Calculating the toxicity of plant protection products

Raja Settivari
10-30-2019
Outline

Plant protection products (Formulations) complexity

Alternative evaluation approaches

The GHS Additivity Formula
  - Performance
  - Internal implementation strategy
  - Current regulatory acceptance

Conclusions
Purpose: Acute Toxicity Testing

Identification of intrinsic hazard properties of chemicals or end-use products upon shorter-term exposure

Basis for hazard communication

• Classification (e.g. EPA or GHS category; LD50 mg/Kg)

<table>
<thead>
<tr>
<th>GHS</th>
<th>CLP</th>
<th>EPA</th>
<th>ANVISA</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 &lt; Cat 1 ≤ 5</td>
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<td>200 &lt; Cat III ≤ 2000</td>
</tr>
<tr>
<td>2000 &lt; Cat 5* ≤ 5000</td>
<td>Not Classified &gt; 2000</td>
<td>500 &lt; Cat III ≤ 5000</td>
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</tr>
<tr>
<td>Not Classified &gt; 5000</td>
<td></td>
<td>Cat IV &gt; 2000</td>
<td></td>
</tr>
</tbody>
</table>

• Product label statements (e.g. signal words – level of hazard)
  – Danger, Warning
Purpose: Acute Toxicity Testing

Inform risk management decisions to protect human health

- Personal Protective Equipment (PPE)
- Transportation requirements
- Use restrictions
- Generic first-aid measures

Dose level selection for sub-chronic and other studies

The classification may impact registrability of a formulation
Acute toxicity testing: “The 6-Pack”

The global regulatory requirements for formulation registration is a suite of 6 animal studies using approximately 60 animals.

<table>
<thead>
<tr>
<th>Guideline Number</th>
<th>Data Requirements</th>
<th>Estimated Animal use</th>
</tr>
</thead>
<tbody>
<tr>
<td>870.1100</td>
<td>Acute oral toxicity - rat</td>
<td>3-9 rats</td>
</tr>
<tr>
<td>870.1200</td>
<td>Acute dermal toxicity</td>
<td>10 rats</td>
</tr>
<tr>
<td>870.1300</td>
<td>Acute inhalation toxicity - rat</td>
<td>10 rats</td>
</tr>
<tr>
<td>870.2400</td>
<td>Primary eye irritation - rabbit</td>
<td>3 rabbits</td>
</tr>
<tr>
<td>870.2500</td>
<td>Primary dermal irritation</td>
<td>3 rabbits</td>
</tr>
<tr>
<td>870.2600</td>
<td>Dermal sensitization</td>
<td>31 mice (LLNA)</td>
</tr>
</tbody>
</table>

Vast majority of acute toxicity studies received by EPA are conducted on formulations.
Plant Protection Product Complexity

- Active ingredient(s) + co-formulants
  - Surfactants, fillers, solvents, thickeners, biocides, anti-freeze, odorants, stabilizers, dyes and pigments
  - Optimize delivery of active ingredient(s)

- Alternative methods should be assessed across multiple formulation types
  - E.g. liquid vs dry; water vs solvent based

- Effective implementation of alternative methods may lead to:
  - Development of sustainable products
  - Greater reduction in animal usage

Formulation Types

- **Liquid Forms**
  - Soluble Liquids (SL)
  - Suspension Concentrates (SC)
  - Emulsifiable Concentrates (EC)

- **Solid Forms**
  - Wettable Powders (WP)
  - Wettable Granules (WDG or WG)

New active chemical
LLNA: ~25 mice

In vivo testing for each formulation

Formulation-1 ~25 mice
Formulation-2 ~25 mice
Formulation-3 ~25 mice
**In vitro alternatives for plant protection products**

<table>
<thead>
<tr>
<th>6-pack endpoints</th>
<th><em>In vitro</em> test (if available)</th>
<th>Applicability to Plant Protection Products</th>
</tr>
</thead>
</table>
| Acute oral         | Not available yet              | • The OECD 432 may have good negative prediction for chemicals not needing classification (JRC, 2013)  
|                    |                                | • Not verified on Agrochemical formulations |
| Acute dermal       | Not available yet              | • Product specific evidence from *dermal absorption* available only for active ingredients |
| Acute inhalation   | Not available yet              | -                                          |
| Dermal irritation  | OECD TG 430, 431, 435, 439     | • Testing ongoing on Agrochemical formulations |
| Ocular irritation  | OECD TG 437, 491, 492          | • Testing ongoing on Agrochemical formulations |
| Dermal sensitisation| Defined approach from several *in vitro* tests | • Defined approaches not agreed for PPP |
Alternatives: What routes can we take?

