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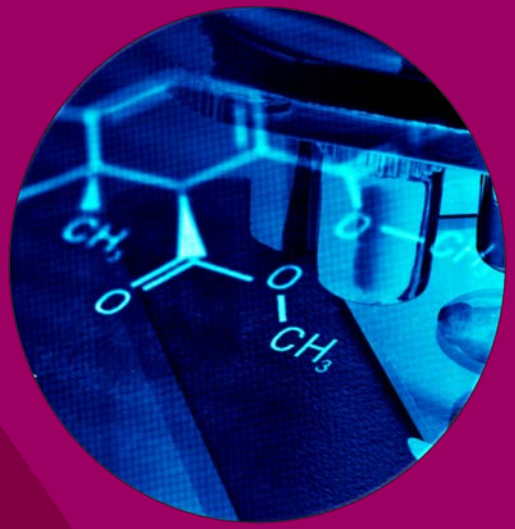
Challenge 25: Maximise



National Centre
for the Replacement
Refinement & Reduction
of Animals in Research

Challenge- Maximising Confidence Whilst Minimising Data Generation for Acute Hazard Classification of Mixtures

Launch Meeting

08 September 2016

Presented by Claire Elliott and Laura Brierley (Syngenta)

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The Challenge- Background

New Agrochemical Formulations (end-use product) are frequently brought to the market.

Agrochemical formulations are mixtures containing:

- One or more active substance
- Co-formulants (i.e. Surfactants, Buffers, Solvents etc.)

The toxicity profiles of new formulations are usually the sum of the individual components

The worst-case regulatory requirement to register product on a global basis is a list of *in vivo* acute toxicity studies, called the “6-Pack”. We’d like to stop doing this, by using existing data:

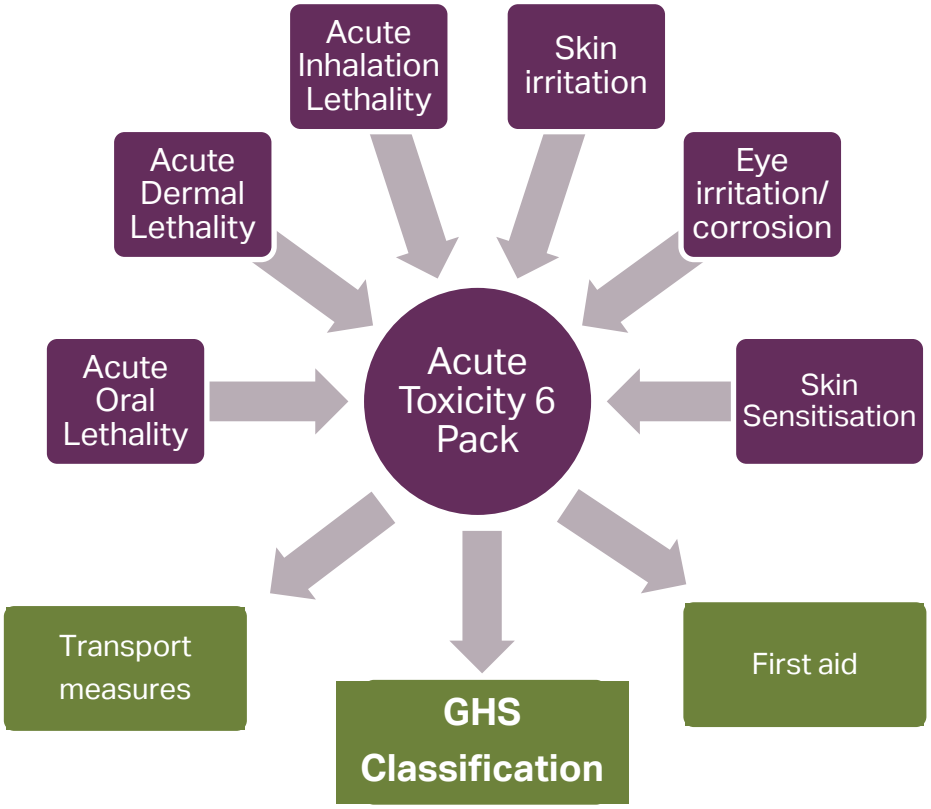
- We have usually tested similar formulations before
- We will also have tested the active substance(s) individually *in vivo*
- Some co-formulants will have been tested individually *in vivo* (most co-formulants occur in many formulations)
- There may be *in vitro* data for the active substance and/or some of the co-formulants

