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EFSA Document Cover Page

Panel on :	**Scientific Committee and Advisory Forum**
Working group :	**Exploring options for providing preliminary advice about possible human health risks based on the concept of Thresholds of Toxicological Concern (WG TTC)**
Subject :	**Draft secretary's Notes 2st WG TTC Meeting**
Submitted by :	**David Carlander, Daniela Maurici**

Document for :

√	**Information**		
	Discussion		
	Possible adoption		
√	**The Working Group members**	**On**	

Confidentiality level :

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EFSA Scientific Committee Working Group on TTC

Secretariat Notes

2nd WG TTC Meeting, 11 March 2009, Brussels
Venue: DG Health and Consumers,
40, Rue Breydel, 10:00 – 17:30

Participants

WG Experts:	BOOBIS Alan, BARLOW Susan (Chair), BULDER Astrid, GALLI Corrado, GUNDERT-REMY Ursula, LOVELL David, SCHLATTER Josef
EU Commission:	DASKALEROS Takis from 16.00 to 16.30
EFSA:	CARLANDER David, MAURICI Daniela and MOHIMONT Luc (PPR)
Ad hoc expert:	WORTH Andrew
Apologies:	LARSEN John Christian, LHUGUENOT Jean Claude. MANTOVANI Alberto, PIERSMA Aldert, SKERFVING Staffan, ZAPPONI Giovanni.

Action points from the meeting

- For the action points related to the draft opinion, please consult the text below.
- Please submit **initial contributions no later than Monday May 11th**, to the EFSA Secretariat to allow for everyone to read them before the May 20th WG Meeting (Schipool, Amsterdam Airport)
- Secretariat to amend the "Expert Contact Details"
- Secretariat to update ExtraNet with presentation given at the meeting by Andrew Worth. Secretariat to upload Extranet with presentation by Gold on Cancer Database (CPDB) and Gold's proposal for sponsoring the Cancer Database
- Secretariat to contact ECHA to learn who is involved in TTC at ECHA
- [redacted] to provide contact details to the Secretariat on DK expert on chemical classification according to the Cramer scheme for a presentation at next TTC meeting

Meeting Discussions

1. Welcome and apologies for absence, Introduction of WG members
The chair welcomed the participants.

2. Adoption of the agenda
The agenda EFSA/SC/TTC/840 was adopted.

3. Declarations of interest (DoI)
[redacted] and [redacted] have been involved in the past in projects related to the TTC approach. All their interests have been already declared at the first meeting and the Annual Declaration of Interests have been updated accordingly. [redacted] is

one of the authors of the COLIPA comments to the EC Scientific Committees Draft TTC Opinion. [redacted] and [redacted] were participants in the 2008 JECFA veterinary drugs meeting in which the TTC approach was discussed in relation to veterinary residues in food. [redacted] and [redacted] are also involved in the FAO/WHO Update Project on methodology for risk assessment in JECFA and JMPR, in which the TTC is discussed.

4. Secretariat notes and update from EFSA

The action points related to the 1st meeting were revised. The experts contact details list, distributed to the WG members, needs to be revised in order to remove the private addresses of the members (whenever they appear) and replace them with the working address, wherever possible.

5. Other TTC activities

The chair opened the meeting. [redacted] was asked to briefly introduce the work of the ILSI Europe Expert Group on "The application of the TTC concept to trace substances in food" where he is a member. The starting point of the WG is how to apply the concept of TTC on substances detected at low concentrations but which are not quantified or qualified (known as the forest of peaks). More info can be found at: http://europe.ilsi.org/activities/taskforces/riskassessment/ThresholdToxicologicalConcern.htm). A first draft of the opinion will most probably be ready in fall 2009.

[redacted] was asked to give a short overview of the ILSI-HESI work on cumulative effects of chemical mixture exposure. The WG is discussing the possibility to use the TTC approach for screening mixtures, assuming that there is no synergy between the different components. A workshop is planned to be held by the end of 2009, together with ECETOC and WHO-IPCS on a case study. A manuscript is in preparation.

