Draft Programme

Workshop on the Threshold of Toxicological Concern: Scientific challenges and approaches

8 – 10 June 2011

Brussels (Belgium)

4/02/2011

PURPOSE OF THE WORKSHOP

Background and objectives

The objective of the workshop will be to explore the scientific challenges to the application of TTC ("Threshold of Toxicological Concern") as a tool to aid decision-making in chemical safety assessment. TTC is the principle whereby a generic exposure value is established below which there is a low probability of adverse effects to human or environmental health. The concept is based on extrapolation of toxicity data from an available database to a chemical compound for which the chemical structure is known - but for which limited toxicity data are available. The broad approach is potentially applicable to any substance (i.e., intentionally added ingredient or inadvertent contaminants or impurities). The application of TTC in safety assessment is dependent on the quality, quantity and relevance of the underlying toxicity database (i.e., the chemical domain) and the availability of a reliable and relevant estimation of the exposure.

The TTC approach is at present used – amongst others - to evaluate the safety of food contact materials, flavouring agents and genotoxic contaminants in pharmaceuticals. The approach has also been suggested for a number of other applications. Wider acceptance and application of TTC would potentially yield benefits; in particular, it would limit toxicity testing and associated safety assessment when exposure to a chemical is below a certain level of concern. This would permit a focus of finite resources of time, finance, animal use and human capital on the evaluation of substances with a greater potential to pose risks to human or environmental health.

The workshop participants will

- Review examples of the application of TTC across different regulatory evaluation frameworks and decision-making programs;
- Identify scientific barriers to broader acceptance of TTC;
- Explore potential opportunities for initiating steps to overcome such barriers.

Expected outcomes

- Broaden the awareness of current applications and practical experiences of TTC;
- Characterise the key scientific challenges associated with the use of TTC for both carcinogenic and non-carcinogenic endpoints;
- Explore the scope and/or limits of methodologies seeking to apply the TTC concept within the context of less-than-life-time exposures or where route-to-route extrapolation is required;
- Identification and understanding of the scientific barriers that impede further adoption of the TTC concept as an integral component of risk assessment;
- Recommendations to overcome barriers and establishment of a community of interest to further advance the application of TTC.

Participants

The workshop is aimed at safety and regulatory scientists from industry, government agencies, animal welfare organisations and academia from all over the world to provide a global perspective.

Workshop Report

A summary of the outcome of the workshop will be published as a peer-reviewed article in *Regulatory Toxicology and Pharmacology* which is the journal of the International Society of Regulatory Toxicology and Pharmacology (ISRTP).

Organising Committee members

Dr. R. Becker	International Society of Regulatory Toxicology and Pharmacology (ISRTP)	US
Dr. P. Daskaleros	European Commission (DG SANCO)	BE
Dr. S. Felter	Procter & Gamble	US
Dr. B. Hubesch	European Chemical Industry Council (Cefic) Long Range Research Initiative (LRI)	BE
Dr. I. Manou	European Partnershiop for Alternative Approaches to Animal Testing (EPAA)	BE
Dr . D. Maurici	European Food Safety Authority (EFSA)	IT
Dr. T. Quill	International Society of Regulatory Toxicology and Pharmacology (ISRTP)	US
Prof. A. Renwick	University of Southampton	UK
Dr. J. Scheel	Henkel	DE
Dr. T. Seidle	Humane Society International (HSI)	UK
Dr. A. Tritscher	World Health Organisation (WHO)	CH
Dr. S. Webb	Procter & Gamble	BE
Ms. T. Wildemann	International Life Sciences Institute – European branch (ILSI Europe)	BE

PROGRAMME

Overall Chair: Susan Barlow
Overall Co-chair: Jim Bridges

Overall Rapporteur: Andrew Renwick
Overall Co-rapporteurs: Ian Dewhurst

Day 1 – Tuesday, 10 May 2011

10.00 – 12.00	Registration	
11.00 – 12.00	*Pre-meeting with officers (chairs, co-chairs, rapporteurs)*	
12.00 – 13.00	**Lunch**	

Session 1:	**Introduction: setting the stage**	
13.00 – 13.45	TTC applications: challenges and approaches	S. Felter
13.45 – 14.05	Perspective of the EC Scientific Committees	T. Sanner
14.05 – 14.25	Perspective of EFSA	S. Barlow
14.25 – 14.45	Perspective of WHO	A. Tritscher
14.45 – 15.05	Perspective of US FDA	M. Cheeseman
15.05 – 15.30	**Coffee break**	

Session 2:	**Introduction to the topic areas for the breakout groups**	
15.30 – 15.50	Introduction to non-cancer end points	A.G. Renwick
15.50 – 16.10	Introduction to cancer end points	M. Cheeseman
16.10 – 16.30	Introduction to route-to-route extrapolation	J. Van Engelen
16.30 – 17.00	Discussion	
19.00	**Dinner**	

