

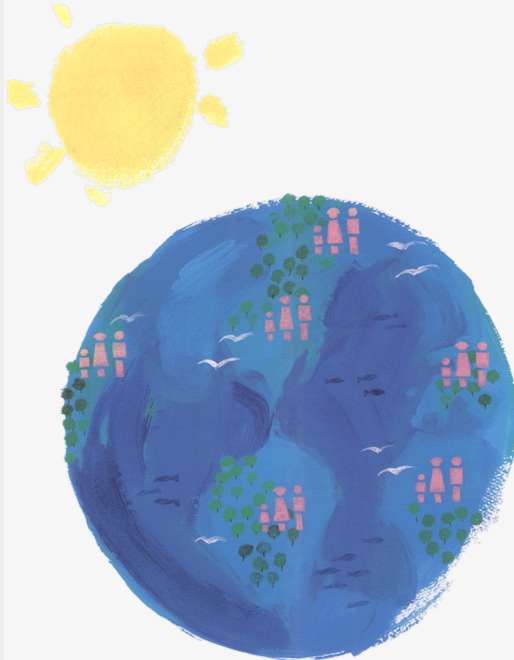
NICEATM

*National Toxicology Program
Interagency Center for the Evaluation of
Alternative Toxicological Methods*

ICCVAM

*Interagency Coordinating Committee on
the Validation of Alternative Methods*

Regulatory Needs and Uses for Acute Systemic Toxicity Data



Deborah McCall

U.S. Environmental Protection Agency

**Acute Chemical Safety Testing: Advancing *In Vitro*
Approaches and Humane Endpoints for Systemic
Toxicity Evaluations**

February 7, 2008

**Natcher Conference Center
Bethesda, Maryland**



History

- Prior to 1927, “minimum lethal dose” was used loosely to describe a dose that would kill all or most of the animals of a given species, while a dose that was slightly less would not kill any animals
- In 1927, J.W. Trevan¹ proposed using “median lethal dose” (LD₅₀) to standardize measurement of acute toxicity
 - Use to standardize new batches of dangerous drugs (I.e., digitalis, insulin)
- Such safety testing soon spread to vaccines and new chemicals and products

¹Trevan, J.W. 1927. The Error of Determination of Toxicity. Proceedings of the Royal Society (London). Series B 101: 483-514.



Regulatory Needs and Uses

- Classification and labeling
- Risk assessment
- Risk management
 - Personal protective equipment
 - Restrictions on use and distribution (e.g. child resistant packaging)

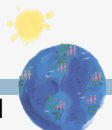
Information from Acute Toxicity Testing

- Lethality ranges
- Point estimate of LD_{50}
- Confidence interval around point estimate
- Toxic signs



Hazard Classification Systems

- Acute systemic toxicity classification definitions and criteria vary among regulatory hazard classification systems
 - Department of Transportation
 - Consumer Product Safety Commission
 - Environmental Protection Agency
 - Occupation safety and Health Administration
 - United Nations - Globally Harmonized System of Classification and Labelling of Chemicals



DOT Packing Group Categories

DOT Category	<i>In Vivo</i> Acute Oral LD ₅₀ Value
1	≤5 mg/kg
2	>5 to ≤ 50 mg/kg
3 (solids)	>50 to ≤ 200 mg/kg
3 (liquids)	>50 to ≤ 500 mg/kg



CPSC Classification System

CPSC Category	<i>In Vivo</i> Acute Oral LD ₅₀ Value
1	≤50 mg/kg
2	>50 thru 5000 mg/kg

EPA Hazard Classification System

EPA Category	Oral LD ₅₀	Dermal LD ₅₀	Inhalation LC ₅₀ ¹
I	≤50 mg/kg	≤200 mg/kg	≤0.05 mg/L
II	>50 to ≤500 mg/kg	>200 to ≤2000 mg/kg	>0.05 to ≤0.5 mg/L
III	>500 to ≤5000 mg/kg	>2000 to ≤5000 mg/kg	>0.5 to ≤2 mg/L
IV	>5000 mg/kg	>5000 mg/kg	>2 mg/L

¹4 hour exposure



EPA Hazard Labeling Statements for Acute Oral Toxicity

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 or using tobacco.
II	WARNING	May be fatal if swallowed. Wash thoroughly with soap and water after handling and before eating, drinking, chewing gum or using tobacco
III	CAUTION	Harmful if swallowed. Wash thoroughly with soap and water after handling and before eating, drinking, chewing gum or using tobacco
IV	CAUTION (optional)	No statements are required.

GHS Hazard Classification System

Category	Oral LD ₅₀	Dermal LD ₅₀	Inhalation LC ₅₀
1	≤5 mg/kg	≤50 mg/kg	≤100 ppm (g) ≤0.5 mg/L (v) ≤0.05 mg/L (d, m)
2	>5 to ≤50 mg/kg	>50 to ≤200 mg/kg	>100 to ≤500 ppm (g) >0.5 to ≤2 mg/L (v) >0.05 to ≤0.5 mg/L (d, m)
3	>50 to ≤300 mg/kg	>200 to ≤1000 mg/kg	>500 to ≤2500 ppm (g) >2 to ≤10 mg/L (v) >0.5 to ≤1.0 mg/L (d, m)
4	>300 to ≤2000 mg/kg	>1000 to ≤2000 mg/kg	>2500 to ≤5000 ppm (g) >10 to ≤20 mg/L (v) >1.0 to ≤5 mg/L (d, m)
5	>2000 to ≤5000 mg/kg	>2000 to ≤5000 mg/kg	Doses equivalent to dermal and oral criteria
Unclassified	>5000 mg/kg	>5000 mg/kg	

Abbreviations: d=Dusts; g=Gases; m=Mists; v=Vapors.

GHS Hazard Labeling Statements

Category	Symbol	Signal Word	Statements
1	Skull-Crossbones	Danger	Fatal if swallowed ¹
2	Skull-Crossbones	Danger	Fatal if swallowed ¹
3	Skull-Crossbones	Danger	Toxic if swallowed ¹
4	Exclamation Point	Warning	Harmful if swallowed ¹
5	No symbol	Warning	May be harmful if swallowed ¹

¹For dermal toxicity hazards, the phrase “in contact with skin” is substituted for “if swallowed, and for inhalation toxicity hazards, the phrase “if inhaled” is used.



Current Test Guidelines – Acute Oral Toxicity

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

Abbreviations: OECD = Organization for Economic Co-operation and Development.

Current Test Guidelines – Acute Dermal and Inhalation Toxicity

- Acute dermal toxicity
 - U.S. EPA Health Effects Test Guidelines 870.1200 Acute Dermal Toxicity (1998)
 - OECD Test Guideline 402 Acute Dermal Toxicity (1987)
- Acute inhalation toxicity
 - U.S. EPA Health Effects Test Guidelines 870.1300 Acute Inhalation Toxicity (1998)
 - OECD Test Guideline 403 Acute Inhalation Toxicity (1981)

Abbreviations: EPA= U.S. Environmental Protection Agency; OECD= Organisation for Economic Co-operation and Development.



Other Uses of Acute Toxicity Data

- Establishing dosing levels for repeated dose toxicity studies
- Aiding in the diagnosis and treatment of toxic reactions
- Aiding in the standardization of biological products
- Serving as a standard for evaluating alternatives to animal tests
- Poison prevention packaging (e.g., oral prescription drugs in CRP)



Other Uses of Acute Toxicity Data

- Aiding in judging the consequences of single, high accidental exposures in the workplace, home, or from accidental release
- Specific organs affected (maybe limited)
- Mode of toxic action (maybe limited)

