



## Title of Challenge: QSARs Mix

### Background

Where substances are manufactured in quantities of over ten tonnes per year, the European REACH regulation requires specific toxicological information for the substance to be registered (European Commission 2006). Similar toxicological information is also required for registering substances in other regions of the world. Companies also routinely conduct toxicology testing for candidate selection during product development. In one area of mandatory toxicity testing, the prediction skin and eye irritation effects, investigators may utilise *in vitro* models for prioritisation of candidates and potential classification, however *in vivo* models may be required for classification of substances. Such animal tests can only be avoided with strong scientific justification. The use of *in silico* prediction methods such as (Quantitative) Structure Activity Relationships ((Q)SARs) and expert systems are starting to build a toolbox for providing scientific justification, but more development is needed to provide adequate information to waive the *in vivo* studies.

(Q)SARs and expert systems for human health endpoints are based on the assumption that the toxicity of a compound is related to its chemical structure. (Q)SARs must meet quality standards and be scientifically validated according to the OECD principles (OECD 2004). 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'. Expert systems are sets of 'if-then' rules or criteria to classify a chemical into various categories (e.g., eye irritant). Currently, these rules are defined by physical and chemical property thresholds. A more promising way forward is the use of structural alerts. These are sets of sub-structures that are identified in a molecular formula; an occurrence of any of these triggers the alert (e.g., skin or eye irritant). It is the sub-structures within a substance that dictate its physical properties, therefore it is important to correlate toxicity directly with these structures rather than the physical chemical parameters that may not always be available.

The current (Q)SARs structural alert tools are limited in the data sources used to develop them and are not amenable to mixtures. A large proportion of substances imported or manufactured in the EU are mixtures. The development of computational models that can be used to interrogate mixtures of chemicals would present a significant innovation in this area, broaden their application and reduce animal use.

The aim of this Challenge is that a model or expert system be created which allows 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.

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.

### Need for collaboration

The development of (Q)SAR/ structural alert tools that are amenable to mixtures requires a multidisciplinary team with expertise in toxicology, bioinformatics, cheminformatics and statistics.

### Overall aim

The overall aim of this Challenge is to use existing toxicological data repositories to develop *in silico* tools which can be used to predict toxicology endpoints for substances of interest in order to waive *in vivo* studies. The developed tools will be of benefit to any company that imports or manufactures chemicals. The tools will also be of use to any company seeking to bridge data gaps in skin and eye irritation.

### Key deliverables

- Identification of structural groups, relevant to the chemical and petrochemical industries, focusing on structural alerts which cause 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 user.

It is important to note that the CRACK IT Challenges competition is designed to support the development of new 3Rs technologies and approaches, which will improve business processes and/or lead to new marketable products. The application must include a plan to commercialise the results into a product or service. This should be taken into consideration when completing your application.

### Sponsor in-kind contributions

Sponsors will provide:

- Expertise in toxicology, (Q)SARs tools and their applications.
- A list of suggested chemicals for the model training set.

### Duration

Up to one year

### Budget

Up to £100K

### Sponsor

Shell

## References

1. European Commission (2006). Regulation (EC) No 1907/2006 of the European Parliament and the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/105/EC and 2000/21/EC. *OJEU*. L136/6.
2. The Organisation for Economic Co-operation and Development (OECD) (2004). The report from an expert group on (quantitative) structure–activity relationship ((Q)SARs) on the principles for the validation of (Q)SARs, OECD Series on Testing and Assessment No. 49. 25 ENV/JM/MONO 24.
3. Saliner A, Patlewicz G, Worth A (2006). Review of Literature-Based Models for Skin and Eye Irritation and Corrosion. European Chemicals Bureau, EUR 22320 EN.