Day 2 – Wednesday, 11 May 2011

Session 3:	**Breakout groups**

BOG 1: Non-cancer - Database and chemical domain	Chair: U. Gundert-Remy Rapporteur: S. Escher
BOG 2: Non-cancer - Grouping of chemicals	Chair: A. Piersma Rapporteur: T. Platzek
BOG 3: Cancer - Database and chemical domain	Chair: M. Cheeseman Rapporteur: L. Edler
BOG 4: Cancer - Grouping of chemicals	Chair: G. Williams Rapporteur: W. Dekant
BOG 5: Route to route extrapolation (Domains of application and exclusions)	Chair: W. De Jong Rapporteur: I. Mangelsdorf

09:00 – 10:30	Breakout group discussions
10:30 – 11:00	**Coffee break**
11:00 – 13:00	Continuation of breakout groups
13.00 – 14.00	**Lunch**
14:00 – 15:00	Interim report back from breakout groups (10 min/group)
15:00 – 15:30	**Coffee break**
15.30 – 18.00	Continuation of breakout groups
19.30	**Dinner**

Day 3 – Thursday, 12 May 2011

Session 4:	**Report back from breakout groups**	
09:00 – 09:30	Report back from breakout groups on non-cancer	*BOG rapporteurs*
09:30 – 10:00	Report back from breakout groups on cancer	
10:00 – 10:30	Discussion	
10:30 – 11:00	**Coffee break**	
11:00 – 11:30	Report back from breakout group on extrapolation	
11:30 – 12:00	Discussion	

Session 5:	**Summing up**	
12:00 – 12:20	Summary	A. Renwick/I. Dewhurst
12:20 – 12:30	Closing	S. Barlow
12:30 – 13:30	**Lunch**	
13.30 – 14.30	*Post-meeting of Organising Committee and officers*	

BRIEFS FOR BREAKOUT GROUPS

The breakout groups should discuss as a first step the overall state of science and in a second step strategies/recommendations on how to solve the raised issues.

BOG #1: Non-cancer Database & Chemical Domain

1. Defining the chemical domain for TTC
   The importance of the chemical domain has been raised in the past, both in published literature and in the opinion on the use of TTC issued by the EU Scientific committees. Focus has been placed on whether a chemical structure is adequately represented by the database of chemicals used to derive the exposure thresholds to support use of TTC in a risk assessment of the chemical. This discussion should focus on the tools and approaches used previously and tools currently available for analyzing the chemical domain and determining how a chemical can be compared to this chemical domain. This should include defining what would be considered in or out of the domain of the chemical space, what the best method would be to assess the chemical space, and how this can be routinely accomplished in the arena of non-cancer toxicological data which will continue to evolve with data being generated. Key here will be a mechanism for keeping data up to date as the database evolves and keeping the domain analysis tools current with the database analysis.

2. Identification of areas requiring an expansion of the non-cancer database
   a. Endpoints –
      i. Past datasets used to derive TTC levels used repeat dose studies covering various endpoints. As the science surrounding TTC has evolved and new data are generated, are there endpoints that were not adequately considered in the original analyses and should have been (e.g., reproduction/developmental; endocrine disruptors)? Another question is whether or not the critical effect of a chemical was identified and the correct point of departure (e.g. NOAEL or BMDL) chosen for the analysis. Is it necessary and are there resources to check the existing non-cancer database to ensure the correct data were used to derive the existing thresholds?
      ii. In order to keep the future use of TTC up to speed with evolving databases, it would be ideal to have a centralized dataset that would be continually maintained to allow inclusion of new data as they become available. This would keep the chemical domain of the TTC dataset from stagnating as well as ensuring the current data are available for use and that any thresholds derived are representative of the state of the science.
   b. Classes of chemicals (e.g., chemicals used in personal care products) – In order to be able to broadly apply the TTC system across diverse industries the chemical groups represented by the non-cancer database must compare favourably with chemicals commonly used in different industries (for example: cosmetics, personal care, and household care products important to those who may be applying TTC). What are the toxicologically important chemical functional groups that are relevant to various industries and are they represented in the TTC databases? It is important to note that the chemical structure is what is important in applying the TTC system and not necessarily the use, as long as the functional group is within the domain of the database. In order to implement this, it would be necessary to identify additional data sources and update the current database to encompass as broad a dataset as possible. The creation of a larger dataset would enhance confidence in the distributions and expand the applicability domain of the analysis.

3. Is metabolic prediction a useful addition to TTC? As is currently done for flavouring groups, consideration of metabolism may be useful for extending the chemical domain as long as the examination of metabolism is grounded in data/published works, as the state of predictive metabolism programs is currently too broad to be reliably applied to risk assessment.

4. If time is available during the breakout group, consider the impact of less than lifetime human exposure on the need for less than lifetime TTC values, on the database(s) needed/available to derive such TTC values and/or the possibility of "correcting" the available chronic TTC values to derive "less than lifetime" TTC values.

BOG #2: Non-cancer Grouping of chemicals

1. Cramer classes
   a. Are there ideas for updating the current Cramer et al. decision tree to reflect up to date chemical data? One approach to this may be to use an expanded data set to develop a new decision tree that is based on a broader chemical footprint with current data. Would it be better to update the current decision tree or start from scratch with a new system, and what would that new system of grouping look like?
   b. Going forward, what opportunities are there to use a different approach? What kinds of tools can be used? Consider that new tools will need to be tied into the evolving database. Development of any new more sophisticated tool is of limited value if a mechanism for maintaining an updated database is not also created.

