AFRL

Assessment of Acute Oral Toxicity for Mixtures Using *In Silico* Modeling Methods

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- Opinions are those of the presenter, and not those of the Air Force, or the Department of Defense (DOD).

Outline

- Background
- Objectives
- Approach
- Results
  - Analysis of Input Data
  - Predictions of GHS acute oral toxicity category
- Challenges
- Impact and Conclusions
- Acknowledgements

Objectives

- While exposure of humans to environmental hazards often occurs with chemical mixtures, the majority of existing toxicity data and tools are for single compounds
  - This is particularly pertinent given the number of unique AF-relevant mixtures used across the force.

- Therefore, our researchers evaluated the prediction of GHS acute oral toxicity category for mixtures using the additivity formula and toxicological data collected in the Integrated Chemical Environment (ICE)

Approach

- By using available experimental data for individual ingredients, our researchers were able to calculate a GHS category for only half of the mixtures.

- The Collaborative Acute Toxicity Modeling Suite (CATMoS) was used to predict LD_{50} values for active ingredients without available experimental data.

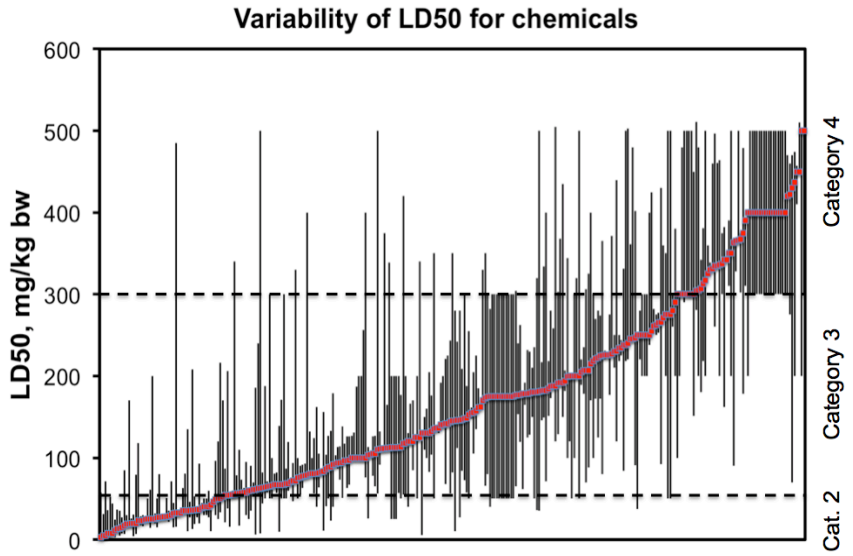
Exposure route	Category 1	Category 2	Category 3	Category 4	Category 5
Oral (mg/kg bodyweight) *See notes (a) and (b)*	5	50	300	2000	5000 *See detailed criteria in Note (g)*
Dermal (mg/kg bodyweight) *See notes (a) and (b)*	50	200	1000	2000	
Gases (ppmV) *See notes (a), (b) and (c)*	100	500	2500	20000	*See detailed criteria in Note (g)*
Vapours (mg/l) *See notes (a), (b), (c), (d) and (e)*	0.5	2.0	10	20	
Dusts and Mists (mg/l) *See notes (a), (b), (c) and (f)*	0.05	0.5	1.0	5	

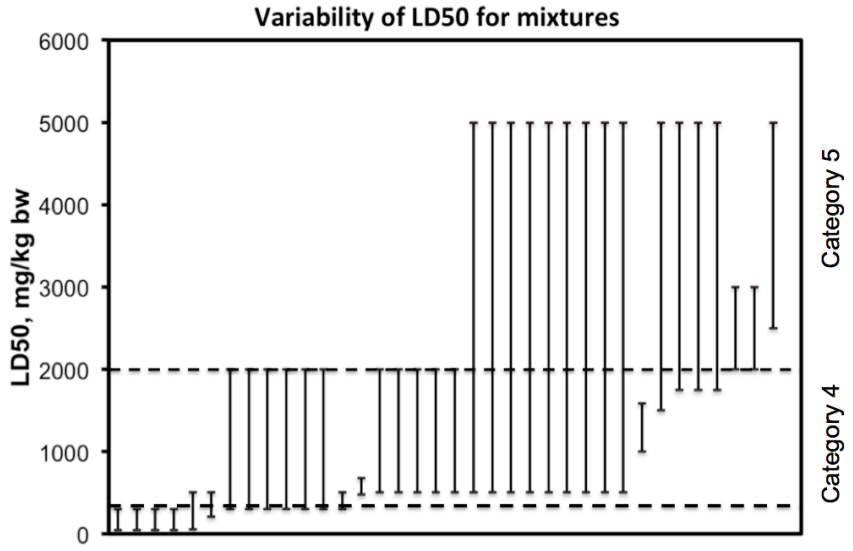
Note: *Gases concentration are expressed in parts per million per volume (ppmV).*

