Performance of the GHS Mixtures Equation for Predicting Acute Oral Toxicity

J Hamm[1]; D Allen[1]; P Ceger[1]; T Flint[2]; J Tao[2]; L O'Dell[2]; A Lowit[2]; N Kleinstreuer[3]

[1]ILS, RTP, NC, USA; [2]Office of Pesticide Programs, U.S. Environmental Protection Agency, Washington, DC, USA; [3]NIH/NIEHS/DNTP/NICEATM, RTP, NC, USA

Introduction

- The Globally Harmonized System of Classification and Labelling of Chemicals (GHS) is used internationally for hazard classification.
- The GHS Mixtures Equation provides a mathematical approach to calculating toxicity of mixtures, considering the toxicity of each mixture component in a weighted manner.
- To evaluate the utility of this approach, we compared LD_{50}s predicted for formulations based on the Mixtures Equation to those determined from in vivo results with the complete formulation. Comparisons were made using both the U.S. Environmental Protection Agency (EPA) and GHS classification systems.
- LD_{50}s based on in vivo results and calculated using the Mixtures Equation for the same substances were collected by EPA from studies submitted for pesticide registration and provided to the National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM).
- We calculated concordance by determining the percentage of formulations for which classifications derived from in vivo data agreed with classifications derived from Mixtures Equation calculations.

Conclusions and Future Directions

- Most "discordant" substances had in vivo LD_{50} values measured between 2000 and 5000 mg/kg or a limit test LD_{50} >2000 mg/kg.
- When considering formulations with LD_{50} >500 mg/kg together, overall concordance increased from 55% to 82%.
- Within-class concordance for less toxic substances was consistently over 85% regardless of classification system.
- Animal tests are inherently variable. Similar underprediction could also be observed following a repetition of the animal test.
- The GHS Mixtures Equation represents an alternative approach to reduce animal testing for formulations, particularly for substances predicted to have low or negligible acute oral toxicity.

Classification and Precautionary Labeling

EPA Categories

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

GHS Categories

Packing Group / OSHA Hazard
- 1 (≤ 5 mg/kg)
- 2 (>5 ≤ 50 mg/kg)
- 3 (>50 ≤ 300 mg/kg)
- 4 (>300 ≤ 2000 mg/kg)
- NC (> 2000 mg/kg)

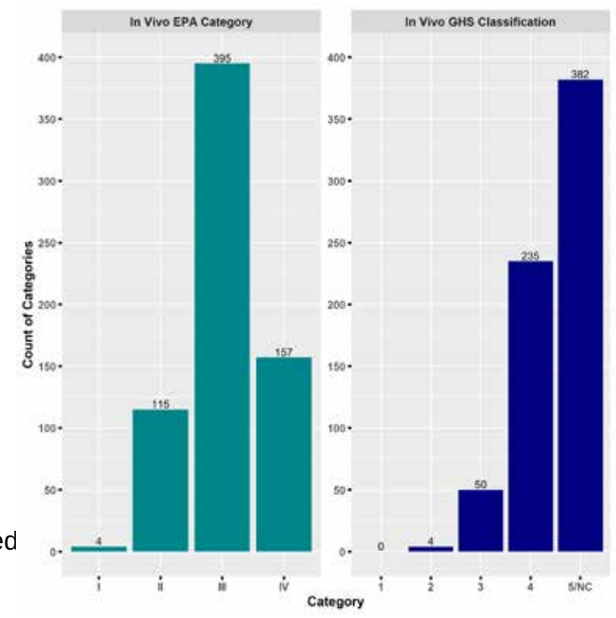
EPA Category	Signal Word	Statement
I (LD_{50} ≤ 50 mg/kg)	Danger/Poison	Fatal if swallowed.
II (50>LD_{50} ≥ 500 mg/kg)	Warning	May be fatal if swallowed.
III (500>LD_{50} ≥ 5000 mg/kg)	Caution	Harmful if swallowed.
IV (LD_{50} > 5000 mg/kg)	Caution (optional)	No statement is required. May use Category III statement

Revised March 2018
Label Review Manual
Chapter 7: Precautionary Statements

https://www.epa.gov/sites/production/files/2018-04/documents/chap-07-mar-2018.pdf

Dataset Description

- 671 formulations from eight companies:
  - 51 antimicrobial cleaning products (AMCPs)
  - 620 agrochemical formulations
- The bar graph shows the distribution of the dataset substances according to their classifications in the EPA and GHS hazard classification systems.
- We used conservative classifications for in vivo LD_{50}s expressed as ranges (e.g., would use 300 mg/kg for 300 to 2000 mg/kg) and limit doses (e.g., would use 2000 for >2000 mg/kg).
- Precautionary labeling for substances, which also impacts packaging and required personal protective equipment (PPE), is based on the LD_{50}.



- The precautionary statements and associated PPE are much more stringent with LD_{50} <500 mg/kg.
- We performed a supplementary analysis that combined all substances with LD_{50} >500 mg/kg together.

Concordance Analysis Summary

All Substances	Primary Approach			Supplementary Analysis		
	Full	AMCP	Agrochem	Full	AMCP	Agrochem
EPA	55% (367/671)	84% (43/51)	52% (324/620)	82% (547/669)	100% (51/51)	80% (496/618)
GHS	72% (484/671)	98% (50/51)	70% (434/620)	NA	NA	NA

Less Toxic Substances	Primary Approach (Cat IV or 5/NC)			Supplementary Analysis (>500 mg/kg)		
	Full	AMCP	Agrochem	Full	AMCP	Agrochem
EPA	87% (138/157)	95% (38/40)	85% (99/117)	93% (514/550)	100% (51/51)	93% (463/496)
GHS	88% (337/381)	100% (49/49)	87% (288/332)	NA	NA	NA

Primary Analysis

- Concordance analysis was determined according to EPA and GHS classification systems

In vivo Classification	EPA Additivity Classification				Within-class Concordance
	I	II	III	IV	
I	3	1	0	0	75%
II	4	30	61	20	26%
III	1	34	197	163	50%
IV	0	1	19	137	87%
Total	8	66	277	320	**55%**

In vivo Classification	GHS Additivity Classification					Within-class Concordance
	1	2	3	4	5/NC	
1	0	0	0	0	0	NA
2	0	3	1	0	0	75%
3	0	4	10	26	10	20%
4	0	0	17	134	85	57%
5/NC	0	1	4	39	337	88%
Total	0	8	32	199	432	72%

- 79% (128/163) of "discordant" substances (EPA Cat III predicted as Cat IV, yellow highlight) had LD_{50} values measured between 2000 and 5000 mg/kg or a limit test LD_{50} >2000 mg/kg. in vivo.

Supplementary Analysis

- Precautionary labeling for substances, which also impacts packaging and required personal protective equipment (PPE), is based on the LD_{50}.
- The precautionary statements and associated PPE are much more stringent with LD_{50} <500 mg/kg.
- We performed a supplementary analysis that combined all substances with LD_{50} >500 mg/kg together.

In vivo LD_{50}	Additivity LD_{50} Prediction (mg/kg)			Within-class Concordance
	≤50	>50 to ≤500	>500	
≤50	3	1	0	75%
>50 to ≤500	4	30	81	26%
>500	1	35	514	93%
Total	8	66	595	82%

More Information

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This project was funded in whole or in part with federal funds from the National Institute of Environmental Health Sciences, National Institutes of Health, Department of Health and Human Services, under Contract No. HHSN273201500010C.

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