Challenge 19: QSARs mix Surgery Q and As

Q. Which *in silico* models do Shell currently use for predicting skin/eye irritation?

A. The physical-chemical rule-base developed at the German Bundesinstitut für Risikobewertung (BfR), which is part of the OECD QSAR toolbox http://www.oecd.org/chemicalsafety/risk-assessment/theoecdqsartoolbox.htm.

Q. Should the CRACK IT tool take the form of software or a webpage?

A. It could be either, or alternatively an Excel based system. Examples on different approaches for reference include the ECOSAR software developed by the US EPA and the spreadsheet based PETROTOX model developed by CONCAWE (both downloadable).

Q. Does this have to be a QSAR/structural alert, or can other tools such as decision trees be developed instead?

A. The Sponsors are open to all *in silico* approaches as long as they address the Challenge i.e. quantitative prediction of skin and eye irritation for mixtures.

Q. Should this tool take the form of one applicable model or could a series of models be developed?

A. The Sponsors are open to both options.

Q. Is it more important that this software to be easy to use or that it makes accurate predictions?

A. Preferably both, but higher accuracy is preferable.

Q. What would quantitative values look like?

A. Ideally the values would be discrete scores which align to those traditionally assigned e.g. in the Draize *in vivo* test, that are used to classify under the Globally Harmonized System of Classification and Labelling of Chemicals (GHS).

Q. Where will the dataset and training set come from?

A. Data can be gathered through the literature as well as from databases such as ECOTOX and the ECHA dissemination portal; the Sponsors can provide guidance with regards to the use of the ECHA database if necessary.

Q. What physicochemical information does the ECHA database provide for substances in addition to molecular structure?

A. This varies depending on how much information has been submitted in the dossiers and the tonnage for which the substance is registered. There is a good library of data, e.g. for water solubility, however it should be noted that this is sometimes predicted rather than experimental.

Q. How much data is in the public domain (including the ECHA database) regarding

mixtures and irritation? What proportion of data points in the ECHA database represent mixtures? Does the ECHA database contain information on mixture compositions?

Currently, searches of the ECHA database for skin and eye irritation endpoints (using eChemPortal) return 5618 and 8016 data points for skin and eye irritation respectively. Approximately 50% of these data are on mixtures. These data may include multiple data points per product, as well as data that may not be relevant to this project. The search was carried out on data of Klimisch 1 reliability; a search including Klimisch 2 data would yield further usable data. Mixture compositional information varies per product dossier. It may be necessary to use an additive/toxic unit approach that could be applied using data on single substances, similar to the approach used in the Petrotox model. The training set cannot be formed of commercially sensitive substances as this information must be made available to users of the tool, all data disseminated via the ECHA portal is available for use.

Q. Is it possible to source data from other sources than the ECHA database?

A. Yes and this may be required to gain sufficient mixtures data.

Q. Can inorganics be included in the dataset?

A. They could be, but the priority should be on organic chemicals initially.

Q. What is the best way to ascertain that the data used is of sufficient quality for inclusion?

A. Initially it will be suitable to include all Klimisch 1 and 2 studies as these are accepted for regulatory purposes although the Klimisch scoring system does not mean erroneous or unsuitable data are not present. Shell can also help by providing expertise to ensure the robustness of the data.

Q. Should the tool provide information on the effect of formulation on irritancy, and is it possible to model this?

A. It should be possible to calculate how much each component contributes to the toxicity, and establish partitioning effects.

Q. Should this tool be validated for human health or against the existing animal tests?

A. Regulators currently accept data from *in vivo* animal tests and therefore to gain regulatory acceptance this *in silico* model must be shown to be at least as predictive as the currently used animal tests.

Q. What internal criteria would Shell use to take this model forward for use in-house?

A. This tool will be acceptable for use by the Sponsors providing it has been shown to be predictive for registered Shell products.

Q. Will this Challenge be deemed successful if the tool is suitable for internal decision making rather than for regulatory purposes?

A. Ideally the tool will be fit for purpose in a regulatory context – this would have the greater 3Rs impact. However there would be value in establishing this tool as an early screen particularly if it would be of use to other companies. In this setting the tool could be integrated into a tiered approach.

Q. Is there intention for this tool to be used by the cosmetics industry?

A. There is scope for this approach to be translated across to cosmetics, however the training set and validation would be different for this purpose and therefore it would be more appropriate to focus on petrochemicals in the first instance depending on the anticipated time required.

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. Please email the NC3Rs to facilitate interaction with the Sponsors at CRACKITenquiries@nc3rs.org.uk.