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

Title and Code Number

Assessing the repeatability of metabolomics within a regulatory context through a multi-laboratory ring-trial – **LRI-C8**

Background

During the last two decades, metabolomics has become a mature and widely used technology in academic research, resulting in tens of thousands of publications. Yet its application to *regulatory* toxicology, with the notable exception of metabolomics applied to chemical grouping, remains limited. The most commonly cited roadblock for the minimal uptake of metabolomics into regulatory toxicology include the lack of agreed standards for collecting, analysing and reporting of metabolomics data and of the conclusions from such studies.

To help address this barrier, ECETOC funded the development of best practice guidelines and reporting standards for a regulatory metabolomics study through the *MEtabolomics standaRds Initiative in Toxicology* (MERIT) project (2017-18). In part due to the lack of best practice and reporting standards, the chemical industry and regulators do not yet know if different metabolomics laboratories would reach the same conclusion in a regulatory toxicity study. There is a need to demonstrate that multiple laboratories, each analysing and reporting metabolomics data from a single toxicity study, can arrive at the same conclusion. There is also a need to test the new MERIT reporting standards for regulatory metabolomics.

Objectives

This project seeks to assess the inter-laboratory concordance in the use of metabolomics technologies in regulatory toxicology by designing, conducting and appropriately reporting an inter-laboratory metabolomics ring-trial.

The project's objectives are to:

1. Design, conduct and report a metabolomics ring-trial designed specifically to evaluate this technology in regulatory toxicology.
2. Evaluate the degree to which ring-trial participants arrive at the same conclusion in a chemical grouping study, *i.e.* where chemicals are grouped based upon their metabolomic responses.
3. Apply the MERIT best practice and reporting guidelines by using them to provide direction to ring-trial participants; also to practically evaluate the completeness of these guidelines and propose any amendments.

Scope

The project is anticipated to be completed in four phases: (1) design the ring-trial to maximise the interpretability and value of the findings to the chemical industry and regulators; (2) conduct the study including chemical exposures, sample preparation, metabolomics data generation, analysis and interpretation; (3) report the study, using the MERIT guidelines, to enable the repeatability of the overall conclusion from the chemical grouping, across laboratories, to be determined; and (4) review the completeness of and recommend any amendments to the MERIT reporting guidelines.

It is anticipated this project will involve a centralised *in vivo* exposure study with samples collected and then distributed to participating laboratories with expertise in metabolomics. It is also anticipated that chemicals will be selected to allow the following hypothesis to be tested: that chemicals acting via a similar mode-of-action will induce similar metabolic responses – and hence group – while those acting via a somewhat different mode-of-action will induce different metabolic responses and not group together.

Applicants should give consideration to the following:

- Type of analytical technology(ies) applied in the ring-trial, including the breadth of coverage of the metabolome and the analytical strategy employed, i.e. use of untargeted, semi-targeted and/or targeted assays.
- Number of participating laboratories to enable robust conclusions to be drawn.
- Study design, including the blinding of samples to the participating metabolomics laboratories, and the number and type(s) of chemicals investigated.

Deliverables

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 poster and/or oral presentation(s) at suitable scientific conference(s). At least one publication shall be open-access.

Cost and Timing

Start in January 2020, duration 2 years
Budget in the order of €460,000

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.

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

- ECETOC report: *Best Practice and Reporting Standards for Applications of Metabolomics in Regulatory Toxicology* (MERIT project, 2017-18, *paper under review*)

DEADLINE FOR SUBMISSIONS: September 1st, 2019

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