- Evidence-/exposure-based testing and waiving
- Read Across strategy
- GHS/CLP additivity formula approach
Exposure considerations

- Relevant routes of exposure:
  A) Mix & Load (open system) (Concentrate)  
  B) Hand-held (Dilution)

Accidental occupational exposure to concentrate end-use product
- Routes: contact (skin, eye) and inhalation
- Labelling & PPE

Occupational or residential exposure to agrochemical actives
- Routes: oral, dermal or inhalation (mostly due to dilutions, applications)
- PPE, when required
Exposure and evidence-based waiving and Read-Across

- Framework set and criteria laid down by OECD in 2016
  OECD ENV/JM/MONO(2016)32

- Major common waiving criteria:
  - **Exposure-based waiving:**
    - Physical state/properties (e.g. volatility, extreme pH)
    - Product size/design prevents exposure
    - Study not technically feasible (e.g. aerosol generation)
    - Properties of AI (e.g. sensitizer; dermal penetration)
  - **Bridging/Read-Across**
    - Is there a similar existing formulation with definitive data?
      - Same physical form
      - Similar concentrations of AI or more dilute
      - Similar co-formulants

- Consider alternative test(s) with good negative prediction (i.e. 3T3 NRU)

- **Evidence-based waiving** for dermal toxicity
  - If the test chemical has shown no adverse effects in an acute oral toxicity test up to 2000 mg/kg bw
  - If the oral LD50 of test chemical is less than 300 mg/kg bw – classified consistent with GHS Cat as oral hazard
  - For materials with lower dermal absorption, waiver possibilities depending on oral LD50 (challenging for formulations)
Use of alternatives instead of animals is possible in some regulatory frameworks:

<table>
<thead>
<tr>
<th>Country</th>
<th>Animal tests (6-pack)</th>
<th>in vitro tests or Exposure-based waiving</th>
<th>Read across</th>
<th>GHS Calculation</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANZ</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>EU</td>
<td>+</td>
<td>+</td>
<td>+ / ?</td>
<td>+ / ?</td>
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<tr>
<td>USA</td>
<td>+</td>
<td>pilot program</td>
<td>+</td>
<td>pilot program</td>
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<tr>
<td>CAN</td>
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<td>pilot program</td>
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<tr>
<td>Brazil</td>
<td>+</td>
<td>+ / ?</td>
<td>+</td>
<td>x</td>
</tr>
<tr>
<td>Other LA</td>
<td>+</td>
<td>x</td>
<td>+ (in some countries)</td>
<td>x</td>
</tr>
<tr>
<td>Asian countries</td>
<td>+</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
</tbody>
</table>

EU - Art 62 of 1107/2009:

• Enter into force Dec 2016: legal obligation to perform alternative approaches, if available
• However, concerns from some MS and prefer in vivo studies

US-EPA/CAN-PMRA:

• 2016/2017: Pilot programs launched on A) waiving of the acute dermal toxicity; B) use alternatives to animal tests (calculations or in vitro)
• ANVISA (2019): May consider acute inhalation waivers
The GHS additivity formula

- Computational method from UN GHS (Globally Harmonized System) classification system based on theory of additivity:
  - Predicts mixture toxicity for C&L without conducting experiments
    - Use composition information and toxicity of single components
    - Prediction of acute systemic toxicity, in terms of toxicity classes for C&L

- Usable as stand-alone non animal replacement method in some geographies
  - (i.e. EU CLP; NZ, AUS regulations on AgChem formulations)

- Also recognized in transport regulations (UN, IATA etc…)

- Minimal cost/effort
Systemic Toxicity- Additivity Formula

Formula:

\[ \frac{100}{ATE_{mix}} = \sum_{n} \frac{C_{i}}{ATE_{i}} \]

<table>
<thead>
<tr>
<th>ATE</th>
<th>= Acute Toxicity Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ci</td>
<td>= Concentration of Ingredient i</td>
</tr>
<tr>
<td>I</td>
<td>= Individual Ingredient I</td>
</tr>
<tr>
<td>N</td>
<td>= Number of ingredients</td>
</tr>
</tbody>
</table>

