



Dear Sir or Madam,

Syngenta Crop Protection LLC is excited that NICEATM and ICCVAM have taken on this important task of coordinating the development of a strategic roadmap for incorporating new approaches into safety testing of chemicals and medical products in the United States. We appreciate the opportunity to comment on the goals and mission that are being undertaken in this project. The refinement, replacement and reduction of animals used in the testing of our products are very important to Syngenta's core values. As this mission takes shape, we are interested in whether the following questions and considerations are being addressed in the process.

- Taking into consideration that not all geographical regions are using the Globally Harmonized System (GHS), are there any discussions about solidified timelines for a move toward harmonisation?
 - Currently, there is no harmonized agreement on acute toxicity, irritation and sensitization study requirements (even among EU member states). Harmonization will aid in aligning study requirements and the use and acceptance of the Acute Toxicity Estimate (ATE), *in vitro* and *in silico* assays.
- Have the various regulatory agencies discussed when acceptance of obtaining a negative result in an eye and skin *in vitro* assay will suffice vs. proceeding on to an *in vivo* study?
- Are the oral and inhalation *in vitro* methods going to be more closely reviewed?
- As the ATE calculations are based on animal data, is there a more qualified method being evaluated to protect human health?
 - ICCVAM should validate these calculation methods to provide more confidence in their results.
 - Further understanding is needed as to why ATE calculations aren't trusted by specific regulatory authorities. What can be done to change their understanding and view on its capabilities?
- Although this is a US based project, how are we going to use our influence to work together in a more effective way with regulatory agencies in other geographical regions?
- No *in vitro* method addresses reversibility in eye irritation and no single method is available to assess this endpoint. Are there any assays being developed to address this?

- Are reviewers at regulatory agencies being trained on the *in vitro* assays?
 - Training will increase confidence in analysis of submitted data. This will enable the reviewer to feel confident in making a refined analysis on the data being submitted. In turn, this will increase confidence in the assays and their functionality.

Another consideration:

The increased cost of conducting multiple *in vitro* studies over individual *in vivo* data, coupled with extension of project timelines, may perhaps be hindering companies from exploring the *in vitro* option.

Syngenta looks forward to the opportunity to work with ICCVAM, NICEATM and the broader scientific community in developing a national strategy, which will in time lead to international harmonisation.

Kind Regards,

Representatives of the Toxicology and Health Sciences Platform