Inga Tluczkiewicz, Inge Mangelsdorf, Harrie Buist, Matthew Martin, Sylvia Escher

**TTCs for oral exposure: Identification of outliers in Cramer class I, II and III using the combined database of RepDose (FhG), Toxbase (TNO), Munro and ToxRefDB (USEPA)**

The Thresholds of Toxicological Concern (TTC) are generic human exposure threshold for structural groups of chemicals below which no risk to human health is assumed and therefore no further testing is needed. Different thresholds have been developed for oral exposure e.g. for genotoxic compounds as well as for 3 broad structural classes according to Cramer et al. that contains low toxic (I), moderately toxic (II) and toxic (III) structures.

Re-evaluation of the TTC values of Cramer class I to III with the FhG database RepDose, that focus on existing chemicals, revealed that the thresholds are in the same range as those initially derived by Munro et al. Thus, the TTC concept is also applicable to existing chemicals and can be applied e.g. for exposure based waiving under REACH.

However, only about 4% of all chemicals in both databases were classified as being moderately toxic so that a reliable threshold for this class could not be derived. The analysis of the NOEL distributions showed that Cramer class I and III overlap to some extend indicating that the Cramer classification fails to discriminate toxic from low toxic chemicals. The observed toxic chemicals in Cramer class I lead to a conservative threshold for low toxic compounds, whereas low toxic chemicals in Cramer class III lead to a less conservative threshold for toxic compounds, indicating that a refinement of the Cramer decision tree regarding the structural classification is needed.

The databases RepDose (FhG), Munro, Toxbase (TNO) and ToxRefDB (USEPA) were pooled to increase the applicability domain and the relevance of the Cramer Classes. Assessment factors for time and interspecies extrapolation were applied to L(N)OEL values to reduce data variability.

The TTC values for oral exposure were determined and appear to be more conservative than those values of Munro. For the identification of outliers cut-off values were applied to exclude high toxic chemicals from Cramer class I and low toxic chemicals from Cramer class III. Analysis of the outliers regarding their structural and physico-chemical properties was performed using the OECD (Q)SAR Application Toolbox, STATISTIKA and ToxMatch. First structural classes of outlying compounds (categories) were identified, that can further be used to assign new steps to the Cramer decision tree. (The views expressed in this abstract are those of the authors and do not necessarily reflect the views or policies of the U.S. Environmental Protection Agency)