

Using The GHS Mixtures Equation in Place of Acute Oral Toxicity Studies for Pesticide Submissions

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Disclaimer

The views presented here are my own and do not necessarily represent those of my current or former employers.

All case studies are fictitious examples chosen to reflect the application of this approach and do not represent formulations from my current or former employers.

Agenda

1. Case Study
2. Watchouts & Learnings from Industry POV

Key References

Hamm et al (2021) Performance of the GHS Mixtures Equation for Predicting Acute Oral Toxicity

United Nations (2025) Globally harmonized system of classification and labelling of chemicals 11th revised edition.

US EPA (2026) Utility of the GHS Mixtures Equation for Acute Oral Toxicity Classification for Pesticide Formulations

The *Standard Additivity Formulation*

The Standard Equation:

$$\frac{100}{ATE_{mix}} = \sum_n \frac{C_i}{ATE_i}$$

ATE_{mix} = acute toxicity estimate of the mixture (mg/kg)

C_i = concentration of ingredient *i* in the mixture (percentage)

ATE_i = acute toxicity estimate of ingredient *i* (mg/kg)

Case Study: Formulation

Ingredient	Concentration of Ingredient (C_i)	All Ingredients >1%
Active	3%	
Surfactant A	2%	
Surfactant B	5%	
Surfactant C	5%	
pH Adjuster	6%	
Solvent A	4%	
Solvent B	75%	

NOTE: include ingredients under 1% if ingredients of particularly high toxicity (i.e., Category 1 or 2)

Case Study: Selecting C_i

Ingredient	Concentration of Ingredient (C _i)	LD ₅₀	Reference
Active	3%	344 mg/kg	US EPA (2010) Reregistration Eligibility Decision for Active XYZ
Surfactant A	2%		
Surfactant B	5%		
Surfactant C	5%		
pH Adjuster	6%		
Solvent A	4%		
Solvent B	75%		

Case Study: Selecting C_i

Ingredient	Concentration of Ingredient (C _i)	LD ₅₀	Reference
Active	3%	344 mg/kg	EPA RED
Surfactant A	2%	1064 mg/kg 846 mg/kg	US EPA (2016) Hazard Characterization Document for Surfactant A. High Production Volume (HPV) Challenge Program ECHA (2015) REACH Registration Dossier for Surfactant A
Surfactant B	5%		
Surfactant C	5%		
pH Adjuster	6%		
Solvent A	4%		
Solvent B	75%		

Case Study: Selecting C_i

Ingredient	Concentration of Ingredient (C _i)	LD ₅₀	Reference
Active	3%	344 mg/kg	EPA RED
Surfactant A	2%	846 mg/kg	ECHA
Surfactant B	5%	GHS Category 4	CATMoS GHS Category Prediction in OPERA
Surfactant C	5%		
pH Adjuster	6%		
Solvent A	4%		
Solvent B	75%		

Table 3.1.2: Conversion from experimentally obtained acute toxicity range values (or acute toxicity hazard categories) to acute toxicity point estimates for use in the formulas for the classification of mixtures

Exposure routes	Classification category or experimentally obtained acute toxicity range estimate (see note 1)	Converted acute toxicity point estimate (see note 2)
<u>Oral</u> (mg/kg bodyweight)	0 < Category 1 ≤ 5	0.5
	5 < Category 2 ≤ 50	5
	50 < Category 3 ≤ 300	100
	300 < Category 4 ≤ 2000	500
	2000 < Category 5 ≤ 5000	2500

Case Study: Selecting C_i

Ingredient	Concentration of Ingredient (C _i)	LD ₅₀	Reference
Active	3%	344 mg/kg	EPA RED
Surfactant A	2%	846 mg/kg	ECHA
Surfactant B	5%	500 mg/kg	OPERA
Surfactant C	5%	>2000 mg/kg	Acute Oral Toxicity Limit Dose Study for Surfactant C MRID # 12345678
pH Adjuster	6%		
Solvent A	4%		
Solvent B	75%		

Case Study: Selecting C_i

Ingredient	Concentration of Ingredient (C _i)	LD ₅₀	Reference
Active	3%	344 mg/kg	EPA RED
Surfactant A	2%	846 mg/kg	ECHA
Surfactant B	5%	500 mg/kg	OPERA
Surfactant C	5%	>2000 mg/kg	MRID # 12345678
pH Adjuster	6%	Rat 1000 mg/kg Mouse 3000 mg/kg	OECD (2021) SIDS Initial Assessment Report for Chemical Category X
Solvent A	4%		
Solvent B	75%		

