

Sources of Uncertainty in derivation and application of the Threshold of Toxicological Concern (TTC) concept: identification and semi-quantitative description

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BACKGROUND/OBJECTIVES

The probabilistic approach using the genotoxicity and non-cancer (Cramer class) Thresholds of Toxicological Concern (TTC) is often perceived as accepting a higher risk than traditional risk assessments. However, robust scientific activities to describe the sources of uncertainty within the TTC approach have not yet been conducted or published. An ILSI Europe Expert Group was formed to examine how much uncertainty may be associated with the application of the TTC approach as compared to a substance-specific risk assessment, thus developing scientific knowledge about the sources of uncertainty being specific to the TTC. The initial phase of the project focuses on qualitative description and ranking of the identified sources of uncertainty, with a subsequent quantitative assessment.

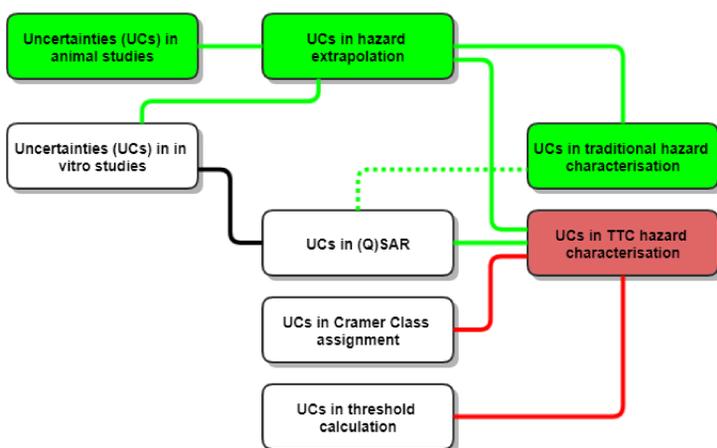


Fig 1. Analyzing the uncertainties specific to TTC and their sources.

Empirical comparisons between TTC based risk assessment and chemical-specific points of departure demonstrate that the TTC concept is sufficiently conservative

- uncertainty describes the lack of knowledge which can lead to either under- or overestimation of the risk assessment outcome.
- highly uncertain risk assessments can also lead to very low risk – by the application of conservative assumptions and/or restriction of exposures to very low levels, i.e. by the introduction of bias.



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KEY QUESTIONS:

1. Which sources of uncertainty are specific to TTC?
2. How large are they compared to traditional risk assessment?

Sources of Uncertainty specific to TTC

- Chemical space/diversity
- Excluded substance groups
- In silico/experimental data
- Applicability of TTC
- Cramer Class misclassification

Sources of Uncertainty common between TTC and substance-specific risk assessment using data

- Variability in animal studies
- PoD selection
- Safety factors
- Database quality
- Choice of 5th percentile

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