Code Number and Title

LRI- B18: Database on Carcinogen Dose-response, including Information on DNA-reactivity, for TTC and beyond

Background

The first tier of the Threshold of Toxicological Concern (TTC) approach as described by Kroes et al. 2004 includes consideration on structural alerts for genotoxicity of the substance to be assessed and utilises a threshold of 0.15 µg / person /day for structures with assumed or confirmed DNA reactivity. Structures without concern for DNA reactivity are taken forward to higher tiers, including the Cramer classification, with corresponding higher exposure thresholds. The TTC-based exposure limit of 0.15 µg/day is based on an evaluation of over 700 carcinogenic chemicals in the Cancer Potency Database (CPDB, http://toxnet.nlm.nih.gov/cpdb/), for which the TD-50's were calculated, with potencies ranging over more than 6 orders of magnitude. To date there has been no consistent consideration of mode of action or human relevance for the inclusion of chemicals in the TTC cancer database.

ILSI Europe has established an Expert Group to review the basis for the first tier TTC of 0.15 µg / person /day (*http://www.ilsi.org/Europe/Pages/Threshold-of-Toxicological-Concern-Expert-Groups.aspx*). This activity involves defining data sources and developing data selection and evaluation criteria to produce an updated TTC Cancer Database.
The starting point will be an existing database of curated entries from CPDB (Aungst et al. 2012 – SOT Poster 287). The Expert Group is developing criteria to categorise compounds for the probability that they are genotoxic carcinogens, based on assessment of the genotoxicity and carcinogenicity data (e.g. probable genotoxic carcinogen, possible genotoxic carcinogen, unlikely to be a genotoxic carcinogen), will validate points of departure and ensure that these are expressed using a common scale, both for substances currently in the database and for substances to be added. The ILSI Europe Expert Group is at present running a proof-of-principle analysis on a subset of the existing database of curated entries from CPDB overlapping with the Kirkland et al. 2014 database of Ames positive substances. The proof-of-principle dataset will be to small to draw statistically relevant conclusions on TTC thresholds for carcinogens, so that more work to address a large dataset will be necessary. While the current Expert Group brings together significant expertise and experience concerning the TTC concept, genotoxicity, carcinogenicity, SAR and databases, it does not have sufficient manpower to collate and review all data for the database.

This Cefic LRI RfP therefore seeks to identify scientists to evaluate studies and other information to build a validated database which will be available to the scientific community for projects e.g. on TTC, SAR, read-across and other alternative approaches. The second objective of the project is to analyse the potential impact on the TTC concept cancer thresholds when applying current understanding of DNA-reactive versus non-DNA-reactive modes of action and current methods in risk assessment of carcinogens to build distributions and to derive thresholds. The datasets and work done by the ILSI Europe TTC Expert Group up to the date will be made available to the group receiving the grant.

Objectives

The objectives of the RfP project are:

- Starting from existing cancer datasets (Aungst et al. 2012) and genotoxicity (Kirkland et al. 2014) datasets: data search and review, using transparent inclusion and exclusion criteria, generation of a fully-curated, quality-controlled, publicly available database of carcinogens of probable human relevance, including
    - Information on dose-response allowing derivation of different Points of Departure (PODs).
    - Information on DNA-reactive versus non-DNA reactive modes of action, e.g. SAR information and reviewed in vitro and in vivo genotoxicity study results
- Weight of evidence data evaluation, using accepted methodology (e.g. WHO MoA framework), leading to categorisation of carcinogens into those likely to be acting via a DNA-reactive mode of action, those where a DNA-reactive MoA has to be assumed, those likley to be acting via a non-DNA reactive MoA, and other categories if appropriate
- Derivation of PODs relevant to human health risk assessment, based on current scientific methodologies. BMDs should be preferred if possible. Where authoritative cancer potency assessments are available, e.g. by IRIS, EFSA or other agencies, these should be taken into account unless the conclusions are based on different scientific criteria.
- Objectives for the data analysis are:
    - Potency analysis of different groups of substances based on mode of action classes (DNA-reactive versus non-DNA reactive).
    - Sensitivity analysis for different assumptions taken, e.g. how do the choice of POD, choice of different extrapolation factors or exclusion of specific substance classes influence the distributions.
    - Discussion whether the results suggest that the TTC cancer thresholds can be refined, and if so, how this could be done while maintaining the characteristics of TTC as a practical tool for prioritisation.
- All substances with available relevant data should be included in the database to obtain a maximally large dataset with adequate statistical power, but also to create transparency about what studies were evaluated, even if they were not further considered due to specific shortcomings (such studies may not require full detail to be included). The database should be as exhaustive as possible, so that it may be necessary for specific analyses to form sub-datasets with substances carrying adequate data. The database structure should enable such processes.
- The resulting database should be public, readily available to other researchers for further research on TTC and other relevant toxicology questions, and fully transparent in terms of data (de)selection and interpretation.
- Wide acceptance of the database generated and applicability to the TTC concept are important objectives of the RfP. Hence, communication and liasion with other scientists and stakeholders previously involved with TTC development will be crucial.

Scope
Structurally-defined, low molecular weight compounds for which tumor data are available from relevant in vivo studies and known or assumed to be relevant for human health are in scope. Out of scope are high molecular weight substances such as proteins or polymers, complex botanicals and substances of unknown or variable composition. Out of scope is also a full decription of MoA or AOPs for the cancer outcome of the substances. MoA information should only be included to a degree required to segregate the substances, with reasonable confidence, into subsets amenable to different risk assessment methodology, i.e. currently a threshold approach for non-DNA-reactive substances and linear extrapolation for DNA-reactive substances.

Deliverables
Collection and review of study information, generation of SAR information (as appropriate), and building the database. Analysis of distributions and the appropriateness of the current TTC cancer thresholds and refinement options, respectively. Discussion of the applied approaches and results thereof with relevant stakeholders to maximise practical and regulatory applicability in different regions.
Together with a final report, the database shall be made public without legal constraints for use of the information by other researchers, in an easily transferrable format, e.g. as Microsoft Access Database. The database should clearly depict data sources, criteria used and decisions taken (if need be in the form of supplementary material).
It is expected that the findings will be developed into at least one peer reviewed publication, following poster(s) and oral presentation(s) at suitable scientific conference(s).

Cost and Timing
Start in 2016, duration 1.5 years
Budget in the order of €190,000

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 indicating their willingness to participate 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 the work could play a role in the regulatory and policy areas. Dissemination plans should also be provided.

DEADLINE FOR SUBMISSIONS: 6 Sept 2015

Please visit www.cefic-lri.org for general information about the LRI funding programme, guidelines for grant applications and links to application documents.