Threshold of Toxicological Concern (TTC):

Introduction into the Tiered TTC Concept and regulatory status globally

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The Threshold of Toxicological Concern is a risk assessment concept that involves establishing an exposure threshold below which there is a low probability of adverse effects for chemicals lacking sufficient toxicity data.

Based on analysis of the distribution of toxicity data from available databases, making conservative assumptions about the potential for toxicity of the untested chemical...
Why is this so important?

• Analytical chemistry is detecting substances at lower and lower concentrations

• Reduce animal testing

• Prioritization of limited resources and to focus on those exposures of concern
A Brief History of the TTC Concept...

• TTC was first formally proposed in 1967 as a way to manage exposures to indirect food additives from packaging and was codified as in the US FDA food packaging regulations in 1995

• “Scientific Evidence and Common Sense"
  • Title of the 1967 publication proposing a TTC concept (Frawley Fd. Cosmet Toxicol 5: 293).
  • "We [have] committed ourselves to an "omnibus" permissive list, containing every conceivable chemical which might even remotely come in contact with food. ....These regulations contain over 43,000 words … "

ILSI Europe
US FDA’s Threshold of Regulation

- The US FDA regulation specifies a limit for projected dietary exposure of 0.5 ppb, translating into a daily exposure of 1.5 ug/day.

- Based on analysis of 477 chemical carcinogens from the Gold et al. (1984) carcinogenic potency database.

Graph adapted from Munro et al., 1990, Rulis 1986.
Beyond a single TTC Limit of 1.5 ug/day

"On the basis of accumulated knowledge, it is theoretically possible to establish a range of threshold values representing the full spectrum of toxicological endpoints including both carcinogenic and non-carcinogenic effects."

— Munro et al., 1999
Cramer et al. (1978) proposed a tool for classifying chemicals according to levels of concern based on chemical structure, (and metabolism, toxicity, natural occurrence)

Uses a decision tree approach to group chemicals into three broad structural classes based on a review of chronic and sub-chronic data for non-cancer endpoints.

- **Class I**: low order of toxicity
- **Class II**: Intermediate
- **Class III**: Possible significant toxicity
Defining the TTC Tiers: Noncancer
The Cramer* Classification Tree

Sorting questions
• Is the substance heterocyclic?
  • Yes – Proceed to Q#8
  • No – Proceed to Q#16
• Is the substance readily hydrolyzed to mononuclear residues?
  • Yes – Proceed to Q#22
  • No – Proceed to Q#33

Classification questions
• Does the substance contain any of the following functional groups: aliphatic secondary amine, cyano, N-nitroso, diazo, triazeno groups?
  • Yes – Classification III
  • No – Proceed to Q#3

Class I: low order of toxicity
Class II: Intermediate
Class III: Possible significant toxicity

Fig. 1. A schematic diagram of a decision tree for the estimation of probable toxicity. Assessors should (a) start with question 1, (b) proceed by "no" or "yes", (c) move from any underscored number encountered to same circled number and (d) proceed to final classes I, II or III. Working downwards through the tree, the symbols designate the following groupings: biological normality (● ● ●), high and low toxicity (● ● ●), heterocycles (→), terpenoids (→ ●); aliphatics (● ● ○); aromatics (● ○ ○); alicyclics (● ● ●).
TTC Tiers for Noncancer Endpoints (90, 540 and 1800 ug/day)

Fig. 1. Empirical cumulative distributions of NOELS of compounds in the reference database and log-normally fitted cumulative distributions (solid lines). Compounds have been grouped into the structural classes I, II and III of Cramer et al. (1978).

Munro et al., 1996
TTC Tiers for Noncancer Endpoints (90, 540 and 1800 ug/day)

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## Munro "5th percentile NOELs" and TTC Exposure Limits

<table>
<thead>
<tr>
<th>Cramer Class</th>
<th>Number of Chemicals</th>
<th>5th percentile NOEL</th>
<th>TTC Exposure Limit*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cramer Class III (most toxic)</td>
<td>137</td>
<td>0.15 mg/kg/d</td>
<td>90 µg/d (1.5 µg/kg/d)</td>
</tr>
<tr>
<td>Cramer Class II (intermediate)</td>
<td>28</td>
<td>0.91 mg/kg/day</td>
<td>540 µg/d (9 µg/kg/d)</td>
</tr>
<tr>
<td>Cramer Class I (least toxic)</td>
<td>447</td>
<td>3 mg/kg/day</td>
<td>1800 µg/d (30 µg/kg/d)</td>
</tr>
</tbody>
</table>

* TTC Exposure Limit incorporates 100X uncertainty factor and assumes 60 kg body weight
TTC Next Expanded to Include Tiers for Chemicals with Structural Alerts (SA’s) for Genotoxicity

- Based on same analysis that led to FDA’s ToR of 1.5 ug/d.
- Limit established for chemicals with SA’s of 0.15 ug/d.
### Kroes et al., 2004 Tiered TTC

<table>
<thead>
<tr>
<th>Tier</th>
<th>Exposure Limit (µg/day)</th>
<th>Exposure Limit (µg/ kg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exclusions (e.g. metals, proteins, bioaccumulation potential; very high potency carcinogens)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemical with Structural Alerts</td>
<td>0.15</td>
<td>0.0025</td>
</tr>
<tr>
<td>No structural alerts (FDA ToR)</td>
<td>1.5</td>
<td>0.025</td>
</tr>
<tr>
<td>Organophosphates</td>
<td>18</td>
<td>0.3</td>
</tr>
<tr>
<td>Cramer Class III</td>
<td>90</td>
<td>1.5</td>
</tr>
<tr>
<td>Cramer Class II</td>
<td>540</td>
<td>9</td>
</tr>
<tr>
<td>Cramer Class I</td>
<td>1800</td>
<td>30</td>
</tr>
</tbody>
</table>

Kroes et al., 2004: FCT, 42: 65-83
External Use/Acceptance of TTC

- Food (JECFA, EFSA);
- Cosmetics (SCCS);
- Pharmaceuticals (EMA, FDA);
- Chemicals
  - WHO
  - REACH
  - Agriculture, Drinking water
External Acceptance of TTC

Most recent efforts: WHO /EFSA TTC workshop Draft conclusions Feb 2015 - key points

• Confirming the TTC approach as a valid, science-based screening tool, useful for the prioritization of chemicals and in chemical risk assessment;

• Supporting the need to establish an independent organization to combine and manage TTC databases;

• Flagging the importance of continuing scientific research for refinement and improvement of the approach.
Summary

• The TTC approach is a pragmatic screening and prioritization tool for low level exposures used > 20 years;
• Application of TTC should be done on a case-by-case basis taking into account information on toxicity and exposure;
• No distinction between toxicity induced by intentionally added ingredients or inadvertent contaminants;
• TTC protective for the population including infants/children (reco is case-by-case for infants under 3 month) Units: ug/kg/day.
Expanding the Applicability of TTC

In concept, TTC is relevant to any human exposure. In practice, it is limited by the underlying databases, supporting analyses, and also by regulatory/legal barriers.

Future Opportunities

• Update/expand the cancer DB (Cefic RfP);
• Update expand the non-cancer databases (Cosmos);
• TTC for route of inhalation;
• TTC for shorter exposures (LTL).
TTC slides kindly provided by Susan Felter, Procter & Gamble