Recent and Ongoing Scientific Projects on the Threshold of Toxicological Concern

Dr. Stephanie Melching-Kollmuss
EFSA/WHO TTC Stakeholder Day Brussels
December 2, 2014
ILSI Europe Update on Activities

Objective

- Overview of recent and ongoing scientific activities initiated by the ILSI Europe Threshold of Toxicological Concern (TTC) Task Force

Topics

- What is ILSI Europe?
- Expert Group on Unexpected Peaks
- COSMOS Expert Groups
- Expert Group Re-evaluation of the Cancer Database
- TTC Status & Research Needs
Ilmon Europe
Structure

- General Assembly
  - All member companies equally represented
  - Nomination Committee
  - Officers*
    - Board of Directors
      - 20 members
        - ≥ 50% academic members
    - Scientific Advisory Committee
      - 20 members
        - > 50% academic members
    - Publication Committee
      - ≥ 50% academic members
    - Food Safety Task Forces
      - Expert Groups
      - ≥ 50% non-industry members
    - Nutrition Task Forces
      - Expert Groups
    - Societal Aspects Task Force
      - Expert Groups

Member company representatives, observers, academia co-chairs

377 scientific publications since 1989
Expert Group on Unexpected Peaks (2009-2011)

• Driver: Trace substance in complex matrices can often not be fully identified by analytical experts, due to the lack of standard materials
• Main aspect:
  Substance classes excluded from TTC application & evaluation of their potential presence
• Outcome:
  • Step-wise approach using expert judgement on the source of the food & information on analytical techniques to assure that the partly identified substance does not belong to classes excluded from TTC
  • By following this step-wise approach, is possible in some cases to apply a TTC threshold of 90 µg/day for a non-fully identified substance in food
ILSI Europe: COSMOS and TTC Expert Groups

COSMOS

• Integrated in silico models for the prediction of human repeated dose toxicity of COSMetics to Optimise Safety: thresholds of toxicological concern (TTC), in silico toxicology, in vitro data and physiologically-based pharmacokinetic (PBPK) modelling

• Funding: European Community's FP7/2007-2013 and the European Personal Care Association Cosmetics Europe

ILSI Europe

• Partner of Work Package WP2

• Expert groups on the development of criteria to be applied in the extension of the current TTC approach to cosmetics ingredients

• Chemical domain of the Munro TTC database only includes few substances related to cosmetics \(\Rightarrow\) enhance oral TTC dataset by studies on cosmetics-related substances: Expert Group 1

• Expert Group 2 on the evaluation of oral-to-dermal extrapolation
ILSI Europe COSMOS TTC EG 1 – Enhancing the Database

**Relevant Chemical Space**
CosIng database (ca 9000 CAS) + US FDA VCRP list (ca 3700 CAS)
⇒ COSMOS 'Cosmetic Inventory'

**Toxicity data**
SCCS, FDA PAFA/CERES, IRIS, EPA
TOXREFDB, NTP, ECHA

(Data inclusion criteria)
(Duration, effects, species etc)

COSMOS Oral Repeated Dose Toxicity Database
Target organ, effect etc. per dose group for ca 230 cosmetic related chemicals
ILSI Europe COSMOS TTC EG 1 – Enhancing the Database

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Munro NOAELs (CosInv substances)
IRIS NOAELs (CosInv substances)

COSMOS TTC Database
Contains NOAEL information from different sources per substance

(Data Inclusion Criteria)
(Duration, effects, species etc)

(Structure Inclusion Criteria)
(Defined organic structure)
ILSI Europe COSMOS TTC EG 1 – TTC Dataset Build

COSMOS TTC Database
Contains NOAEL information from different sources per substance

Curation Framework
Basic rule: lowest NOAEL

Quality Control
• Most potent 10% of each Cramer class or significant discrepancies between NOAELs
• 130 substances reviewed by toxicologist group in 2012-2014

NOAEL Standardisation
• Duration extrapolation
• LOAEL to NOAEL extrapolation

COSMOS TTC Dataset
One oral NOAEL per substance. Ca. 500 new substances added. Cramer Class III less potent than of Munro dataset. Combined Munro /COSMOS dataset confirms Munro thresholds.
ILSI Europe COSMOS TTC EG 1 – TTC Dataset Build

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Publication planned to be submitted Q1/2015
Dataset will be publicly available
ILSI Europe COSMOS Expert Group 2

- Driver: Second aspect of application of TTC to Cosmetics: systemic exposure by dermal route to be assessed with oral data
- Note: this is widely done with substance specific data, not specific to TTC ⇒ Methodologies available.
- Approach: Review of different methodologies to estimate systemic exposure based on phys-chem parameters, (Q)SAR and/or in vitro / in vivo data
- Outcome: Recommendations on a state of the art tiered approach for inclusion of dermal availability information into the TTC decision tree
- The resulting manuscript intended to be submitted for publication in Q1/2015
Expert Group started in 2013: Reanalysis of the TTC Cancer Potency Dataset

- Derivation of the 1.5 & 0.15 µg/day thresholds for potential carcinogens was based on distributional analysis of a database comprising a mixture of genotoxic and non-genotoxic carcinogens, using linear extrapolation to a risk value of 1 in $10^6$ to determine the virtually safe doses in humans.