Source: UN GHS Purple Book

Results: Analysis of Input Data

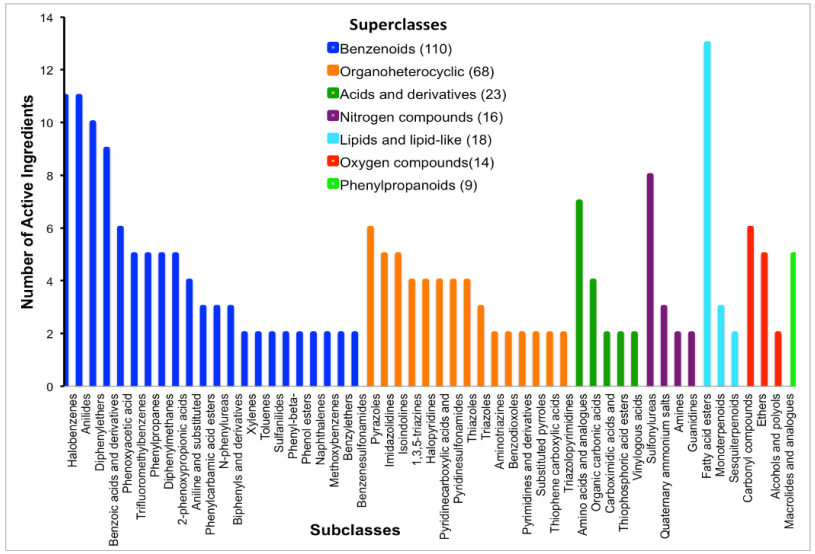
- Variability of Input Data
  - Out of 10,384 chemicals in the ICE repository, 1,417 chemicals have 2 or more LD_{50} values, with 514 chemicals falling into 2 or more GHS categories
  - Variability of experimental data is also observed for mixtures



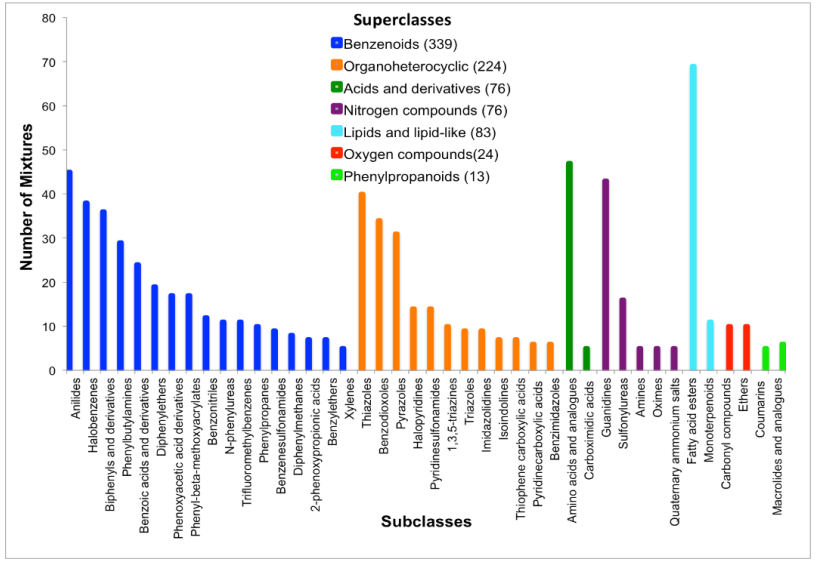


Results: Analysis of Input Data cont'd

- Structure-based classification (chemicals)
  - 13 fatty acid esters
  - 12 pyrethroids
  - 11 halobenzenes
  - 11 anilides



