Calculating the toxicity of plant protection products
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></th>
<th>GHS</th>
<th>CLP</th>
<th>EPA</th>
<th>ANVISA</th>
</tr>
</thead>
<tbody>
<tr>
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<td>0 &lt; Cat 1 ≤ 5</td>
<td>0 &lt; Cat 1 ≤ 5</td>
<td>0 &lt; Cat 1 ≤ 5</td>
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<tr>
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<td>Cat IV &gt; 5000</td>
<td>Cat IV &gt; 5000</td>
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</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>
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<tbody>
<tr>
<td>Acute Testing</td>
<td></td>
<td></td>
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<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
**In vitro alternatives for plant protection products**

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

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>
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<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>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>
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</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:

\[
\frac{100}{\text{ATE}_{\text{mix}}} = \sum_{i=1}^{N} \frac{C_i}{\text{ATE}_i}
\]

- **ATE** = Acute Toxicity Estimate
- **C_i** = Concentration of Ingredient i
- **I** = Individual Ingredient I
- **N** = Number of ingredients

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- Additivity 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>
<tr>
<td>Dermal LD₅₀:</td>
<td>Benzenesulfonic acid, mono-C11-13-branched alkyl derivs., calcimu salt (From coformulant Y)</td>
<td>4.596</td>
<td>1100</td>
<td>( \frac{4.596}{1100} = 0.0042 ) Then ( \frac{100}{0.0042} = \text{LD50 23809} )</td>
</tr>
<tr>
<td>Oral LD₅₀:</td>
<td>Ethoxylated Fatty Alcohol (Synperonic 13/10)</td>
<td>4.36</td>
<td>500</td>
<td>( \frac{4.36}{500} + \frac{8.99}{1530} = 0.0145 ) Then ( \frac{100}{0.0145} = \text{LD50 6896} )</td>
</tr>
<tr>
<td>Vapours:</td>
<td>Cyclohexanone</td>
<td>8.99</td>
<td>1530</td>
<td>( \frac{8.99}{1530} = 0.00145 ) Then ( \frac{100}{0.00145} = \text{Vapour LC50 122.40} )</td>
</tr>
</tbody>
</table>

**Inhalation LC₅₀:**

- **Aerosols:**
  - Pyraclostrobin
  - Polyether modified trisiloxane (Break Thru S233)
  - 2-ethylhexan-1-ol (From Coformulant X)
- **Vapours:**
  - Cyclohexanone

<table>
<thead>
<tr>
<th></th>
<th></th>
<th>0.58</th>
<th>6.05 + \frac{4.84}{100} + \frac{3.486}{15} = 17.2365</th>
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<tbody>
<tr>
<td></td>
<td>1.08</td>
<td>1.5</td>
<td>Then ( \frac{100}{17.2365} = \text{Aerosol LC50 5.80} )</td>
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<tr>
<td></td>
<td>1.5</td>
<td></td>
<td>( \frac{8.99}{11} = 0.817 ) Then ( \frac{100}{0.817} = \text{Vapour LC50 122.40} )</td>
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</table>
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

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<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>
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<td>160</td>
<td>37</td>
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<td>5</td>
<td>2</td>
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</table>

<table>
<thead>
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<th>Formulation Types</th>
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<th>Gel</th>
<th>Solids</th>
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<tr>
<td></td>
<td>SL</td>
<td>EC</td>
<td>SC</td>
</tr>
<tr>
<td></td>
<td>52</td>
<td>51</td>
<td>33</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

- 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?

- no
  - Use Additivity data for *in vivo* study design/dose selection
  
  - Conduct requisite *in vivo* studies with 3Rs considerations

- yes
  - Can a waiver fulfill one or more requirements?
    
    - no
      - Provide waiver rationale

    - yes
      - Conduct and submit GHS Calculation

- 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>
<thead>
<tr>
<th>Endpoint</th>
<th>ATE thresholds</th>
<th>GHS</th>
<th>CLP</th>
<th>EPA</th>
<th>ANVISA</th>
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<tr>
<td><strong>Acute oral toxicity</strong></td>
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</tr>
<tr>
<td>(ATE/LD₅₀ in mg/Kg)</td>
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<tr>
<td>(ATE/LC₅₀ in mg/L air)</td>
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<td>0.5</td>
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<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>
<td>0.5 &lt; Cat III ≤ 2.0</td>
</tr>
<tr>
<td>1.0</td>
<td>1.0 &lt; Cat 4 ≤ 5.0</td>
<td>1.0 &lt; Cat 4 ≤ 5.0</td>
<td>1.0 &lt; Cat 4 ≤ 5.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cat IV &gt; 2.0</td>
</tr>
<tr>
<td>5.0</td>
<td>Cat 5: Not classified &gt; 5.0</td>
<td>Not classified &gt; 5.0</td>
<td></td>
<td></td>
<td>Cat IV &gt; 2.0</td>
</tr>
</tbody>
</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?