Other methods to group (e.g., *in silico* tools; physico-chemical data; SAR) – could be used instead of or in addition to Cramer for grouping chemicals. EFSA has outsourced a project on this and the contractors are due to report by March 2011, so the conclusions of that work will be available at the time of the workshop.

BOG #3: Cancer Database & Chemical Domain

1. Defining chemical domain to offer increased assurance of determining whether a chemical is within domain. The importance of the chemical domain has been raised in the past, both in published literature and in the opinion on the use of TTC issued by the EU Scientific committees. Focus has been placed on whether a chemical structure is adequately represented by the database of chemicals used to derive the exposure thresholds to support use of TTC in a risk assessment of the chemical. This discussion should focus on the tools and approaches used previously and tools currently available for analyzing the chemical domain and determining how a chemical can be compared to this chemical domain. This should include defining what would be considered in or out of the domain of the chemical space, what the best method would be to assess the chemical space. One important question for chemical domain inclusion for cancer is whether comparison with structural alert groups for genotoxicity is sufficient for a chemical to be considered in the domain from a chemical structure perspective. Such considerations may be combined with use of physical chemical properties or some other estimation/comparisons of bioavailability. This question is especially important in light of the fact that it is unlikely this dataset will be significantly expanded in the future with additional bio-assay data.

2. Are there other chemical functional groups in addition to those defined as a “cohort of concern” by Kroes et al 2004 that are not suitable for TTC, or which should have a more potent tier (e.g., hydrazines? PAHs)?
   a. For currently excluded groups (e.g., N-nitroso compounds), should another TTC tier be established?

3. For chemicals outside of the domain, what tools can be used to bridge across to allow TTC to be used? (e.g., *in vitro* testing? *In silico* tools?)

4. The database is based on TD50’s, but the database itself is not publicly available
   a. Should the database be refined to include MOA data (to allow evaluation of sub-distributions); or to ensure only values from human-relevant tumors are included?
   b. Consider basing on LED-10 vs TD50 – Would use of LED-10 (BMDL10) in place of TD50 approach give significantly different threshold values and would this bring the TTC values more in line with approaches used by other agencies for cancer risk assessment (EFSA; USEPA)?
   c. Is it necessary to evaluate other databases with cancer potency values (e.g., US EPA IRIS) to ensure that TTC is sufficiently protective?

5. If time is available during the breakout group, consider the impact of less than lifetime human exposure on the need for less than lifetime TTC values, on the database(s) needed/available to derive such TTC values and/or the possibility of "correcting" the available chronic TTC values to derive "less than lifetime" TTC values.

BOG #4: Cancer Grouping of Chemicals

1. Identification of structural alerts for grouping chemicals according to their genotoxicity potential – is this the best way?
    a. Tools – e.g. DEREK, ToxTree, others? Need for consistency, transparency as to how/what is being grouped.
    b. Considering how well developed the knowledge of structural alerts for genotoxic carcinogenicity is, it is a concern that several computer programs analyzing for structural alerts can give so many different conclusions. A consistent and reliable source of structural alert analysis is critical for application of the TTC decision tree. Availability of such a tool to all is also critical to ensure consistent application.

2. Another point for discussion for the breakout group might be to address what is needed to move from the "cancer" tiers to the "non-cancer" tiers. Current published works (Kroes et al 2004 primarily) have simply used a lack of genotoxicity structural alerts. Is this sufficient?

BOG #5: TTC and exposure routes

The TTC concept was developed for the evaluation of substances present in food and the majority of the animal toxicology data used to derive the TTC values was based on oral studies in rodents. However human exposure to chemicals is also commonly by the inhalation route (e.g. workplace, ambient and indoor air) or by topical exposure (e.g. cosmetics, workplace).

Some route-specific toxicity databases are now available for inhalation and topical exposure? If so, are they adequate for the establishment of route-specific TTC values?

If not, is it scientifically valid to extrapolate data on systemic effects, derived from studies employing the oral route, to inhalation or exposure via the dermal route? If so, how could that be done?

Issues that need to be considered in application of TTC values derived from oral studies to other routes include:

i) would first-pass metabolism and detoxication following oral administration have significantly influenced the 5th percentile NOAEL value in the oral database and what consequences would this have for application to other routes (see Kroes et al., 2007)?
ii) the rate and completeness of penetration of the chemical from the site of exposure
iii) the possibility of major changes in ii) due to co-exposure to other chemicals or for other reasons e.g. damage at the site
iv) the potential for metabolism at the site(s) of exposure and its possible influence on toxic metabolite formation

v) distributional differences on entering the systemic circulation

In some cases there may be toxicokinetic data for a particular chemical that enables a specific route to route extrapolation to be made but often this is not the case. If not can defaults be applied and if so on what scientifically justified assumptions can they be based? A further challenge is whether TTC could be applied if exposure to a chemical is by more than one route.