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Challenge 28: RespiraTox

NC 3Rs National Centre for the Replacement Refinement & Reduction of Animals in Research

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

Sponsor: Shell

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Launch Meeting

7 September 2017

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The Challenge:

The overall aim of the Challenge is to develop a QSAR-based tool that reliably predicts human respiratory irritancy potential of chemicals.

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Why was this Challenge developed? (scientific)

- 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.
- 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 inhalation toxicology studies.
- It is difficult to extrapolate the rodent respiratory hazard data to human respiratory irritation.

Why was this Challenge developed? (business)

- Under the REACH 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.

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Why was this Challenge developed? (3Rs)

- The respiratory irritancy potential of chemicals is typically assessed and extrapolated from modified rodent acute inhalation toxicity studies.
- These *in vivo* toxicity studies are classified as severe under the UK's Animals (Scientific Procedures) Act.
- Require additional dose groups to acute inhalation toxicity study.
- The goal is to replace *in vivo* tests with *in silico* models, reduce the number of animals used for respiratory irritation, and refine and build upon existing models.

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Deliverables

- Develop a QSAR model that predicts human respiratory irritation for both single chemicals and mixtures.
- The model should fulfil all five OECD principles for QSAR models.
- 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.
- Demonstrate that the QSAR model can reliably predict human respiratory irritation using a validation set of chemicals with known results.
- The model should be delivered as a user-friendly tool.
- The QSAR tool should be made widely available across all relevant industries

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Sponsor in-kind

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

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Thank you for listening

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

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