The Challenge- Background

The information on the toxicity profile from the 6 pack is used for various pieces of regulation, GHS classification being the most relevant

These studies can cause pain and discomfort to animals and, in some cases, use death (or imminent death) as an endpoint. However:

- Steps have been taken to limit pain and discomfort to animals
- Recent guidelines published have allowed for waiver or reduction in the numbers of animals used for some of these studies
- There is no single regulatory approved *in vitro* or *in silico* alternative to these studies



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The Challenge- Overall Aim

To develop a reliable predictive model which can confidently classify mixtures of chemicals

- **Focus: acute oral toxicity, skin and eye irritation and relevance for human safety.**

The model should:

- fulfil acute GHS Classification and Labelling requirements for agrochemical mixtures
- use existing toxicity information on components and formulations
- for a new agrochemical formulation:
  - inform you whether a classification can confidently be predicted with existing data, excluding the need for additional *in vivo* or *in vitro* studies
  - identify if a new study (preferably *in vitro*) is required that will put you in a situation where a classification can confidently be predicted

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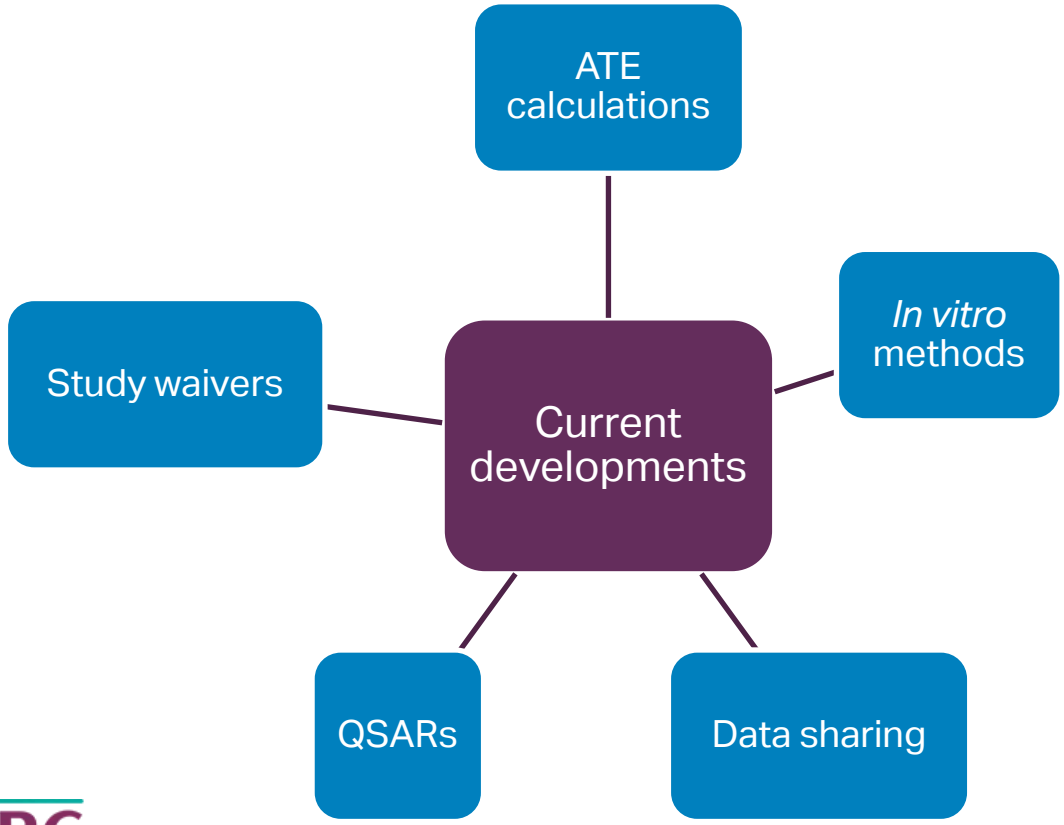
Why was this Challenge developed? Scientific

There is currently no single alternative method (*in vitro* or *in silico*) that can reliably predict the acute toxicity of mixtures or that is accepted by regulatory agencies



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Current state of the art

Current Acceptable Alternatives

- Some validated *in vitro* methods (i.e OECD test guideline (TG) 439 ,430, 431, 435, 437, 438, 439, 492) – Most of these are not stand-alone replacement.