Information needed

• Acute toxicity of mixture components or ATE (Acute Toxicity Estimate)
• Concentrations of mixture components

Ingredients

• Include: Ingredients with a known acute toxicity which fall into any GHS category
• Ignore: Non-toxic ingredients
Systemic Toxicity- Additivitiy Formula

• Accounts for the contribution of each component to the toxicity of the mixture

• All ingredients treated equally, doesn’t give more weightage to active ingredient(s)

• Does not consider the type of solvent (dosing vehicle). Assumes the use of same solvent for all co-formulants.
  • May alter bioavailability (Cmax and AUC), which may affect systemic toxicity

• Assumes that chemicals are not interactive
Sources of information

• MSDS

• Robust Databases with regulatory acceptance (EChA inventory, Actor etc…)

• LD50 /LC50 where available,

• The appropriate conversion value from Table that relates to the results of a range test, or

• The appropriate conversion value from Table that relates to a classification category
# The actual calculation

Examples with increasing complexity

<table>
<thead>
<tr>
<th>Hazard category</th>
<th>Classified components</th>
<th>Conc. % of substance</th>
<th>LD₅₀/LC₅₀ or ATE</th>
<th>Calculation / total concentration of all substances in hazard category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral LD₅₀:</td>
<td>Contains no classified substances</td>
<td>0</td>
<td>Not applicable</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>
| Dermal LD₅₀:    | Benzenesulfonic acid, mono-C11-13-branched alkyl derivs., calcium salt (From coformulant Y) | 4.596 | 1100 | 4.596/1100 = 0.0042  
Then 100/0.0042 = LD₅₀ 23809 |
| Oral LD₅₀:      | Ethoxylated Fatty Alcohol (Synperonic 13/10)  
Cyclohexanone | 4.36  
8.99 | 500  
1530 | 4.36/500 + 8.99/1530 = 0.0145  
Then 100/0.0145 = LD₅₀ 6896 |
| Inhalation LC₅₀: | Aerosols:  
Pyraclostrobin  
Polyether modified trisiloxane (Break Thru S233)  
2-ethylhexan-1-ol (From Coformulant X)  
Vapours:  
Cyclohexanone | 6.05  
4.84  
3.486  
8.99 | 0.58  
1.08  
1.5  
11 | 6.05/0.58 + 4.84/1.08 + 3.486/1.5 = 17.2365  
Then 100/17.2365 = Aerosol LC₅₀ 5.80  
8.99/11 = 0.817  
Then 100/0.817 = Vapour LC₅₀ 122.40 |
Case Study: In-house evaluation of GHS additivity approach

- A database of acute toxicity studies for 225 agrochemical formulations
- Included solvent-based and water-based liquids and solids

<table>
<thead>
<tr>
<th>Product Class</th>
<th>Herbicides</th>
<th>Insecticides</th>
<th>Fungicides</th>
<th>Fumigants</th>
<th>Nitrification</th>
<th>Blanks (no active)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>160</td>
<td>37</td>
<td>18</td>
<td>5</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Formulation Types</th>
<th>Liquids</th>
<th>Gel</th>
<th>Solids</th>
</tr>
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<tbody>
<tr>
<td>SL</td>
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<td>EC</td>
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<td>CS</td>
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<tr>
<td>Others</td>
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<tr>
<td>WG</td>
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</tr>
<tr>
<td>GR</td>
<td></td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>WP</td>
<td></td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

- Acute Toxicity Estimate (ATE) of the formulation was derived using the Additivity Formula
  - Oral toxicity: >50% had LD50 higher than 5000 mg/Kg or >75% higher than 2000 mg/Kg
  - Dermal toxicity: >97% had LD50 higher than 5000 mg/Kg
  - Inhalation toxicity: >92% had LC50 higher than > 5.0 mg/L a

- In general represent lower hazard potential
In-house evaluation of GHS additivity approach