- The database is old, and the criteria for study inclusion and cancer potency estimate selection need adaptation to current knowledge and standards. New data to be added as available.

- In addition, segregating the database into DNA-reactive carcinogens, other types of genotoxic carcinogens (e.g. clastogens) and non-genotoxic carcinogens confirm the existing thresholds or define thresholds reflecting better current knowledge and approaches to carcinogen risk assessment.

- Current status: Expert Group agreed on conceptional aspects, identified datasets to work from, and develops the rule framework to search, assess and group the substances to enable the analysis.

- Activity will probably run until 2016, manuscript and dataset to be published.
Expert Group Cancer Potency Database - Approach

Database of compounds positive for carcinogenicity

Positive for mutagenicity

Assess if the TTC value of 0.15 μg/d is still appropriate

Negative for mutagenicity

Other genotoxicity

negative

Assess if the Cramer class III TTC value is appropriate

positive

Assess which TTC value is necessary and whether detected using structural alerts
Bioassays
Evaluate evidence for in vitro (bacterial) mutagenicity
- Positive: Probable mutagen
- Equivocal or negative: Extended evaluation of genotoxicity
  - Positive: Probable mutagen or clastogen/aneugen
  - Negative WoE: No evidence for genotoxicity: define PODs and Safe Doses

Capture

At this point, can already run initial analysis with mutagenic carcinogen group

Check performance of QSAR tools to identify both groups of probable genotoxins

FDA-CPDB (v.2012) & Kirkland et al. 2014 database + Data Search for new data
ILSI Europe TF View on the Status of the TTC Concept

TTC Concept cannot solve other general challenges of toxicology / risk assessment
- Route to route extrapolation
- Dose-response relationships
- Novel endpoints
- Exposure /Co-Exposure assessment
- Expertise and due diligence in application
- Transparency in risk assessment

Expecting something different?
ILSI Europe TF View on The Status of the TTC Concept

- Several aspects can be improved (see next slide) – should always be adapted to progress in science
- Still, the current concept is conservative and fit for the defined purposes (Who would try to connect a Smartphone to their 1967 car?)
- Scientific concept providing an alternative method to animal testing
- Society and risk managers expect safety assessors in authorities, academia and industry to provide conclusions. TTC is one of the possible tools.
## Research Needs

### As identified by the TTC Workshop 2011

(DeWhurst & Renwick 2013 Reg Tox Pharm 65:168-177)

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<thead>
<tr>
<th>Opportunities: fine-tune the method by expanding the toxicological databases and reviewing the chemical classes in the COC, and to update and modify the Cramer et al. (1978) and Kroes et al. (2004) decision trees</th>
<th>Status /Aspects</th>
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<td>• Database expansions were e.g. coordinated by ILSI/HESI NA for antimicrobials and COSMOS/ILSI EU on cosmetic related substances (oral route)</td>
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<td>• Cancer database update has started</td>
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<td>• Cramer scheme addressed by IOFI – further work is needed</td>
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| Future revised and expanded toxicological databases should be freely available and searchable | Not all current TTC databases are truly freely available for future work by other groups. This should become a requirement for all funding of work. Work based on proprietary data can often only provide supporting evidence. |

| Any changes to the Cramer et al. (1978) and Kroes et al. (2004) decision trees or to the TTC values derived from revised databases should be subject to transparent global peer review, in order to ensure wide regulatory acceptance | Relevant data are accessible and more will become available. What is needed is engagement and consensus by regulators and academia to create solutions for public health for non-regulated natural and man-made substances. |

| (additional aspect) | Uncertainty associated with TTC as compared to specific data-based assessment should be addressed scientifically. |
Expert Group Contributors*:
Computational Experts, Analytical Experts, Toxicologists

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<th>Organization</th>
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* COSMOS and Cancer Potency EGs – omitted many more from previous years
ILSI Europe Publications on TTC


S. Koster, A. Boobis, *et al.* Application of the TTC concept to unknown substances found in analysis of foods. *Food and Chemical Toxicology* 2011;49:1643-1660.


