Cancer thresholds, Cohort of Concern and other excluded substance groups

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The TTC approach

- A TTC value is:
  - A human exposure value for a chemical of unknown toxicity below which the probability of adverse effects on human health is considered to be very low following (oral) exposure for a lifetime

Murray-Rust et al, 1997
Why carcinogenicity is an issue in the application of the TTC approach

- It is not currently possible to predict reliably the carcinogenicity of a specific chemical on the basis of structure alone.
- When chemicals are carcinogenic, carcinogenicity is usually the most sensitive endpoint (assuming low-dose linear extrapolation).
- Hence, a TTC value based on carcinogenicity should be protective of all potential adverse effects.
A Web page (Margin of Exposure) provides a broad perspective on possible cancer hazards from human exposures to chemicals that cause cancer in high dose rodent cancer tests. Exposures are given in graphic and table formats, including high historical exposures to workers, pharmaceuticals, natural chemicals in the average diet, air pollutants, food additives, and pesticide residues.

A supplement to the CPDB was added in August 2007, which includes results on 66 new chemicals and new results for 52 chemicals already in the CPDB. All Web pages on this Web site have been updated to reflect these additions, including plots, summary tables, and Excel files. Click here for a list of new chemicals and a list of earlier chemicals with new data.
Extrapolation to VSD

Response (incidence) vs Dose

Linear extrapolation

Model fitted to experimental observations

TD50

VSD
If assume 10% of chemicals are carcinogens, there is only 4% chance that risk will be $\geq 10^{-6}$ with TTC of 1.5 $\mu$g/person per day.
The TOR/threshold of concern (1.5 µg/person per day) was based on the probability, in the absence of evidence, that any new chemical was likely to be a carcinogen.

What is acceptable exposure for a compound that is predicted to be a genotoxic carcinogen?
Potency of specific groups of compounds

Cohort of Concern (CoC)
Exclude from TTC approach on basis of structure

Kroes, 2005
TTC for compounds with evidence of genotoxicity

Specific groups of potent genotoxic carcinogens (CoC) excluded

Relative probability density

-Log$_{10}$ Dose (mg/kg bodyweight per day)

Potency

Identification of genotoxins and the TTC approach

- Exposure at a level of ≤ 0.15 µg/person per day (0.0025 µg/kg bw per day) to compounds which are genotoxic (excluding CoC) would be of negligible risk.
- Exposure to compounds that are not genotoxic should not be of concern at levels some way above 0.0025 µg/kg bw per day.
- Provides basis for tiered approach to TTC, with different TTC values for likely genotoxins and non-genotoxins.
- Prediction of potential genotoxins?
Structural alerts for genotoxicity

From Ashby & Tennant, 1988
Threshold of Toxicological Concern (TTC) for Cramer classes

Thresholds:
- 0.15 mg/kg/d (1.5 µg/kg/day)
- 0.9 mg/kg/d (9 µg/kg/day)
- 3 mg/kg/d (30 µg/kg/day)

NOEL (mg/kg/day):
- N=137
- N=447
- N=28

(TTC = NOEL/100)
Bioaccumulative compounds

**Rat**

![Graph showing TCDD concentrations in rat liver and adipose tissue](image)

- Miniero et al, 1996

**Human**

- Aylward et al, 2005

  - PTMI: 70 pg/kg bw
  - TD50: 23.5 ng/kg bw/d

**Equation**

\[
Y = (0.721 \pm 0.043)X - (0.20 \pm 0.30)
\]

**Statistics**

- \( R = 0.969 \)
- \( P_R = <<0.001 \)
- \( F(1,16) = 262 \)
- \( P_F = <<0.001 \)
Proteins

- Hazelnut
- Peanut
- Celery
- Fish
- Shrimp

LOAEL
NOAEL

Ballmer-Weber et al, 2015
Inorganic compounds and organo-metallics

- Inorganic compounds
- Metals, including essential metals, and organometallics
- Organo-silicon compounds

- Not represented in Munro et al database
- Some are bioaccumulative and/or very potent
  - Lead: Not possible to establish a PTWI (no threshold)
  - Cadmium: PTWI = 2.5 µg/kg bw (EFSA) (cf 0.36 µg/kg/day) [Cramer class III = 1.5 µg/kg/d]
Endocrine active substances

- TTC values are adequately protective for the types of adverse effect that standard reproductive and developmental toxicity studies can detect.
- Some substances with a steroid structure have potent endocrine activity, which may lead to adverse effects.
- It would be premature to draw any firm conclusions about the application of the TTC approach in relation to substances that might have endocrine activity.
- If there are data showing that a substance has endocrine activity, then the risk assessment should be based on those data, rather than using the TTC approach.
- For untested substances, those with steroid structures should not be evaluated using the TTC approach.

Estradiol: ADI = 0.05 µg/kg bw per day (JECFA)
Exclusion categories (2015)

- High potency carcinogens (i.e. aflatoxin-like, azoxy-, N-nitroso compounds, benzidines)
- Inorganic chemicals
- Metals, including essential metals, and organometallics
- Organo-silicon compounds
- Proteins
- Steroids
- Substances known/predicted to bioaccumulate (e.g. polyhalogenated-dibenzodioxins, -dibenzofurans, -biphenyls)
- Insoluble nanomaterials
- Radioactive substances
Proposed EFSA-WHO decision tree (2015) (part 1)

1. Is the substance part of the exclusionary categories?

   NO
   
   2. Are there structural alerts or chemical-specific genotoxicity data, such as DNA-binding and Ames tests, that indicate the chemical may be a DNA-reactive carcinogen, based on the weight of evidence?

      NO
      
      Non-genotoxic considerations [OPs+ Cramer classes]

      YES
      
      These steps can be taken concurrently or in reverse order, depending on need.

3. Does estimated intake exceed TTC of 0.0025 μg/kg bw/day?

   YES
   
   Risk assessment required

   NO
   
   Substance would not be expected to be a safety concern - low probability that lifetime cancer risk exceeds 1 in $10^6$
Next steps

- ILSI Europe Expert Group: Reanalysis of the Cancer Potency Database Underpinning the 0.15 µg/day Tier of the TTC (started mid-2013)

- CEFIC Long-range Research Initiative Request for Proposals: Database on Carcinogen Dose-response, including Information on DNA reactivity, for TTC and beyond (deadline 06/09/15)