<table>
<thead>
<tr>
<th>Classification system</th>
<th>Threshold used for negative vs positive</th>
<th>Accuracy %</th>
<th>Sensitivity %</th>
<th>Specificity %</th>
<th>Sample size</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute Oral Toxicity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GHS cat 5/EP A Cat IV</td>
<td>5000 mg/Kg bw</td>
<td>70.9</td>
<td>68.1</td>
<td>90.2</td>
<td>159</td>
</tr>
<tr>
<td>CLP cat 4/ANVISA Cat IV</td>
<td>2000 mg/Kg bw</td>
<td>87.8</td>
<td>71.1</td>
<td>92.3</td>
<td>213</td>
</tr>
<tr>
<td><strong>Acute Dermal Toxicity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GHS cat 5/EP A Cat IV</td>
<td>5000 mg/Kg bw</td>
<td>92.7</td>
<td>60.0</td>
<td>93.7</td>
<td>170</td>
</tr>
<tr>
<td>CLP cat 4/ANVISA Cat IV</td>
<td>2000 mg/Kg bw</td>
<td>99.5</td>
<td>100.0</td>
<td>99.5</td>
<td>237</td>
</tr>
<tr>
<td><strong>Acute Inhalation Toxicity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GHS cat 4/CLP cat 4</td>
<td>50 mg/L air</td>
<td>96.7</td>
<td>66.7</td>
<td>99.1</td>
<td>123</td>
</tr>
<tr>
<td>EPA cat IV/ANVISA cat IV</td>
<td>2.0 mg/L air</td>
<td>98.4</td>
<td>80.0</td>
<td>99.2</td>
<td>123</td>
</tr>
</tbody>
</table>

TP/FP: True Positives/False Positives, TN/NP: True Negatives/False Negatives

• Weaker performance in predicting oral ATE in 2000 – 5000 mg/Kg bw range for acute oral toxicity

• High accuracy and specificity for prediction of agrochemical mixture toxicity

• Integrating this approach for negative prediction may allow up to 95% reduction in _in vivo_ testing

Corvaro et al., 2016
In-house evaluation of GHS additivity approach

Oral Vs Dermal toxicity:

• For single substances, acute dermal toxicity is often lower than corresponding toxicity via oral route

• The acute dermal toxicity was in the same toxicity class or in lower toxicity classes compared to the acute oral toxicity across all tested formulation types

Oral Vs Inhalation toxicity:

• The oral ATE class would predict the same or a worse case inhalation ATE in 95% of cases across all the categories

• Orally non-toxic (i.e. non classified) formulations are unlikely to be toxic via inhalation route

Corvaro et al., 2016
GHS/CLP additivity formula: Regulatory acceptance

GHS Calculation method is currently

• An approach acceptable by EU law, Australia, New Zealand
• Potential to be legally binding in absence of further guidance (UK CRD, Nov, 2017)
• Included in global over-arching regulations on transportation

However,

• Not yet acceptable in many other countries, including some EU member countries
• Missing a clear evidence of being satisfactory “across the board” for all endpoints/categories
• Unclear criteria on information sources (EChA DB, MSDS, etc…)

Need cross-talk between stakeholders with data, for harmonization on predictivity (strength/weaknesses) of ATE calculation
GHS additivity approach: Implementation

- **R&D use:**
  - Formulation development
    - Design,
    - Screens to prioritize the formulation with lower toxicity

- **Regulatory use:**
  - Used in all EU-only business cases
  - Used as a predictive tool before any *in vivo* study to proactively act on animal welfare
  - Dose selection
  - Higher confidence for formulations with negative predictions
New Product Formulation

Identify Submission Countries

GHS Additivity Formula accepted in jurisdiction?

Can a waiver fulfill one or more requirements?

no

yes

Provide waiver rationale

no

yes

Conduct and submit GHS Calculation

Use Additivity data for in vivo study design/dose selection

Conduct requisite in vivo studies with 3Rs considerations

Acute Oral (423)

Acute Dermal (402)

Acute Inhalation (436)
Conclusions

• No accepted experimental stand-alone replacements for evaluating acute systemic toxicity of formulations

• Excellent performance of the GHS additivity method indicates its use as a stand-alone replacement to characterize negative outcomes

• Require cross-talk between stakeholders with data, for harmonization on predictivity (strength/weaknesses) of ATE calculation
Acknowledgements

• Sean Gehen
• Marco Corvaro
• Ricardo Acosta Amado
• Reza Rasoulpour
• Dan Wilson
Thank you!
Discussion: Evaluating mixtures for acute lethality
Challenges for evaluating acute systemic toxicity of mixtures

