CRACK IT

Challenge 25: Maximise Surgery Q&As.

Q. What is the acceptance range for regulators for a new approach, i.e. is there a 'threshold' that will be required?

A. Based on various recently published OECD Test Guidelines for new methods there should be around 80% accuracy (i.e. with balanced sensitivity and specificity). The higher the accuracy, the more likely the approach is to be accepted. Internal acceptance criteria may first need to be devised as a starting point and then the model refined. GHS classification categories are not exact values but fall into a range of values, so it may be possible to think creatively about how to capture the different ranges with the new approach.

Q. How will the quality of data used to inform the new approach be evaluated?

A. Klimisch scores will be available for some studies, but this may not be the case for all of them, particularly the older ones. Data in the ECHA database (https://echa.europa.eu/regulations/clp/cl-inventory) should only be from studies assigned a Klimisch score 1 or 2. However, depending on study designs, the same type of study testing the same chemical can yield results that are 20-30 fold different. Even for studies that are classed as Klimisch 1 or 2, there may not be sufficient information on exposure or time periods. The aim is to build a 'gold standard' database of reliable data. Data from old studies/compounds may not be labelled or referenced sufficiently and therefore may have to be excluded.

Q. Can calculations (e.g. Finney's harmonic mean) used for lubricants be used for GHS purposes for agrochemical mixtures?

A. This approach can be used for acute systemic endpoints. For skin and eye irritation endpoints this approach does not work due to the levels of surfactants that are present in most liquid formulations.

Q. How will variability between animals be taken into account in a new approach?

A. There is less inter-animal variability for the skin endpoints than for eye endpoints. For eye irritation, there has been retrospective analysis on this subject carried out by Cosmetics Europe/ECVAM which has been published (Barroso J. *et al.* Arch Toxicol. **2016** Mar 21.).

Q. Are there plans to link up this Challenge with the cosmetics and personal care products industries?

A. There is no formal plan to collaborate specifically within this Challenge. However, these industries face exactly the same issues as the agrochemical industry so there may be scope in the future to build on the product developed though this award.

Q. Will there be *in vivo* data available for all the individual components of the mixtures (i.e. a complete *in vivo* dataset)?

A. There will be some mixtures for which all components have *in vivo* data available but others for which there is only *in vivo* data on some of the components. Classification data on

individual components (but not full *in vivo* study reports) may be available via MSDS or Classification inventories (e.g. the EChA database)

Q. How will it be possible to commercialise and share the new approach more widely if confidential data is used to validate it?

A. This is a key issue that will also need to be addressed to ensure regulatory acceptance. Use of publically available classification data and or/extracts of results that are available for single ingredients will be possible, even if access to confidential study data for a specific formulation may not be. A balanced approach will be needed.

Q. Is there sufficient data in existence to convince regulators of the approach?

A. There will need to be a discussion with the regulatory agencies about how much data needs to be used for developing and validating the new approach. Power analysis calculations may help to identify what is needed. Previous 'safe harbour' data sharing activities such as those undertaken by the US EPA/NICEATM may also give provide further opportunities to collect more confidential data.

Q. Are the co-formulants used across industry similar? Are the same solvents/surfactants used by different companies?

A. The co-formulants used by different companies will be similar. Occasionally a novel formulation will include a new solvent/ surfactant, but these are likely to be from a similar chemical class. The differences between companies will lie in the combinations of the co-formulants and active ingredients, for example, a solvent-based formulation (e.g. where the active ingredient is not water soluble) will contain many more co-formulants than a water-based one or a solid one.

Q. Will bioavailabilty of the formulation drive the toxicity/irritation?

A. There is often skin penetration data for formulations and ADME information from acute oral studies for active ingredients (but not single co-formulants) which will help to assess this. The aim will be to use existing data for this Challenge rather than to generate new data.

Q. How will the robustness of the model be evaluated?

A. Once the training set has been used to develop the model, the Sponsors can provide data on other mixtures to validate the model, and the composition of these mixtures will not necessarily have to be revealed.

Q. What modes-of-action are involved in mixture toxicity? Does the parent substance or metabolite drive the toxicity, and how do absorption and metabolism play a role?

A. For acute oral studies, the active ingredient tends to drive the classification which is why for this endpoint acute toxicity estimate (ATE) calculations are effective. This may well not be the case for other endpoints where combinations of the surfactants with other ingredients may be driving irritation.

Q. How will differences in bioavailability be accounted for? The composition of the mixture will significantly affect this, for example, the use of a solvent which increases solubility, or interactions between the active ingredient and co-formulants.

A. Oral bioavailability or the fraction absorbed is generally available for active substances in a vehicle. It is difficult to model absorption when co-formulants are present. The Sponsors may be able to provide more data and parameters as the project progresses to aid this.

Q. To what extent is the GHS system useful in predicting effects in humans considering it is completely reliant on classifications made using animal data?

A. The difficulty with agrochemicals as opposed to pharmaceuticals for example, is a lack of human data which to compare the classification to. It is largely thought (e.g. for industrial chemical lubricants) that chemicals tend to be over-classified using this system (i.e. it is conservative) and it is important to demonstrate to regulators that the novel approach does not under-classify. Equally, there should not be too much over-classification as this is also undesirable.

Q. I have expertise in certain areas, but not in all areas that are required to solve the Challenge. How can I find other expertise?

A. Speak to the NC3Rs office (crackitenquiries@nc3rs.org.uk) and we will do our best to help connect you with the expertise you are seeking. You can also make use of the Challenge-specific LinkedIn pages that have been established.

Q. Who should we email with questions?

A. General questions can be sent to the NC3Rs. Questions regarding a specific Challenge can be sent to the Sponsors, but enquiries should be sent to ALL Sponsor parties for a particular Challenge. If preferred, please email the NC3Rs to introduce you to the Sponsors at CRACKITenquiries@nc3rs.org.uk.