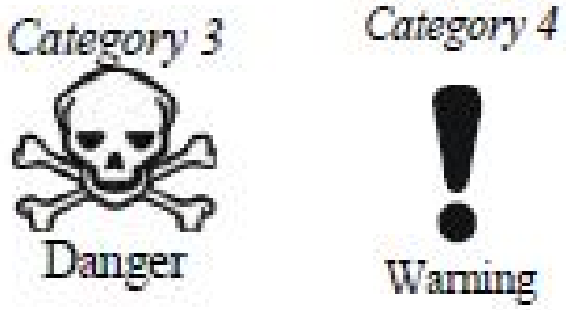
Other FDA Centers

- Center for Drug Evaluation and Research is responsible for the safety and efficacy of over-the-counter and prescription drugs
  - CDER does not use or request single dose toxicity studies
- Center for Devices and Radiological Health is responsible for the pre-market approval of medical devices
  - Acute toxicity testing for devices is performed using device extracts administered by the intraperitoneal route

Occupational Safety and Health Administration

- Under the Occupational Safety and Health Act (1970), the Hazard Communication Standard requires chemical manufacturers, chemical importers, distributors, and employers with hazardous chemicals in their workplaces to provide hazard labeling and safety data sheets to protect employees.
- Data submission is not required

OSHA Category	Oral LD_{50}
1	≤5 mg/kg
2	>5 to 50 mg/kg
3	>50 to 300 mg/kg
4	>300 to 2000 mg/kg



Use of Non-animal Alternatives

Agency	Primary Use of Acute Oral Data	Animal Testing Required?	Alternatives Accepted?
CPSC	Hazard labelling	No; existing data can be used	Any validated alternatives; will consider others on a case-by-case basis
DOT	Hazard labelling	No; existing data can be used	Any validated alternatives
DoD	Risk evaluation, exposure limits	During testing and demonstration of new substance development	Yes, in preliminary stages of new substance evaluation
EPA OPP	Hazard labelling; worker protection	Yes	Waivers may be granted
EPA OPPT	Risk evaluation	No	Yes
OSHA	Hazard communication/labelling	No; existing data can be used	Any validated alternatives; or weight-of-evidence approach

Summary

- Acute oral toxicity data are typically used for hazard classification and labeling and risk evaluation
- Agencies are typically flexible in their consideration of non-animal alternatives
- DoD uses alternatives in preliminary evaluations of substances. EPA OPPT accepts and uses alternatives.
- CPSC, DOT, and OSHA would accept validated alternatives, but there are no validated replacement methods or defined approaches for acute oral toxicity
  - CPSC may accept alternatives on a case-by-case basis and OSHA may accept a weight-of-evidence approach
- EPA OPP is accepting waivers and is proactively working with stakeholders and other acute lethality alternatives

Modeling Endpoints for Acute Oral Toxicity Data

Hazard

EPA

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

Hazard

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

+ Nontoxic (>2000 mg/kg)

Packing Group

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

Hazard

GHS

+ Quantitative LD50 values