CEFIC Long-range Research Initiative
Request for Proposals (RfP)

Title and Code Number:
Omics & Read Across - **LRI C6**

Background
Omics has enjoyed a great deal of success in research. Nevertheless, the use of omics data in regulatory assessment has been hindered, in particular, by the different approaches to the processing of the data can lead to different outcomes even from the same data set.

Development and acceptance of common foundation methods on data analysis and reporting will assist in the acceptance of omics analysis as a fundamental tool for use in regulatory toxicology. This can be achieved by setting the guidelines for the foundation methods for data analysis that would allow an easy comparison between datasets, but not preclude the use of further analytical methods considered appropriate by the analyst.

A survey conducted by ECETOC found that to date, omics data has never been used to support a submission under REACH, though there has been use in supporting pesticide submissions in the USA. A problem is the lack of agreed consistent methods that can be applied to the analysis of 'omic data.
In a research environment analysis methods are justified in publications in the scientific literature that have been independently reviewed. The regulatory environment however requires a more prescriptive approach where studies must be consistent, reproducible and comparable in order reach consistent decision making.

To start debate within the regulatory science community, an ECETOC expert team developed a 'strawman' framework for transcriptomics and other big data analysis for regulatory application. This debate has taken place through several meetings with ECHA, the OECD (EAGMST) and most recently a multi-stakeholder ECETOC workshop on Applying 'Omics Technologies in Chemicals Risk Assessment (Madrid, 10-12 October, 2016).

All these discussions and debates have led to the preparation of three different Research for Proposals (RfPs):

1. Towards the development of an Omics Data Analysis Framework (ODAF) for regulatory application
2. Integrating Multiple Molecular-level Data Streams to understand (a) range of normal adaptation vs pathology and (b) molecular generated gene expression changes and persistence over time
3. Omics & Read Across

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The third one is described below but the three individual RfPs are intended to be all interconnected as being part of the whole Omics package under the ECETOC-LRI long-term Transformational Programmes. Therefore, it is expected that researchers engaged on these projects will participate with the steering team and collaborate, share and exchange information with other grant awardee teams to the support the development of complimentary work products.

All RfPs will build on the output from the ECETOC Workshop.

Objectives

Using a read-across approach, industry scientists and regulatory bodies (e.g. ECHA, EPA and FDA) seek to determine the toxicity profile of a compound with no/limited toxicity information by comparing features and activities of this compound to structurally similar compounds. Typically, chemical/structural similarities are employed. However, similar biological activity among compounds in the read-across would provide additional useful information. Important questions are 1) how much data is necessary and sufficient for a robust read-across argument and 2) what types of biological data are most useful.

1. Develop practical guidance on the use of chemical structural and biological activity data to provide assurance of similar toxicological activity for read across
2. Produce a mock dossier for ECHA to see if this is the kind of thing they accept

Scope

- Using existing data bases identify two or three test cases for read-across using chemical classes with different types of toxicity (i.e. don't use chemical classes that all target the liver). Then, develop dossiers for all of these test cases using 1) chemical/structural data and 2) biological data (that must include omics data).
- The analysis will:
    a. Identify what kinds of data are necessary to make sound a read-across argument.
    b. Identify what types of bioinformatic algorithms are most useful for read-across.
    c. Identify how much biological data is needed for read-across. Some questions that could be asked are the following:
        i. How many tissues or cell types are required?
        ii. Is single time point information sufficient or are multiple time points needed?
        iii. Must read-across be performed using data derived from target tissues/cells or can surrogate tissues/cells be used?
        iv. How much biological activity coherence is necessary; is there a quantitative threshold required?

- Integrate biological and chemical structural data into the final dossiers. Determine the best-practice for this integration.
- Define the range of cases that need to be addressed (MoA yes/no, info-rich, info-poor, complications of metabolism).

Deliverables:
Mock dossiers that includes the case for why or why not high throuput molecular data on biological activity supports read across for two or more add-ons
The final report shall contain an executive summary (2 pages max), a main part (max. 50 pages) and a detailed bibliography.
It is expected that the findings will be developed into at least one peer reviewed publication, following postering(s) and presentation(s) at suitable scientific conference(s).

Cost and Timing
3 years, start early 2018
Budget in the order of €400k

Partnering/Co-funding
Applicants should provide an indication of additional partners and funding opportunities that can be appropriately leveraged as part of their proposal. Partners can include, but are not limited to industry, government/regulatory organizations, research institutes, etc. Statements from potential partners should be included in the proposal package.

Fit with LRI objectives/Possible regulatory and policy impact involvements/ Dissemination
Applicants should provide information on the fit of their proposal with LRI objectives and an indication on how and where they could play a role in the regulatory and policy areas. Dissemination plans should also be laid down.

References
- *Workshop, 3-4 March 2016, Malaga (WS report available:* ECETOC. 2016. Noncoding RNAs and Risk Assessment Science. 3 – 4 March 2016. Málaga. Workshop Report no.32. European Centre for Ecotoxicology and Toxicology of Chemicals, Brussels, Belgium)

- *Workshop, 10-12 October 2016, Madrid (for those who are interested, the WS report can be available on request. Please contact ECETOC secretariat: alice.brousse@ecetoc.org CC ian.cummings@ecetoc.org)*

Buesen, R. et al. 2017. Applying 'omics technologies in chemicals risk assessment: Report of an ECETOC workshop. Regulat. Toxicol. Pharmacol.

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Articles in preparation:

Sauer, U.G. et al. 2017. The challenge of the application of 'omics technologies in chemicals risk assessment : background and outlook. Regulat. Toxicol. Pharmacol.

Kauffmann, H.-M., et al. 2017. Quality assurance of 'omics technologies considering GLP requirements. Regulat. Toxicol. Pharmacol.

Gant, T., et al. 2017, A. Developing a generic ‚omics reporting framework exemplified by microarray gene analysis (working title)

Bridges, J., et al. 2017. Framework for a weight-of-evidence analysis of ‚omics data during hazard assessment. Regulat. Toxicol. Pharmacol.

DEADLINE FOR SUBMISSIONS: 31 August 2017

Please see www.cefic-lri.org for general LRI objectives information, project proposal form and further guidance for grant applications.