LRI-B8 Threshold of Toxicological Concern (TTC) for inhalation exposure

Improvement of the TTC concept for inhalation exposure and derivation of thresholds with the database RepDose

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The Threshold of Toxicological Concern (TTC) concept developed generic human threshold values by grouping compounds into structural groups (reviewed by Barlow *et al*., 2005). Thresholds were derived by analyzing in vivo studies with oral exposure. The present projects aims to develop a new grouping concept to derive TTC values for exposure after inhalation. It was investigated in more detail, whether local activity has to be considered.

First a robust project database was generated. The Fraunhofer RepDose DB (www.fraunhofer-repdose.de, Bitsch *et al.,* 2006) was extended to 296 chemicals by adding further public peer-reviewed repeated dose inhalation studies. The resulting TTC RepDose dataset consists of 107 subacute, 104 subchronic and 85 chronic repeated dose toxicity studies in rodents.

Two datasets were discrimanted within this project, chemicals with local effects at the LOEC (lowest observed effect concentration) versus chemicals with systemic effects at LOEC. Chemicals with both, local and systemic effects, were added to both datasets. 138 chemicals were grouped into the local and 210 chemicals into the systemic dataset. 30 chemicals without any effect up to the highest tested dose were analysed separately (NOA). The minimal values of both datasets are very low with 5×10^{-5} ppm and increase to 8247 ppm in the systemic dataset and to approx. 2000 ppm in the local dataset.

Non sucessfull grouping approaches:

In subsequent analyses, it has been checked whether the type and severity of local effects occurring at high, moderate and low potency can be used for the grouping of compounds. Local effects were classified as adverse, potentially adverse and non–adverse by an experiences histopathologist at Fraunhofer ITEM. The hypothesis that high and low toxic chemicals might also differ with regard to their nature of effects e.g slight effects such

as inflammation or irritations may occur mainly in the group of lower toxic compounds, whereas more severe effects such as pathological changes in tissues (hyperplasia, metaplasia) in the group of high toxic compounds could not be confirmed. Type and nature of toxicological effects were, however, included in the analysis of structural groups as described later on. Also structural alerts for skin and eye damages were investigated but can not serve to group compounds for inhalation toxicity levels. On reason here, is that the chemical domain of compounds being included in the TTC RepDose DB differs from the chemical domain of compounds, which have been used to derive structural alerts for skin and eye damage.

Succefull grouping strategy

Structural rules indicating a high or low toxicity after inhalation exposure were investigated. Three potency categories per dataset (local or systemic) were defined to roughly distinguish between compounds with low and high toxicity.

21 structural groups of compounds were identified, for which lower or high toxicity can be associated to characteristic structural elements. 14 structural features were allocated to the high toxicity group (termed T (toxic) 1 to 14). 7 structural features were identified as indicator structural features for high NOEC values leading to allocation to the low-toxicity structural groups (L (low) 1 to 7). Compounds which could not be allocated to any of the above structural features are allocated to the group “no specific structural feature” (0). Each structural group/or pairs of structural groups were then analysed in more detail considering the following aspects:

- Structural homogeneity: Evaluation of structural features and if needed distinction of further structural subgroups dependent on additional frequently shared functional groups.
- Analysis of toxicological potency and frequency of affected targets and related effects in the entire group, comparison to structural subgroups.
- Evaluation of metabolism/bioactivation in vivo.
- Evaluation of absorption differences by correlation of NOEC values to K_{ba} (blood/air partition coefficient).

This analysis resulted in altogether 28 structural features 9 L-groups and 19 T-groups . 165 compounds (54%) were allocated to a toxic group (T) and 85 compounds (28%) to a low toxic group (L). Up to now 59 chemicals (19%) were not grouped based on their chemical structure and toxicity.

Some SF-groups were similar to structural alerts for genotoxicity, which indicate a potential

hazard for genotoxic carcinogencity. These SF were analysed separately, to evaluate whether their compounds are probably more toxic and might shift the derived TTC values in the T and L group. The median NOEC values as well as the 5th percentiles of the reactive SF-groups were in the same range or even higher than the corresponding T and L-groups and confirm their TTC values.

Conclusion

In this project a concept for grouping organic chemicals has been successfully developed, which clearly distinguish classes of high and low toxic compounds. Beside structural information this concept relies on the evaluation of toxic potency (NOECs), effects observed in in vivo studies, differences in absorption and published data on mechanism and mode of action. Based on the evaluated dataset in this project a threshold of 2.3 x 10^{-5} ppm (2.7 µg/person/day) is proposed for compounds containing any of the SFs of the T-group and 0.047 ppm (3979.3 µg/person/day) for L-group compounds.

The proposed TTC values in this project are explicit for inhalation toxicity, as only studies with inhalation exposure are used for their derivation. A validation of the proposed grouping concept is however advisable to increase its reliability, in particular for those 11 SF groups with less than 5 members. Currently, structural features specific for moderately toxic compounds are not evaluated. Here more work has to be done to add specific structural rules and thereby decrease the amount of not yet classified compounds. Broad databases with repeated dose toxicity data are available for studies with oral exposure e.g. ToxREf DB (U.S. EPA; Martin *et al*., 2009) and RepDose database (Tluczkiewicz et al. 2011). Also some additional studies with inhalation exposure may result from the still increasing ECHA DB. The present analysis has shown that local activity has an impact on LOEC values e.g. local NOEC values trigger the 5th percentiles of eight subgroups in the present new classification. Only few rules are, however, specific for local and or systemic effects. Therefore, it might be possible, to define a global TTC concept for inhalation and oral exposure, e.g. by including route specific differences into this concept.

The 296 in vivo studies of the RepDose TTC inhalation database, the structural descriptors of the compounds and the physico chemical properties are available online under www.fraunhofer-repdose.de.