LRI AIMT12: COMPARING QUANTITATIVE UNCERTAINTY OF TRADITIONAL VERSUS NAMS BASED HAZARD CHARACTERIZATION

Background

The transition to next generation risk assessment (NGRA), has the ultimate goal of phasing out animal testing from safety assessments while maintaining or increasing the level of protection. This can only be successful if stakeholders gain confidence in the application and interpretation of NAM data and understand the sources and size of uncertainties associated with both, the methods used for hazard characterization in the traditional risk assessment approach and in NGRA.

This project is intended to develop several case examples informing regulatory scientists on how to perform uncertainty analysis, but more importantly to provide learnings on which input data and assumptions influence uncertainty the most when applying animal data and/or non-animal data. With that, the project is intended to feed into the development of decision frameworks which could inform regulatory scientists on the types of methods to deploy for hazard characterisation. The results will provide insights into the inherent uncertainties of each hazard characterisation approach (traditional and NAM-based) for different cases and identify areas for further research. Previous considerations on uncertainty analysis, mainly by EFSA and WHO/IPCS, focused on methods for qualitative and quantitative uncertainty analysis but only generate a few case examples and excluded NGRA. Most risk assessments by agencies nowadays include some generic verbiage on uncertainties, but there is lack of consistency and familiarity with the respective approaches and lack of resources to develop semi-quantitative or quantitative assessments. Cefic LRI seeks to close some of the gaps in experience with this project.

Objectives

This project is looking to deliver transparent, balanced, and quantitative evidence about uncertainties in the derivation of safe exposure levels based on animal data versus NAM-derived data. The underlying assumption is that there will be methodology and data situations as well as protection goals where NAM-based assessment bears less uncertainties, and other situations where it will be animal-data based assessments. The project is not intended to deliver black-and-white judgements on which of both approaches is generally preferrable, but provide knowledge on influencing factors, source, and size of uncertainties, to enable informed decisions by risk assessors and managers.

The project's objectives are

1. to perform probabilistic and deterministic quantitative uncertainty analyses (largely in line with the methodologies and terminology described by WHO/IPCS and EFSA) for human health (ecotoxicology should be included, if possible) hazard

characterisation of selected case examples (2-4) of test substances in specific uses.

1. to cover different hazard characterisation tools used in non-animal approaches (e.g., NGRA or Defined Approaches) with the case studies – for example such based on well-established AOPs and such where NGRA is based on less specific bioactivity data

1. to compare hazard characterisation up to derivation of safe exposure levels via traditional and NGRA approaches for each substance, both for substances with many versus few in vivo toxicology data.

Scope

The project can focus on human health hazard characterisation or (preferably) include both human and environmental safety assessments. Exposure assessment uncertainties are out of scope as far as external exposures are concerned, but PBK/ qIVIVE/ADME is in scope as far as applicable to the case studies.

Case studies are to enable direct comparison, i.e. data have to be available in each case both from in vivo and in vitro/in silico approaches. Extrapolation from Points of Departure to Reference Values/safe levels is in scope.

Out of scope

Uncertainty in exposure assessment is out of scope as far as it concerns external exposure, as the case studies are intended to compare different approaches to assessing hazard potential for the same external dose and receptor.

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(s) and presentation(s) at relevant scientific conference(s).

Cost and Timing

Start in Q4 2025, duration 1 year

Budget in the order of €250.000

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.

DEADLINE FOR SUBMISSIONS: June 27th , 2025 at 11:59 PM (Central European Time).

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. Please note that if awarded the project, the institute must be able to accept Belgian Law (or an equivalent European legal framework) in the contract. If there are questions, please email lri@cefic.be.

Related links

- *OECD (WHO/IPCS (2018) Guidance document on evaluating and expressing uncertainty in hazard characterization, 2nd ed, ISBN 9789241513548)*
- *EFSA Scientific Committee, Benford D et al (2018a) Guidance on uncertainty analysis in scientific assessments. EFSA Journal 16(1), 5123.*

Timing: Q4 2025, duration 1 year

LRI funding: €250.000

LRI research programme overview

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