6. Outline of the TTC draft opinion and work programme

The document EFSA/SC/TTC/841, outline for TTC draft opinion, was discussed:

– Point 1: Introduction to TTC

[redacted] will draft the introduction of the draft opinion. For the current use of the TTC concept in the different EFSA panels, the data collected with the questionnaire developed by PSD (art. 36 contractor for TTC approach in assessing pesticides metabolites toxicity) will be used. The interim report of PSD will be made available to the WG for the May meeting.

– Point 2: Databases (DBs) underpinning the TTC concept.

The existing DBs in use were briefly discussed. It was agreed that GLP was not a pre-requisite for studies to be useful, particularly as data on particularly toxic substances might not have been generated under GLP. Concern was expressed about the age of some of the studies in the DB of Munro. There was also a need to understand the range of the NOELs for the substances falling below the 5th percentile (how low do they go?).

Question: Do we need to expand the existing DBs or re-analyse the existing data and plotting them in a different way? A proposal was made to examine the Munro database considering data on substances falling below the 10th percentile for class 1 and 3. Once the outcome of that exercise was clear, a decision could be taken on whether to search the open literature for newer data on a portion of the substances already in the DB, to see if new studies might lower the NOELs.

Actions:

[redacted] will calculate the cut off value for the 10th percentile.

[redacted] would look into the original studies for chemicals in class 3 to see if they would agree with the calculated NOELs that fall into the 10th percentile.

[redacted] will have a similar look at chemicals under the 10th percentile for class 1. [redacted] will also have a look at the other databases (DBs) to see what kind of data they contain, which endpoints have been studied, what level of detail they contain and whether they would be usable if we wished to enhance the TTC DB.

The Carcinogenic Potency DB, also known as the Gold DB, was discussed. The Gold DB has not been updated since 2001. EFSA received in 2008 a proposal for financing an update of the Gold database, but did not join this project. The Gold proposal will be circulated to the WG since it may contain interesting information for the discussion of the draft opinion. The WG discussed that an update of the Gold DB is unlikely to substantially change the present picture of the DB. It was pointed out that some of the data included are from old studies where the number of animals used per dose/experiment was five times less than what would now be acceptable. This implies that the statistical power of the recent experiments is higher.

There will be a need to comment on the issue of age of exposure at the start of carcinogenicity bioassays. The EPA considers and extra uncertainty factor should be built in to take account of that, but the UK Committee on Carcinogenicity disagrees commenting that the early exposure data are very poor.

It was pointed out that the use of linear extrapolation to derive a TTC value to cover the possibility of genotoxic carcinogenicity was contrary to the EFSA view that linear extrapolation should not be used for the risk assessment of genotoxic carcinogens. However, it was agreed that since the MOE approach preferred by EFSA does not yield a quantitative estimate of risk, for pragmatic reasons, there was no other option that to use the outcome of linear extrapolation for the TTC approach.

Actions:
Secretariat to circulate the Gold proposal and slides
[redacted] (maybe with the help of [redacted] and [redacted], not present at the meeting) will draft the text on cancer DBs.
[redacted] will draft the part about the non- cancer DBs.
[redacted] will draft a section on the pragmatic need to use linear extrapolation for the TTC

– Point 3: Derivation of the human threshold exposure values.
It is important to agree on the adequacy of the uncertainty factors (100 used by Munro). The need and usefulness of additional specific endpoints to set the thresholds was discussed. Is the 100 safety factor applicable in all instances? Are there endpoints not adequately covered by the use of 100 safety factor? What about threshold values for immunotoxicity, allergenicity, reprotox and developmental tox? The problem is the adequacy of the data to be put in the DB.

Actions:
[redacted] to link with [redacted] (who volunteered at the 1st meeting) to have a look at the reprotox data in the Munro DB.