Case Study: Selecting C_i

Ingredient	Concentration of Ingredient (C _i)	LD ₅₀	Reference
Active	3%	344 mg/kg	EPA RED
Surfactant A	2%	846 mg/kg	ECHA
Surfactant B	5%	500 mg/kg	OPERA
Surfactant C	5%	>2000 mg/kg	MRID # 12345678
pH Adjuster	6%	1000 mg/kg	OECD SIDS
Solvent A	4%	15,010 mg/kg	US EPA (2021) Inert Reassessment – Exemption from the Requirement of a Tolerance for Solvent A
Solvent B	75%		

Case Study: Selecting C_i

Ingredient	Concentration of Ingredient (C _i)	LD ₅₀	Reference
Active	3%	344 mg/kg	EPA RED
Surfactant A	2%	846 mg/kg	ECHA
Surfactant B	5%	500 mg/kg	OPERA
Surfactant C	5%	>2000 mg/kg	MRID # 12345678
pH Adjuster	6%	1000 mg/kg	OECD SIDS
Solvent A	4%	15,010 mg/kg	EPA
Solvent B	75%	"Non-Toxic"	N/A: Presumed non-toxic (e.g., water)

Case Study: Selecting C_i

Ingredient	Concentration of Ingredient (C _i)	LD ₅₀	Reference
Active	3%	344 mg/kg	EPA
Surfactant A	2%	1064 mg/kg 846 mg/kg	EPA ECHA
Surfactant B	5%	Category 4 (300–2000 mg/kg) 500 mg/kg	OPERA
Surfactant C	5%	>2000 mg/kg	Study Submission MRID # 12345678
pH Adjuster	6%	Rat 3000–5000, Mouse 1000	OECD SIDS
Solvent A	4%	15,010 mg/kg	EPA
Solvent B	75%	Non-Toxic	N/A

Revisiting The Ingredient Assumptions

Include



All Ingredients >1%

- Only ingredients of particularly high toxicity need to be included if <1% (i.e., Cat 1 or 2)



Ingredient mixtures

- An ATE of an ingredient can be used if applicable



Range/Category Data for Ingredient

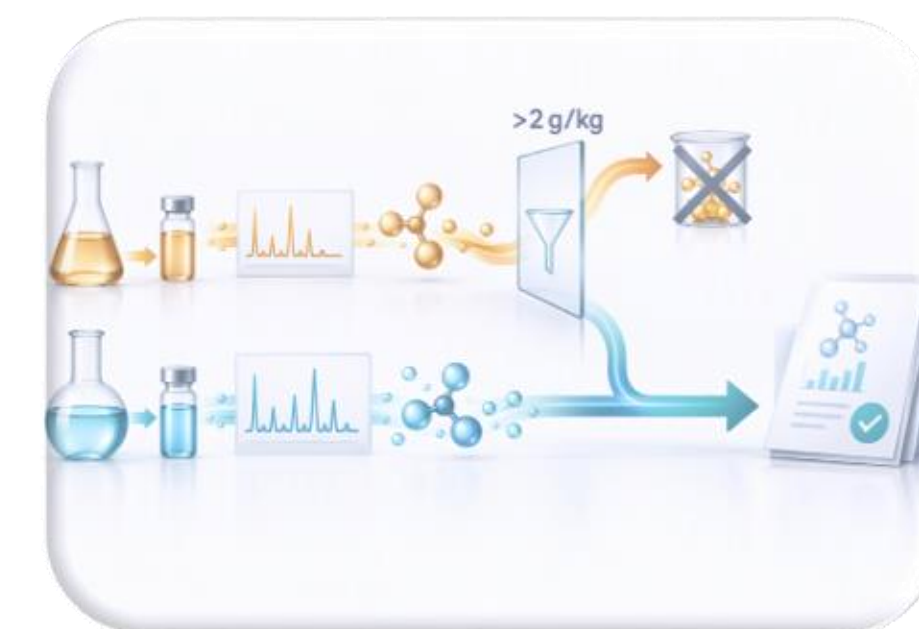
- Convert to Point Estimates
- OR more conservative value

Don't Include



"Non-Toxic" & Low Hazard Ingredients

- Presumed non-toxic (e.g., water)
- LD50 >5000 mg/kg



Data From Limit Tests Not Used

- Limit dose test (i.e., >2000 mg/kg)

Case Study: The *Standard* Calculation

$$\frac{100}{ATE_{mix}} = \sum_n \frac{C_i}{ATE_i}$$

Ingredient	$\frac{ATE_i}{(LD_{50})}$	Concentration of Ingredient (C_i)	Include?	$\frac{C_i}{ATE_i}$	
Active	344 mg/kg	3%	Yes	0.009	$\sum_n \frac{C_i}{ATE_i} = 0.027$
Surfactant A	846 mg/kg	2%	Yes	0.002	
Surfactant B	500 mg/kg	5%	Yes	0.010	
Surfactant C	>2000 mg/kg	5%	No	N/A	
pH Adjuster	1000 mg/kg	6%	Yes	0.006	
Solvent A	15010 mg/kg	4%	No	N/A	
Solvent B	Non-Toxic	75%	No	N/A	$\frac{100}{0.027}$
ATE_{mix}				3692 mg/kg	
EPA Category III					