- Structure-based classification (mixtures)
  - 69 contain pyrethroids
  - 43 are guanidines containing imidacloprid or dinotefuran



Results: Predictions of GHS Acute Oral Toxicity Category

ICE GHS Category	Predicted GHS Category 1	2	3	4	5	Total	SEN	SPE
1	0	0	0	0	0	0		
2	1	0	1	0	0	2	0	1.00
3	0	1	16	7	1	25	0.64	0.96
4	0	0	8	54	37	99	0.55	0.91
5	0	0	1	9	136	146	0.93	0.70
						272	0.53	0.89

Accuracy = 76 % MCC = 0.56

Overestimated 20 = 7.4 %

Underestimated 46 =16.9 %

Predictions using the "median" LD_{50} values for active ingredients

ICE GHS Category	Predicted GHS Category 1	2	3	4	5	Total	SEN	SPE
1	0	0	0	0	0	0		
2	1	0	1	0	0	2	0	0.98
3	0	1	20	4	0	25	0.80	0.93
4	0	4	13	59	23	99	0.60	0.82
5	0	0	3	28	115	146	0.79	0.82
						272	0.55	0.89

Accuracy = 71 % MCC = 0.51

Overestimated 50 =18.4 %

Underestimated 28 =10.3 %

Predictions using the "low" LD_{50} values for active ingredients

Results: Predictions of GHS Acute Oral Toxicity Category cont'd

ICE GHS Category	Predicted GHS Category 1	2	3	4	5	Total	SEN	SPE
1	0	0	0	0	0	0		
2	1	0	1	0	0	2	0	1.00
3	0	0	19	4	0	23	0.83	0.96
4	0	1	6	62	24	93	0.67	0.84
5	0	0	2	22	112	136	0.82	0.80
						254	0.58	0.90

Accuracy = 76 % MCC = 0.58

Overestimated 32 =12.6 %

Underestimated 29 =11.4 %

Predictions using ICCVAM LD_{50} values for ingredients

ICE GHS Category	Predicted GHS Category 1	2	3	4	5	Total	SEN	SPE
1	0	0	0	0	0	0		
2	1	0	1	0	0	2	0	1.00
3	0	0	22	6	2	30	0.73	0.97
4	0	1	8	85	47	141	0.60	0.80
5	0	0	7	67	256	330	0.78	0.72
						503	0.53	0.87

Accuracy = 72 % MCC = 0.46

Overestimated 84 =16.7 %

Underestimated 56 =11.1 %

Predictions using ICCVAM and predicted by CATMoS LD_{50} values for ingredients

Challenges

- The majority of mixtures in the ICE repository are agrochemical formulations that provide only the concentration of their active ingredients. However, inactive ingredients can change properties and the LD_{50} value of active ingredients

- Variability and reproducibility of the experimental results for both mixtures and their ingredients play a significant role in the accuracy of prediction of GHS acute toxicity classification.

- In the current approach, CATMoS was used to predict the LD_{50} values for ingredients without the experimental data. The application of several different *in silico* methods, such as QSAR and read-across, can improve the accuracy and reliability of predicted results.

Impact and Conclusions

- The additivity formula was applied to predict the GHS acute oral toxicity category classification for mixtures collected in the Integrated Chemical Environment (ICE)
- Experimental and predicted CATMoS LD_{50} values were used for active ingredients
- The predictions of GHS classification were made for 503 mixtures/ formulations with 72% accuracy
- The structure-based analysis of the misclassified mixtures didn't identify any specific structural features associated with the mispredictions.

- Results demonstrate that CATMoS together with an additivity formula can be used to predict the GHS acute oral toxicity category for chemical mixtures

Acknowledgements

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- Reference: Chushak, Y., Gearhart, J. M., & Ott, D. (2021). “In Silico Assessment of Acute Oral Toxicity for Mixtures” Chem. Res. Toxicol. 34, 345.

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Questions?