RespiraTox: *In silico* model for predicting human respiratory irritation

Background

Inhalation of certain chemicals may potentially cause irritation to the respiratory tract resulting in inflammation, which if unresolved can lead to irreversible fibrosis of the lungs (Cometto-Muñiz JE and Cain WS, 1995). Examples of respiratory irritants include acetic acid, benzoyl chloride and formic acid.

Currently there are limited *in silico*, *in vitro* and *in vivo* models to determine the respiratory irritation potential of new or existing substances. Assessing whether a chemical will cause respiratory irritation in humans is often determined by observations in rodent acute (single) and repeat dose inhalation toxicology studies. However, there are no specific test protocols in place to determine the irritancy potential of respiratory toxicants or allergens. In the absence of specific or well defined guidelines, respiratory irritation results are extrapolated from the acute inhalation toxicity studies (the Organisation for Economic Co-operation and Development (OECD) test guidelines (TG) 403 and 436) performed on rats (OECD, 2009a, OECD 2009b). This involves the modification of protocols to include endpoints for respiratory irritation and requires additional dose groups. For example, RD50 data (concentration producing a 50% respiratory rate decrease as determined by the Alarie test (Alarie Y, 1966)) in rodents is often used as a surrogate for irritation potency of respiratory irritants. However, it is difficult to extrapolate the rodent respiratory hazard data to human respiratory irritation.

Under the REACH (Registration, Evaluation, Authorisation and Restriction of chemicals) regulations, the registrant may be able to demonstrate that a substance poses no respiratory risk if exposure via the inhalation route is not expected. However, for most substances exposure via the inhalation route is likely to be common, and if the substance is a skin or eye irritant then it may be difficult to justify a waiver for acute inhalation studies. Without robust models for respiratory irritation, it is possible that chemicals may pass through the R&D pipeline and reach the market place with the potential liability of being respiratory irritants. The goal of this Challenge is to develop an accurate *in silico* tool that is capable of predicting human respiratory irritation potential.

3Rs benefits

The respiratory irritancy potential of chemicals is typically assessed and extrapolated from modified rodent acute inhalation toxicity studies (OECD TGs 403 and 436 (OECD, 2009a, OECD, 2009b)). These *in vivo* toxicity studies are classified as severe under the UK's Animals (Scientific Procedures) Act and require additional dose groups. A typical modified acute inhalation toxicity study uses approximately 42 animals/study.

Development of a QSAR tool that reliably predicts the respiratory irritancy potential of chemicals in humans will allow for the early identification of potential toxicities in candidate chemicals without having to use *in vivo* studies, and contribute to the scientific justification to waive the *in vivo* studies for respiratory irritation for those taken forward to registration.

Need for collaboration

Potential applicants for this Challenge are expected to have an expert level understanding and experience in the development and validation of QSAR models, toxicology, chemistry and statistics. The final model is expected to be delivered as a user-friendly tool.

Overall aim

The overall aim of this Challenge is to develop a QSAR-based tool that reliably predicts human respiratory irritancy potential of chemicals. The tool should fulfill the five OECD principles for QSAR validation to demonstrate the statistical and mechanistic reliability of the model. This will endorse the model's use under regulatory context (e.g. REACH, Environmental Protection Agency (EPA)).

Key deliverables

- Develop a QSAR model that predicts human respiratory irritation for both single chemicals and mixtures.
- The QSAR model output should include an estimate of confidence in the prediction.
- Methodology to solve the Challenge in the absence of any test guideline for respiratory irritation (e.g. selection of a surrogate for the respiratory irritation endpoint, an extrapolation strategy to read-across from other toxicological endpoints by inhalation).
- Demonstrate that the QSAR model can reliably predict human respiratory irritation using a validation set of chemicals with known results.
- The model should fulfill all five OECD principles for QSAR models.
- The model should be delivered as a user-friendly tool and a methodology for determining the user experience should be described in the application.
- The QSAR tool should be made widely available across all relevant industries, and the methodology used to make predictions must be clear and 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 detailed plan to commercialise the results into a product and/or service. This should be taken into consideration when completing your application.

Sponsor in-kind contributions

- Expertise in toxicology and human health, QSAR development and QSAR testing.
- Sharing of data from acute toxicity studies.

Duration

Up to one year.

Budget

Up to £100k

Sponsors

Shell

References

Alarie Y (1966). Irritating properties of airborne materials to the upper respiratory tract. *Arch Environ Health* 13(4): 433–449.

Cometto-Muñiz JE and Cain WS 1995. Relative Sensitivity of the Ocular Trigeminal, Nasal Trigeminal and Olfactory Systems to Airborne Chemicals. *Chem Senses* 20(2): 191-198.

OECD (2009a). Test No. 403. Acute Inhalation Toxicity, OECD Guidelines for the Testing of Chemicals, Section 4, OECD *Publishing, Paris*. DOI: http://dx.doi.org/10.1787/9789264070608-en.

OECD (2009b). Test No. 436. Acute Inhalation Toxicity – Acute Toxic Class Method, OECD Guidelines for the Testing of Chemicals, Section 4, OECD *Publishing, Paris*. DOI: http://dx.doi.org/10.1787/9789264076037-en.

Guidance Document On The Validation Of (Q)SAR Models: ENV/JM/MONO(2007)2 http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?doclanguage=en&cote=env/jm/mono(2007)2.