WHO Project to Review
the Threshold of Toxicological Concern Approach

Call for data

Posted 5 August 2013

Background
The Threshold of Toxicological Concern (TTC) is an important concept to predict the potential for toxicity based on chemical characteristics and estimated exposure. The underlying principle is that the toxic potency of a compound is a function of both, chemical structure and extent of exposure. In light of ever improving methods in analytical chemistry, it is to be expected that many more unintended chemicals will be detected in our environment, including food and drinking water, as well as in our bodies. To allow for a risk assessment of these new exposures in light of insufficient compound-specific data, other methods need to be applied to estimate the potential human health impact to prioritize for further actions and make informed risk management decisions.

Initial applications of TTC date from the mid-1990’s and were limited to use in the Food and Drug Administration (FDA)’s risk assessment of migrants from food packing materials (Threshold of Regulation TOR) and JECFA’s assessment of flavors (Munro, 1996). In 2004, Kroes et al. published a proposed methodology for applying the TTC approach for more general use and included additional TTC toxicity thresholds (see Attachment 1). After passing some exclusion criteria, a chemical can be placed in one of 5 tiers based on chemical structure:

- 0.15 ug/d: Chemicals with structural alerts for DNA reactivity
- 18 ug/d: Organophosphates
- 90 ug/d: Cramer Class III
- 540 ug/d: Cramer Class II
- 1800 ug/d: Cramer Class I

This proposal is an expansion of the work done by the US FDA (1995) to establish a single-tiered TOR and work championed by Munro et al. (1996) to establish exposure limits for classes based on the Cramer Decision tree (1978) and a toxicity database of evaluated chemicals.

Overall the TTC approach integrates data on exposure, chemical structure, metabolism, and toxicity consistent with risk assessment principles. It has been proven to be a pragmatic, scientifically-valid approach for prioritization and safety evaluation of compounds with relatively low oral exposure and for which limited compound specific data are available. Application of a science-based systematic approach will allow risk managers to prioritize actions and target further testing and evaluation strategies. It is important that scientific research continues to provide support, refinement, and improvement to the TTC approach to assure its adequacy, appropriate application, and usefulness for public health protection.

The objectives and expected outcome of the project
This project intends to provide recommendations as to how the existing TTC framework may be updated and expanded by updating/revising the Cramer classification scheme and
expanding the TTC approach to other structural classes, thereby building on existing and ongoing work in this area.

The specific scope of the project will be to recommend a single, consistent and science based TTC approach. The project will make recommendations on the following:

1. Revisions to the Cramer Classification Scheme;
2. Revisions/additions to the TTC toxicity thresholds; and
3. Harmonized methodology for applying the TTC approach (i.e.: the TTC Decision Tree published by Kroes et al. (2004)).

**Call for data - Deadline [30 September, 2013]**

WHO is seeking submissions of published and unpublished technical information to support the development of a harmonized methodology for the application of TTC to food chemical risk assessment. The information will provide a comprehensive understanding of state of the science of TTC risk assessment and enable the development of recommendations on updating/revising the TTC approach.

**Confidential and/or unpublished information**

WHO recognizes that some of the information and relevant data may be unpublished or of a confidential nature. With regard to unpublished information and data, this remains the property of the author for subsequent publication by the owner as original material. Unpublished confidential studies that are submitted will be safeguarded in so far as it is possible to do so without compromising the work of WHO. Specific issues relating to confidentiality should be discussed directly between the information and data owners and WHO. For these and other issues please contact WHO at the contact provided below.

**Information requested:**

- Existing proposals and underlying science supporting, refining, or improving the Cramer Classification Scheme;
- Existing proposals and underlying science supporting, refining, or improving the TTC class toxicity threshold values;
- Existing science supporting the scientific validity of the TTC approach and addressing the issues regarding toxicological endpoints and dose-response relationship;
- Existing proposals and underlying science supporting, refining, or improving application of the TTC approach (for example of proposed methodology see Attachment 1 - Kroes et al. (2004));
- Reviews, surveys or other information concerning public perception of the TTC approach; and
- Any other relevant information that falls within the scope of the project.

**Call for data**

Information and data should be submitted to the Secretariat by [30 September, 2013] to the address below, preferably by electronic means, either via e-mail (if not too large) or on CD-ROM.
Contact Information

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References:


Attachment 1: Kroes et al. (2004) TTC Decision Tree