CEFIC Long-Range Research Initiative

Request for Proposal (RfP)

LRI Project code: LRI-B8

Title: Threshold of Toxicological Concern (TTC) for inhalation exposure

Deadline: 31 August 2010

Background:
The TTC concept assigns threshold values of structural classes of compounds below which no risk for human health is assumed. So far, these thresholds values have been derived from a database of in vivo studies with oral exposure thus limiting the applicability of the derived thresholds to dietary intake. In 2004, Kroes et al published a detailed decision tree, which guides the user through a couple of decisions to allocate the appropriate thresholds value to the untested compound. TTCs are conservative as e.g. the TTCs in Cramer class 1 to 3 (Cramer et al 1978) are derived from the 5th percentile of the NOEL values. So that there is a probability of 95% that the NOEL value of the untested substance is higher than the TTC value. The TTCs have already been used to assess the risk of e.g. food contaminants, flavouring substances or impurities in pharmaceuticals (Barlow S 2005; Cheeseman et al 1999; Delaney 2007; Kroes et al 2000; Kroes et al 2007; Munro et al 1998).

Further applications like metabolites from pesticides, cosmetics and household products are under discussion. Thus it can be stated that the TTC concept is a relatively simple and useful tool, which can be used to omit animal testing for those substances where the exposure is below the corresponding TTC value. The scientific discussion is in progress to determine whether general TTCs like those for Cramer class 1 to 3 are needed or category specific TTCs like already developed for organophosphates.

Consumers spend typically about 20 h per day in indoor environment, thus, the question of the health relevance of the chronic exposure to indoor air pollutants, taken up by inhalation, plays an important role. For many substances which are typically found in such environments, relevant data are not available. Therefore, it would be desirable to develop the TTC concept further with the objective of creating a tool to derive threshold limit values (inhalation), based on structural characteristics of a given substance to make animal testing for risk assessments e.g. under REACH unnecessary.

Recently, the TTC concept has been evaluated with regard to inhalation exposure (Carthew et al 2009). The TTC values derived are lower than those derived for the oral route. Carthew et al. also derived lower local compared to systemic thresholds. This indicates that there might be a need to modify or supplement the current Cramer decision tree e.g. with special structural descriptor for local and systemic toxicity. The analysis of the current Cramer classification with 203 compounds from the database RepDose reveals that
the TTC concept in its current version and especially the Cramer classification is not simply applicable to inhalation exposure and fails to discriminate toxic from low toxic compounds (Escher et al 2010).

Scope and Objectives:
The overall objective of this proposal is to derive TTCs for inhalation toxicity. Prerequisite to analyse the correlation of grouped substances and the corresponding NOEC values is a database that allows the handling of complex datasets.

In particular

- To upgrade and extend the RepDose database on in vivo studies, with inhalation exposure (> 250 substances). In addition to the NOEC and LOEC values, a special focus should be set on target organs, effects as well as mode of action. This information is needed to develop inhalation specific TTC values. The derived project database shall be made available and accessible via AMBIT, ownership will be with CEFIC, and the database will become public domain.

- Development of a strategy to derive new potency classes for inhalation toxicity that considers local and systemic toxicity. The following issues should be addressed:
  
  o Local toxicity versus systemic toxicity and consequences for grouping
  o Structural alerts
  o Mode of action

Descriptors contributing to the grouping of chemicals will be also part of the project database.

- Identification of structural features or other properties correlated to local toxicity or systemic toxicity that lead to very high NOEC values.

- Regrouping of compounds and derivation of robust TTC values for inhalation exposure.

At the end of the project the results should address the following questions:

  o Are there route-specific parameters that had to be used to modify the TTC concept for inhalation exposure?
  o Which strategy results in robust TTC values for inhalation exposure?
  o Is the derived refinement strategy also applicable to oral exposure?
  o Is it possible to derive precisely distinguished potency classes to derived reliable TTC values?
  o Which inhalation TTCs are derived for which grouping?
Monitoring:
The Principal Investigator will be required to submit a progress report at 12 months during the course of the programme. At the end of the project, a detailed review of the research and its accomplishments will need to be provided by the Principal Investigator e.g. as publication in a peer-reviewed journal. The investigators are encouraged to present their preliminary findings in appropriate scientific meetings.

Budget and Timing:
It is anticipated that the project will start mid of 2010 and be finished within 18 months. The budget is in the order of 250,000 €.

References:


Carthew P, Clapp C, Gutsell S. 2009. Exposure based waiving: the application of the toxicological threshold of concern (TTC) to inhalation exposure for aerosol ingredients in consumer products. *Food and Chemical Toxicology* 47:1287-1295
Escher S E, Tluczkiewicz I, Batke M, Melber C, Buist H, Kroese D and Mangelsdorf I