

Introduction to Thresholds of Toxicological Concern Concept and how *in vitro* methods and TTC complement each other

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During the past decade, many basic and some highly sophisticated *in vitro* models were developed to depict specific molecular, cellular and tissue effects of chemicals. Most *in vitro* models, and *in silico* models alike, are useful to investigate specific modes of action, but cannot provide general safety assurance in the absence of information on modes of action and toxicokinetics and –dynamics of a given compound throughout the multitude of tissues of an integrated organism. This is the point in animal data-free risk assessment where the value of read-across and Thresholds of Toxicological Concern (TTC) approaches becomes apparent. TTC thresholds are based on large datasets of oral cancer and non-cancer repeated dose *in vivo* toxicity data and describe *de minimis* exposures below which there is a low risk of any appreciable risk to human health. At this point in time, the TTC concept and read-across are the only options to perform repeated dose systemic risk assessments when there is a lack of time, resources and /or legal acceptance to run animal studies on specific natural or man-made chemicals. Therefore, it is important to understand its scientific basis, where it can be applied with confidence, where improvements are being developed and for which cases it should not be applied currently. *In vitro* methods can be particularly useful to identify the latter, provided that they are sufficiently sensitive. Ongoing collaborative research to derive TTC thresholds based on *in vivo* no/low-effect plasma concentrations (internal TTCs) will result in a large dataset with useful information for In-Vitro-In-Vivo-Extrapolation.

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