CRACK IT

Challenge 19: QSARs Mix - Computer Based Prediction

Using Structural Alerts to Assess Toxicity Endpoints

Presented by

Tom Austin (Ecotoxicologist), Risk Science Team, Shell Health

Launch Meeting
12 September 2014

Introduction

- The European REACH regulation and other regions of the world require specific toxicological information for the substance to be registered.
- *in vivo* skin and eye irritation data are required for chemicals imported or manufactured in amounts greater than 10 tonnes per year.
- Companies also routinely conduct toxicology testing for candidate selection during product development.
- Investigators may utilise *in vitro* models for prioritisation of candidates and potential classification, however *in vivo* models may be required for classification of substances.
- Herein lies the opportunity to develop *in silico* method such as (Quantitative) Structure Activity Relationships ((Q)SARs).
- Expert systems are starting to be built for providing scientific justification to waive the *in vivo* studies although further development is needed, particularly for mixtures.

NC 3Rs

CRACK IT

The Challenge

- The aim of the QSAR is challenge is to develop a model or expert system that will allow for the reliable prediction of skin and eye irritation based on structural information or ‘structural alerts’.

- Specifically, this tool should be able to predict the toxicity associated with a mixture of substances assuming a proper compositional analysis of the test mixture and applying a weighted average score approach.

Use of structural alerts in soup test for LRI project

The use of structural alerts in predictive methods is being increasingly recognised a useful concept.

A CEFIC LRI (Long-range Research Initiative) began last year with the objective of defining **alerts from (sub)structures** of environmental chemicals to predict the formation of **non-extractable residues (NER)** and their metabolites in soils and sediments.

This proposal was based on the findings of an ECETOC task force which identified the potential of this technique.

It is proposed that a similar approach for skin and eye irritation is feasible and may then be applicable to other endpoints.

NC 3Rs

CRACK IT

Petrotox – example of a mixture based approach

Petrotox is a spreadsheet based model which predicts the aquatic toxicity of complex petroleum substances developed by CONCAWE

Generally, petroleum hydrocarbons exert a narcotic mode of toxic action and therefore toxic unit theory of additivity may be applied

Petrotox takes into account how being in a mixture may affect a compounds exposure to the test media i.e. whether it is more soluble in the product phase or in this case the components of the skin and eye.

NC 3Rs

CRACK IT

Why there is a need: Current skin and eye irritation testing paradigm

- Companies performing *in vivo* studies for skin and eye irritation for registration of new substances can utilise large numbers of rabbits per year.
- These *in vivo* irritation studies are invasive, particularly the Draize eye test, further supporting replacement of the *in vivo* models.
- *In vitro* models for skin and eye irritation are being developed (eg, Episkin, Epiderm, SkinEthicRHE, HCE, MatTeK)
- Even though acceptance of these methods is improving, certain regions still insist on traditional *in vivo* studies,
- Further development of tools in this area is therefore required. There is a need for quick, effective, cost effective methods for screening and prioritisation

NC 3Rs

CRACK IT

Why there is a need: currently available solutions – areas for development

- A 2006 European Commission report (Saliner *et al*. 2006) concluded 'that the further development, validation and documentation of *in silico* systems for local toxicity to the skin and eye are necessary'.
- Currently, the *in silico* models defined by physical and chemical property thresholds and sets of rules (e.g. the BfR rules for skin/eye irritation contained within Toxtree)
- Current solutions are generally qualitative
- There is a need to attempt to become more quantitative. Predicting the Primary Dermal Irritation Index (PDII) or Draize scoring system may be a possible solution
- A 'structural alerts' approach similar in mechanism to MultiCASE's 'biophores' using irritation scores from experimental data rather than 'CASE' values (which can be difficult to relate to traditional toxicity measures)