– Point 4: Discussion of the Cramer et al. chemical class separation.

Action:
Secretariat to invite the Danish expert suggested at the first meeting [redacted] to give a presentation on the process of the chemical classification according to the Cramer scheme.

– Point 5: Possible use of physicochemical data and QSAR/read across to improve TTC as a tool.
The WG discussed whether the physicochemical characteristics of the chemical in the Munro DB were sufficiently representative of the "chemical space/the world of chemicals"
Consider the possibility to include information about electron density, polarity, molecular weight, vapour pressure, partition coefficient Log P/Log Kow values, as characteristic of the substances. This work could be outsourced by EFSA via an art. 36 call.

Action: Secretariat to explore the possibility of an art. 36 for data collection.
Point 5 will be addressed more in details at a later stage.

– Point 6: Use of kinetic data to improve TTC as a tool.
New software is available to explore the metabolic profile of a substance and how it would be detoxified.

Actions: EFSA secretariat will ask to [redacted] or [redacted] (CEF panel member) if they can direct us to information about software for predicting metabolism.

– Point 7: Relevant toxicological endpoints.
To be address more in details at the next meeting.

Actions: The **EFSA Secretariat** will screen the Munro paper (1996) and identify how many studies have used a particular endpoint type (e.g. how many used body weight, blood effects, reproductive effects etc) to derive the different NOELs.

– Point 8: Exclusion criteria for applying TTC approach.

Actions: [redacted] volunteered to draft a chapter on exclusion criteria (e.g. why metals have not been included). Some general text should be added to cover possible pitfalls on pulling out certain groups of chemicals (e.g. OPs) with the result that TTC values increase.

– Point 9: Applicability of TTC for mixtures.
This subject is being addressed by the ILSI-HESI WG. It should be mentioned in the EFSA opinion but will be addressed by cross-reference to the ILSI-HESI work.

– Point 10: Non-oral route of exposure, route to route extrapolation, species differences.
Action: [redacted] will provide some text for the next meeting

– Point 11: Exposure.
Action: [redacted] will start working with colleagues at her institute to develop some text.

– Point 12: Applicability of TTC in the various EFSA areas.
This point will be addressed at a later stage. The draft opinion will need to be circulated for panel consultation once ready.

7. COLIPA's comments on the TTC Opinion of the DG SANCO non-food Committees.
[redacted] (DG SANCO) gave a brief overview of the progress made by the WG of the non- food DG SANCO Committees on the draft opinion on the applicability of the TTC for risk assessment of chemicals, in particular for cosmetics. The comments received at the public consultation were such that additional discussions were needed. The non-food Committees have just been renewed and a meeting is scheduled to address the comments received. The date for the finalisation of the draft opinion is not known at present.

8. Applicability of QSAR TTC

[redacted], [redacted], gave an interesting presentation about the JRC activities on Computational Toxicology and on the Toxtree programme for classifying chemicals into the 3 Cramer classes (see also ppt presentation uploaded on the Extranet). The outcome of a JRC validation exercise (published as Patlewicz et al., 2008) was discussed and the JRC is now working on improvements proposed as a result of that exercise. The JRC has a DB of the original 82 compounds used by Cramer et al to develop their decision tree and a DB containing the 600 or so chemicals in the Munro DB.

[redacted] is, together with [redacted], responsible of the JRC-EFSA project on the applicability of QSAR analysis in assessing pesticide active metabolites toxicity.

Actions:
Secretariat to obtain the DBs of Cramer and Munro chemicals from JRC in case it would form a useful electronic basis for us to expand in future work.

9. Dates of the next meetings

3rd WG TTC	May 20th Wednesday, Schipool (Amsterdam airport)
4th WG TTC	July 10th Friday, Brussels
5th WG TTC	October 8th Thursday, Rome
6th WG TTC	December 10th Thursday, Brussels

Meeting times will be from 10.00 to 17.30.

End of meeting
The experts where thanked for their valuable input during the meeting.