- ATE (Acute Toxicity Estimate) calculations have good accuracy for the systemic toxicity endpoints but limited predictivity for skin/eye irritation and skin sensitisation

- Other *in silico* methods such as QSARs are routinely used for the prediction of single ingredients but none of these are sufficient for mixture toxicity prediction of agrochemicals.

3Rs drivers for the Challenge

- **More than 1000 animals are used per annum** for acute oral, skin irritation and eye irritation studies across the agrochemical industry.
- Although steps are taken to refine processes, high concentrations of test items are used which can lead to pain and suffering

Acute Oral Toxicity:

- The determined endpoint is an estimate of the LD_{50}- the dose which is lethal to 50% of the animals (usually rats)
- An estimated 500-1500 rats/year are used in these studies across the AgChem industry

Eye and Skin Irritation Studies:

- Eye irritation studies measure conjunctival, iris and corneal effects in rabbits
- Similarly, skin irritation studies measure the irritation and/or corrosion potential
- *In vitro* screens are employed prior to the *in vivo* tests to screen out any severe eye or skin irritant
- Approximately 850 rabbits/year are used in these studies across the AgChem industry

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3Rs drivers for the Challenge

- The Challenge has the potential for significant 3Rs impact both in the short and long term:

Short term

- The challenge output could prevent some mixtures being taken into animal studies

Longer term

- confidence in the prediction of classification may lead to regulatory acceptance and the waiving of the *in vivo* studies for acute toxicity endpoints for skin, oral and eye irritation.

Controlled data sharing between companies could eliminate the need to conduct additional testing *in vivo* but still allow companies to submit registrations with accurate assessment of all co-formulants.

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Business Advantages of the Challenge

The challenge will develop an innovative business model, with the potential for commercialisation, that can be used across the agrochemical industry and potentially beyond

- Business advantages may include:
  - Reduced timelines for data
  - Reduction in costs for acute studies
  - Commercial advantage
  - Ability to share data across the industry while maintaining confidentiality
  - Reduced animal usage - better public image for respective businesses

Deliverables

We want **innovative algorithms** that can **reliably predict** the acute oral toxicity, eye irritation and skin corrosion of novel mixtures that will **permit GHS classification** with an **associated measure of the confidence** with the potential to **remove the requirement for further *in vivo* or *in vitro* or *in silico* work**.

This should include an evaluation of the performance for the proposed approach:

- A database for the different kinds of toxicity data for formulation components
- Transparency in the generation of the classification for the agrochemical formulations
- Evidence and case studies of the reliability of the predicted classification.
- Assessment of the performance of the platform (made against formulations that have known *in vivo* data).
- A confidence range with known limits.
- Any additional information required to enable a confident classification.
- User friendly readouts

…and, from a business perspective:

- A new product with the potential for commercialisation
- Improvement to the current business process for obtaining GHS classifications for novel formulations
- An innovative and flexible commercial model to facilitate sharing of information between companies while maintaining data ownership:
  - Awareness of the regulatory environment and expectations.
  - A designed process for meeting the Challenge brief whilst retaining the confidentiality of formulation compositions.

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What we don’t want…

- Another ATE calculator
- Solely the GHS classification as an output without any further explanation
- A repeat of previous challenges

Sponsor in-kind

The sponsor will provide:

- Expertise on regulatory toxicology including acute toxicity data on mixtures and components.
- Toxicological data, classifications and formulation compositions for formulations that have been tested directly *in vivo* for acute oral toxicity, eye and skin irritation.
- Acute oral, eye and skin irritation toxicity information for formulation components, where available. This will include combinations of *in vivo*, *in vitro* data and classifications as and when available.

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Thank you for listening

The Sponsors are happy to discuss the challenge and potential applications with people in the run up to the submission deadline

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