NC 3Rs

CRACK IT

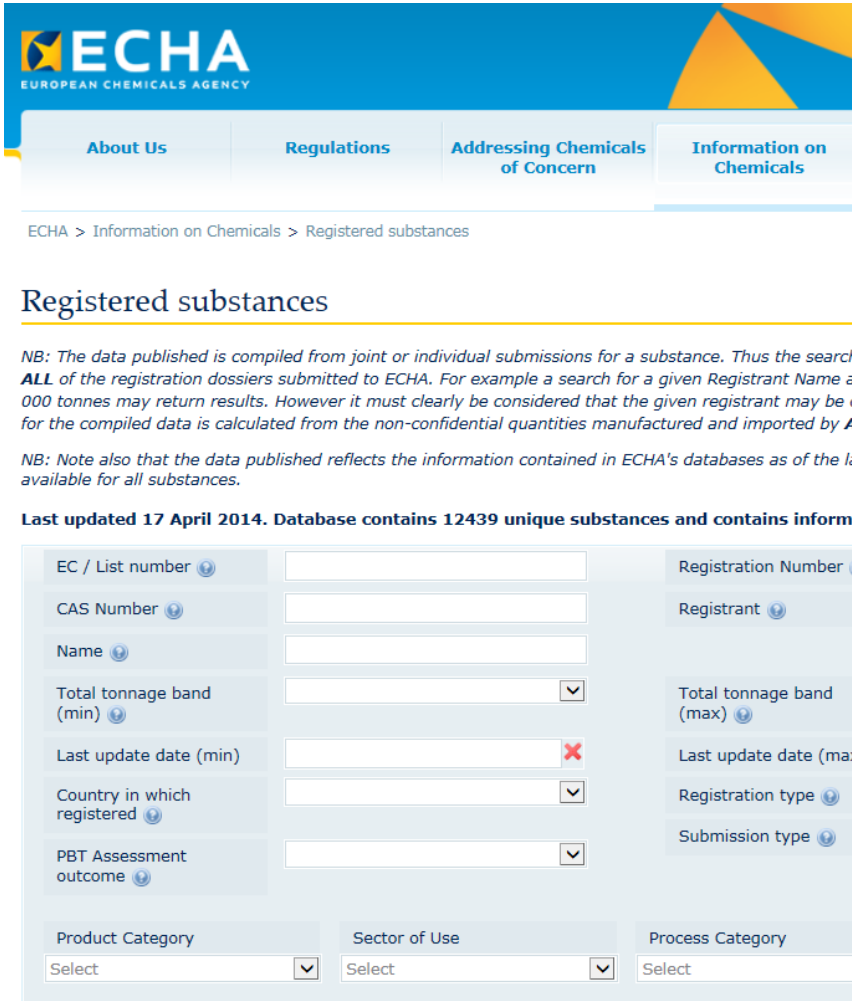
A vast new data source: ECHA dissemination portal

Product dossiers submitted to ECHA are made publicly available via the dissemination portal

As of April 17th 2014 the database contains 12439 unique substances from 47909 dossiers.

Over 5618 Klimisch 1 data points for skin irritation

8016 Klimisch 1 data points for eye irritation



Science benefits

If successful these tools will:

- Provide a more predictive and relevant tool-set to predict potential toxicity related to skin and eye irritation that can be used to reduce *in vivo* studies.
- Enable rapid screening of potential candidates.
- Decrease development costs and time-to-market.
- With further development, the approach could be translated to other toxicity endpoints such as reproductive and developmental toxicity.

3Rs benefits

Companies performing *in vivo* studies for skin and eye irritation for registration of new substances can utilise >250 rabbits per year.

These irritation studies are invasive, further supporting replacement of the *in vivo* models.

The proposed model will improve the predictive capacity of the current *in silico* models, permitting the early identification of potential toxicities in candidate selection without having to use *in vivo* studies and contribute to the scientific justification to waive the *in vivo* studies for skin and eye irritation for those taken forward to registration.

Key Deliverables

- Identification of structural groups, relevant to the chemical and petrochemical industries, focusing on structural alerts which contribute to skin or eye irritation.
- A tool that has the ability to predict the toxicity of mixtures assuming compositional information is available.
- The tool must be easily accessible to the end-user.
- The developed tool should be made widely available across all relevant industries and the predictions must be transparent to the end user and regulators.

Nature of in-kind support

Sponsors will provide:

Expertise in toxicology, (Q)SAR tools and their applications in a **regulatory context.**

Input on chemicals to be included in model training set.

Thank you

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

Contacts are:

Mr. Tom Austin

Email: Tom.Austin@shell.com

Dr. Satinder Sarang

Email: Satinder.Sarang@shell.com

Dr. Charles Eadsforth

Email: charles.eadsforth@shell.com

NC 3Rs

CRACK IT