• Explore the applicability of GHS additivity approach to broader formulation types and industry sectors
  – Corvaro et al., 2016
    • High accuracy and specificity for prediction of formulation toxicity
  – Van Cott et al., 2018
    • Acute systemic toxicity of many formulations is not the sum of the ingredients toxicity. Ingredients in a formulation can interact to result in lower or higher toxicity than predicted by the GHS additivity formula
  – Adler-Flindt and Martin, 2019
    • Calculation method predicted 80% of the PPPs correctly
    • Cytotoxicity assays (NRU and hFF cells) did not reliably reflect differences in toxicity between AI and formulation
Challenges for evaluating acute systemic toxicity of mixtures

• Global acceptance of data generated using alternative methods
  – Lack of confidence – not all countries recognize calculation method
  – Limited verification in the literature – need for additional retrospective analysis to demonstrate applicability across chemical types and companies
  – Regional preference for certain studies
    • Inhalation studies: may be waived in EU, ANVISA
    • Dermal studies: may be waived at US EPA, PMRA
  – For global submissions – end up testing for all acute endpoints
Challenges for evaluating acute systemic toxicity of mixtures

• Mechanistic information on actives and co-formulants
  – Known MoA for some actives/chemistry classes, however, not for all (e.g. plant or soil metabolites)
  – Can we use AI MoA information in model development (for target-specific MoA) (e.g. mitochondrial toxicity, cholinesterase activity etc)

• Reproducibility of *in vivo* systemic toxicity LD50/LC50 values for PPPs
  – Less literature on animal variability. General pharmacokinetic variability in absorption
  – Current guidelines with limited animals/group and vehicle effects may impact reproducibility
    • Dermal absorption is greater in rats than in human skin
    • Inhalation – there are differences in humans vs rodents
Challenges for evaluating acute systemic toxicity of mixtures

• Lack of accurate LD50/LC50 values for co-formulants

• In additivity method, water is assumed to be the default solvent for all actives and co-formulants. Usually this information is not available from MSDS. May affect ATE predictions
  – Due to interactions between vehicle and the ingredients
  – Altered bioavailability

• Methods to evaluate interaction between co-formulants
  – Additive/synergistic effects

• Need for testing at 5000 mg/kg bw?
  • E.g., EPA Vs GHS classification (categories and scoring criteria)
Criteria for classification are still variable across geographies

<table>
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<tr>
<th>Endpoint</th>
<th>ATE thresholds</th>
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<tbody>
<tr>
<td>Acute oral toxicity (ATE/LD₅₀ in mg/Kg)</td>
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</tr>
<tr>
<td>0</td>
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<tr>
<td>Acute dermal toxicity (ATE/LD₅₀ in mg/Kg)</td>
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<td>2000 &lt; Cat 5* ≤ 5000</td>
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<td></td>
<td></td>
<td>Cat IV &gt; 5000</td>
</tr>
<tr>
<td>5000</td>
<td>Not classified &gt; 5000</td>
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<td>Acute inhalation toxicity (ATE/LC₅₀ in mg/L air)</td>
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<tr>
<td>0.05</td>
<td>0.05 &lt; Cat 2 ≤ 0.5</td>
<td>0.05 &lt; Cat 2 ≤ 0.5</td>
<td>0.05 &lt; Cat II ≤ 0.5</td>
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<tr>
<td>0.5</td>
<td>0.5 &lt; Cat 3 ≤ 1.0</td>
<td>0.5 &lt; Cat 3 ≤ 1.0</td>
<td>0.5 &lt; Cat III ≤ 2.0</td>
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<tr>
<td>1.0</td>
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<td>1.0 &lt; Cat 4 ≤ 5.0</td>
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<tr>
<td>2.0</td>
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<tr>
<td>5.0</td>
<td>Cat 5* Not classified &gt; 5.0</td>
<td>Not classified &gt; 5.0</td>
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<td></td>
<td>Cat IV &gt; 2.0</td>
</tr>
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<td>20</td>
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</tr>
<tr>
<td>5000</td>
<td>Not classified &gt; 5000</td>
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</table>
Challenges for evaluating acute systemic toxicity of mixtures

• What are the types of mixtures where acute tox predictions are needed?

• Building datasets that will allow models for mixture toxicity to be more effectively developed

• What are the considerations regarding mixtures composition and maintaining confidentiality? Are there tools available to allow such analyses?