Code Number and Title:

LRI-AIMT4: Use of non-animal data to supplement and strengthen read-across

Background

"Read-across" is essentially a means of judging the toxicity potential of a data-poor "target chemical" based on inference from a related "source chemical" whose toxicity is well characterized. The read-across concept resonates strongly with a variety of stakeholders who share the common goal of avoiding unnecessary testing, (and associated costs and animal use), yet at the same time protecting public health. There are two main types of read-across: an analogue approach based similarity in chemical structure between a relatively small number of analogues, and a category approach across a broader group of chemicals based on similarity in the presumptive mode of action for the end point of interest (ECHA, 2012).

Despite the strong motivation to pursue read-across, its potential benefits have yet to be realized due to a number of challenges which preclude read-across justifications. One challenge is the paucity of predictive tools to support extrapolation between the data-poor target chemical and the descriptive regulatory guideline studies which typically are available for the source chemical. Another challenge lies in read-across to justify the absence of toxicity, as there are often no signals or measures to form a basis for extrapolation. Finally, read-across is often done on an end point-by-end point basis, which is quite laborious, time consuming and expensive, yet often leaves unanswered the question of whether or not the total breadth of potential toxic effects was sufficiently covered.

While these are formidable challenges, recent advances in Predictive Toxicology and high data content methodology are presenting new opportunities to supplement and strengthen read-across (ECETOC, 2012). These newer methods include the use of panels of in vitro assays, 'omics technologies, and continually evolving cheminformatics methods (e.g., QSAR, SAR). Omics methods are particularly suitable for read-across in light of their ability to assess *global* changes in response to chemical exposure, thus addressing some of the limitations of the end point-by-end point approach. Furthermore, additional predictive power can be obtained when they are used in an integrated, weight of evidence approach, rather than as stand-alone methods. By establishing biological response signatures based on panels of *in vitro* assays coupled with genomic signatures, it may be possible to justify the absence of toxicity simply on the basis of sufficient similarity in these signatures. Informatics tools such as the Connectivity Map approach designed to compare drug signatures are already available and could be applied to read-across as well.

Although regulatory agencies are not currently ready to use these new technologies as the sole basis for read-across, these approaches may be ready to supplement and strengthen read-across in the not too distant future. If successful, this could represent a

major breakthrough in the read-across arena, and could save industry significant sums of money, while greatly reducing animal use and bolstering the amount of data on many more chemicals. Critical to the acceptance of these new approaches is the use of data visualization tools which can distill complex data sets into meaningful information. Also, new approaches should integrate into existing frameworks, such as OECD's adverse outcome pathway program and OECD Toolbox.

Objectives

The overarching objective of this research program is to develop non-animal approaches to supplement and strengthen read-across for mammalian toxicology end points. Integrated approaches which combine cheminformatics (computational), *in vitro* models and/or 'omics technologies are of particular interest as they can cover a broad "waterfront" of potential responses in an cost- and time-efficient manner. Specific objectives to be achieved include:

1) Design of an integrated approach which provides global response signatures to address the similarity (or lack thereof) between structural analogs or chemicals within a presumptive mechanistic category.
2) Proof of principle studies on test chemicals within a mechanistic category or analog series to demonstrate the effectiveness of the approach to support read-across
3) Outputs which utilize simple to understand data visualization and summarization tools to facilitate end user understanding and acceptance.

Scope

The project should be directed at end points of mammalian toxicity, with a preference for methods that can strengthen read-across for repeat dose toxicity, reproductive toxicity, cancer and/or other complex end points. The project should be considered as an initial proof of principle study for the proposed approach. It is expected that the results will be presented at scientific meetings and published in peer reviewed journals. Assuming the results are promising, it would be of interest to also arrange for presentation of the data to key end users, such as ECHA, JRC and chemical industry partners.

Deliverables

The final report will comprise 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 a peer reviewed publication, following presentation at a suitable scientific conference.

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.

Cost and Timing

Start in May 2014, duration 2-3 years

Budget in the order of €200.000

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.

References

ECHA (2012). Experts Workshop on Reach-Across Assessment, with the active support of Cefic LRI. Background paper.

DEADLINE FOR SUBMISSIONS: 10 January 2014

Please see www.cefic-lri.org for general LRI objectives information, project proposal form and further guidance for grant applications. For further assistance do not hesitate to contact lri@cefic.be.