Title and Code Number:

LRI-B14: Skin Sensitisation - Chemical Applicability Domain of the Local Lymph Node Assay (LLNA)

Background

Since the publication of the OECD AOP for skin sensitisation, there have been even greater efforts to anchor the development and evaluation of assays to key events within the AOP. Much of that type of evaluation is likely to use the LLNA as its benchmark. Whilst the LLNA has been through an extensive validation phase relative to the incumbent assay of the time, the GPMT, to date there has been no systematic evaluation of the chemical applicability domain of the LLNA, i.e. an exercise to define in chemical terms which classes of chemicals are well predicted, which are liable to be wrongly predicted and which are unpredictable by this in vivo method. This is particularly critical when considering the outcomes of new in vitro test methods in order to be able to discriminate whether the result is reasonable or whether the outcome is impacted by uncertainty in the LLNA which is used as a basis of comparison.

Objectives

From a scientific perspective, the applicability domain should be defined in terms of the chemicals that were used in the validation exercise: compounds whose chemical properties were not represented in the validation set are outside the applicability domain. The project's objectives are to:

1. Identify and evaluate existing QSARs/SARs that have been developed on the basis of guinea pig data and compare the trends to those in the LLNA.
2. Characterise quantitatively the mechanistic domains that have been already established qualitatively.
3. Review how well the known bio-activation processes are represented in the LLNA and the GP are aligned.
4. Evaluate the range of key physicochemical properties are covered by the LLNA: hydrophobicity values as modelled by LogKow, and size as quantified by covered by the MW and volatility as modelled by vapour pressure.
5. Compare and contrast the physchem characteristics and the mechanistic domains of the chemicals included in the in vitro validation sets against the LLNA data available.

Scope

The scope will be limited by the available data that can be readily found in the peer reviewed literature. The ECHA REACH website will be utilised as an additional resource of information.

Deliverables

The outcome would be at least one publication in a peer reviewed journal as well an LLNA dataset that could be used to evaluate new non-animal test methods being developed. A final report shall contain an executive summary (2 pages max), a main part (max. 50 pages) and a detailed bibliography.

Cost and Timing

Start in early 2014, duration 9-12 months

Budget in the order of €50.000 – 60.000

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.

Synergies across related activities will be pursued as appropriate. For example; JRC are sponsoring an activity to develop IATA for skin sensitisation under the framework of an OECD project, this activity could complement work here by providing further information on the scope of the LLNA.

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.

Work here would complement work by the JRC/OECD on IATA on skin sensitisation using the AOP already published. The short term impacts are that the work would help Industry registrants to provide scientific justifications of when a LLNA was or was not most appropriate to use as a first choice test under REACH. In addition, this type of

information would be informative for Regulators to evaluate the results of future LLNA tests.

References

1. OECD AOP for skin sensitisation: ENV/JM/MONO(2012)10/PART1 EN
2. Aptula AO, Roberts DW. Mechanistic applicability domains for nonanimal-based prediction of toxicological end points: general principles and application to reactive toxicity. Chem Res Toxicol. 2006 Aug;19(8):1097-105.

DEADLINE FOR SUBMISSIONS: 1 September 2013

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.