GHS Mixtures Equation: The *Alternate* Additivity Formulation

The Alternate Equation:

$$\frac{100 - \left(\sum C_{\text{unknown}} \text{ if } > 10\% \right)}{ATE_{\text{mix}}} = \sum_n \frac{C_i}{ATE_i}$$

Ingredient	ATE_i (LD ₅₀)	Concentration of Ingredient (C _i)	Include?	$\frac{C_i}{ATE_i}$	$\sum_n \frac{C_i}{ATE_i} = 0.025$
Active	344 mg/kg	3%	Yes	0.009	
Surfactant A	Unknown	2%	Unknown	Unknown	
Surfactant B	500 mg/kg	5%	Yes	0.010	
Surfactant C	Unknown	5%	Unknown	Unknown	
pH Adjuster	1000 mg/kg	6%	Yes	0.006	
Solvent A	Unknown	4%	Unknown	Unknown	
Solvent B	Non-Toxic	75%	No	N/A	89 0.025
ATE _{mix}				3600 mg/kg	
EPA Category III					

Weight of Evidence: What?

Any additional available data that can help support the hazard classification

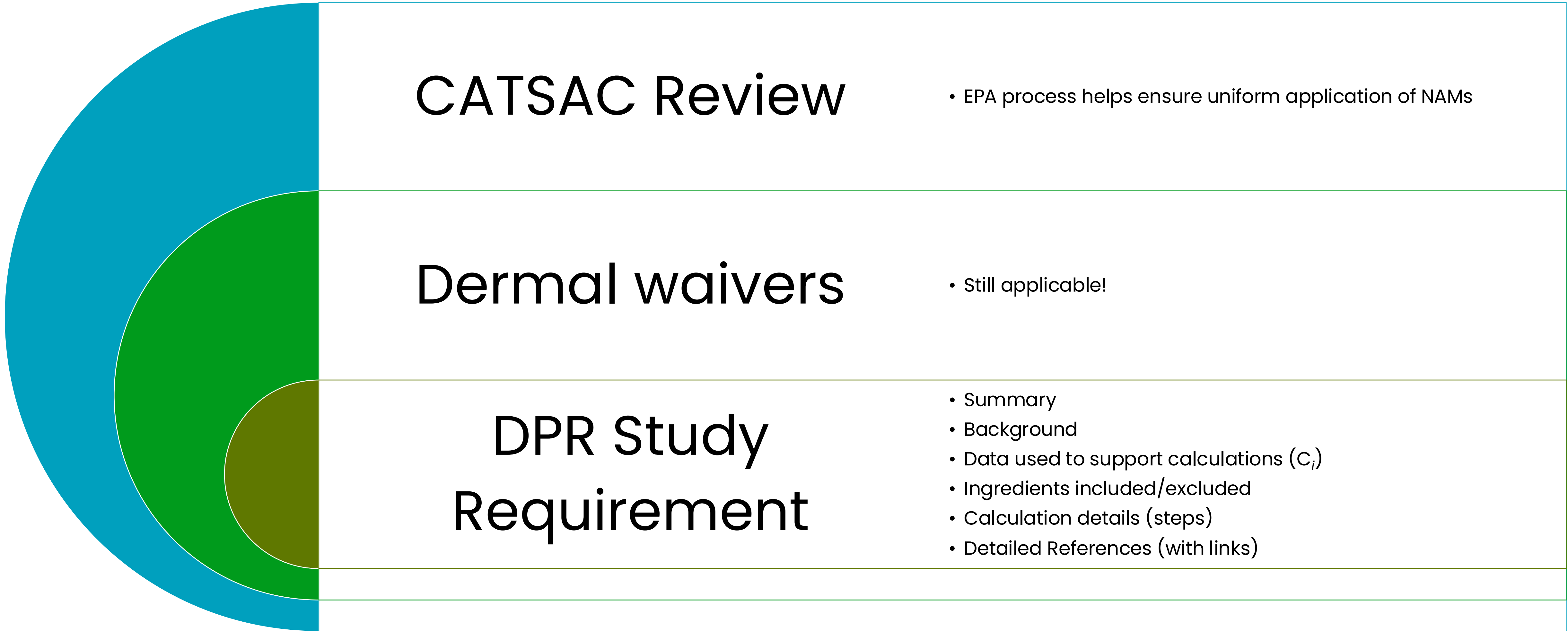
Internal Data / Studies

- Exact mixture registered
- Bridgeable formulations
- AI portfolio
- Similar AI

External Data

- Competitive Analysis

Industry POV & Watchouts





Thank You!

<https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/strategic-vision-adopting-new-approach-2>



syngenta

Questions?