

Assessment of the risk to humans posed by exposure to low levels of chemicals

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The Threshold for Toxicological Concern (TTC) is an approach used to assess the risk (if any) posed by chemicals to which humans are exposed at very low levels but when no toxicity data are available. The approach was evaluated at a workshop (Brussels, 8th-10th June 2011) organised by ILSI Europe with the participation of academia, industry, non-governmental organisations and regulators. The findings are summarised in a [paper published in the peer-reviewed journal Regulatory Toxicology and Pharmacology in February 2013](#).

Today, improved analytical methods means that many substances present at low or very low concentrations in the environment can now be detected. In many cases, little or no toxicological data are available for these previously undetectable substances, making it difficult to assess their impact on public health. However, the Threshold of Toxicological Concern (TTC) is an approach that can be used to assess the risk (if any) posed by these substances. The approach is based on the fact that chemicals with similar structure exhibit a similar level of toxicity in the body. In other words, they become toxic at around the same level of intake. Three structural classes of chemicals have been identified. These are of low, medium or high toxicity. A TTC value has been established for each structural class, below which there is no appreciable risk to health. The TTC values are based on analyses of no-observed adverse effect levels, or NOAELs for short, from repeated dose toxicity data for each structural class.

To use the TTC approach, the chemical under investigation must be assigned to its appropriate structural class. The level of intake of the chemical is then compared with the appropriate TTC value and a decision can be made on whether or not further toxicological investigations are needed. However, if the chemical under examination has a structural alert for genotoxicity (i.e. it is capable of causing cancer by directly altering the genetic material of target cells), a generic TTC value of 0.15 µg (microgram) per person per day applies.

In principle, the TTC approach can be used for the safety evaluation of any substance which has a chemical structure that is known and an estimate of human exposure can be made. It can be used as an initial assessment/screening tool to determine whether a more comprehensive risk assessment is required. Advantages include more focused and efficient use of resources and the possible reduction of unnecessary animal testing.

Organisations using the TTC approach include U.S. Food and Drug Administration, JECFA (the Joint Expert Committee on Food Additives of the U.N.'s Food and Agriculture Organization and the World Health Organization) and EFSA (European Food Safety Authority). It is used as a pragmatic risk assessment or prioritisation tool in several areas of chemical risk assessment including food contact materials and food flavouring agents. It has also been considered for exposure-based waiving of toxicity testing under REACH (REACH is a European Regulation and an acronym for the Registration, Evaluation, Authorisation and

Restriction of Chemicals). However, despite its applications and current uses, the TTC approach is controversial because the validity of the approach is critically dependent on the validity of the databases used to derive TTC values.

Overall, the paper concluded that the TTC approach is a valid first tier approach for chemical risk assessments and prioritisation. However, it was acknowledged that prior to the application of the TTC approach, all available toxicity data on the chemical should be collected and evaluated and the TTC approach should only be used in cases where the available data are inadequate for normal risk characterisation. The current TTC values were considered adequate and fit for purpose; however, opportunities were identified to expand the toxicological databases used to derive them. For example, expansion of the database for non-cancer effects, to include some highly specific classes of chemicals (e.g. UV filters and reactive hair dyes) and modes of action (e.g. endocrine disruption) would enhance its applicability and regulatory acceptability. The paper also identified the need to update and modify the decision trees used to assign chemicals to their appropriate structural class. Any changes to the TTC values derived from revised databases or to decision trees should be subject to transparent global peer review, in order to ensure wide regulatory acceptance.

For further information please see:

[Dewhurst I & Renwick AG. \(2013\). Evaluation of the Threshold of Toxicological Concern \(TTC\) – Challenges and Approaches. Regulatory Toxicology and Pharmacology 65: 168-177](#)

EUFIC (2007) Food Today Article. New system for assessing chemical safety