



# Use of TTC and Human Relevance

George E. N. Kass, PhD

Future Challenges in Developing Assessment Methodologies for Human Health Effects – Tokyo, 14 November 2018

# Disclaimer

The views, thoughts and opinions presented are not necessarily those of EFSA

# Introduction to the concept of TTC

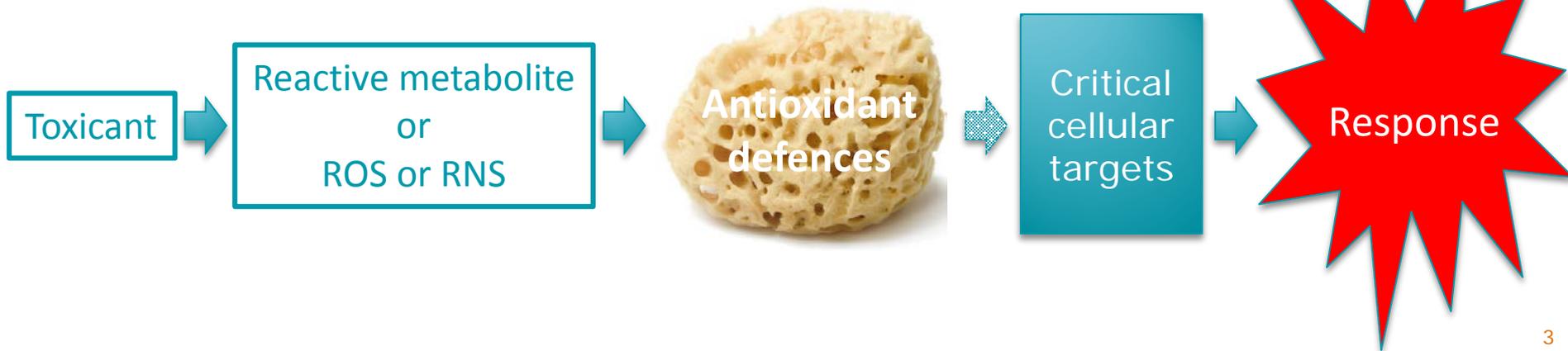


German: 'Alle Ding sind Gift und nichts ohn' Gift; allein die Dosis macht, das ein Ding kein Gift ist.

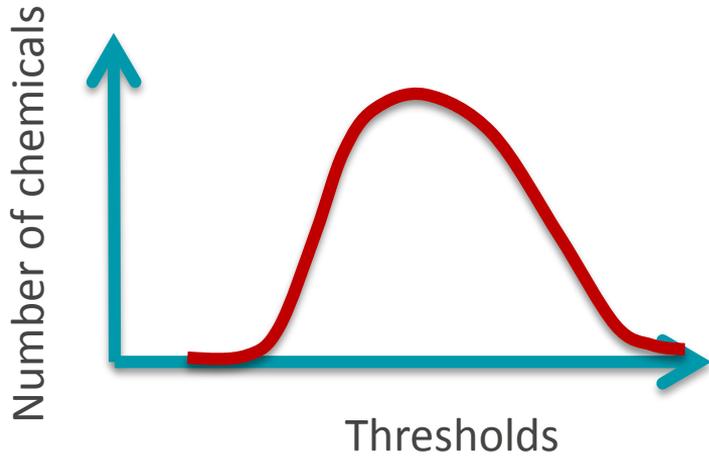
English: All things are poison and nothing (is) without poison; only the dose makes that a thing is no poison.

**Theophrastus von Hohenheim**  
**'Paracelsus'**  
**1493 (or 1494) - 1541**

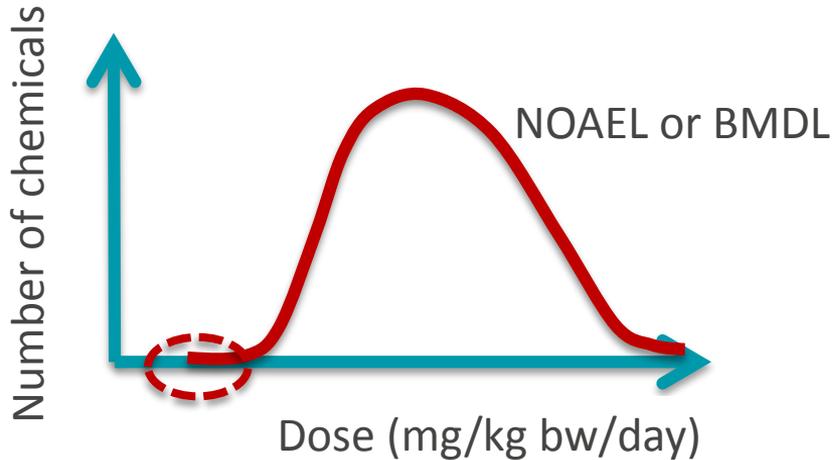
## Concept of threshold



# Introduction to the concept of TTC



# Introduction to the concept of TTC



ELSEVIER

Food and Cosmetics Toxicology

Volume 5, 1967, Pages 293-308



BIBRA Annual Scientific Meeting

Scientific evidence and common sense as a basis  
for food-packaging regulations \*

J.P. Frawley

Hercules Incorporated, Wilmington, Delaware 19899, USA

# FDA develops the concept of TOR

- 1980's & the US Food and Drug Administration (FDA)
  - Concept of 'virtually safe doses' (VSDs) for humans from **carcinogenic potency** data from animal studies (Rulis, 1987).
  - VSD = estimate of the dietary exposure to a carcinogen which could give rise to less than a one in a million lifetime risk of cancer.
  - The distribution of VSDs was used to generate a **Threshold of Regulation (TOR)**.
    - a concentration of 0.5  $\mu\text{g}/\text{kg}$  of diet (0.5 ppb) or 1.5  $\mu\text{g}/\text{person per day}$

# FDA develops the concept of TOR

- FDA considered that with a dietary exposure to an individual substance below the TOR, the consumers would be protected 'with reasonable certainty of no harm', even if that substance was later shown to be a carcinogen.
- 1995: FDA incorporated this threshold value in its TOR policy for substances present in **food contact materials**.

## 1990-1996: Development of the TTC concept by Munro and colleagues

- Compilation of a database of 613 chemicals
  - Oral toxicity studies
  - Non-cancer endpoints with corresponding NOELS
  - Sub-chronic, chronic and reprotox studies



Pergamon

*Food and Chemical Toxicology* 34 (1996) 829-867



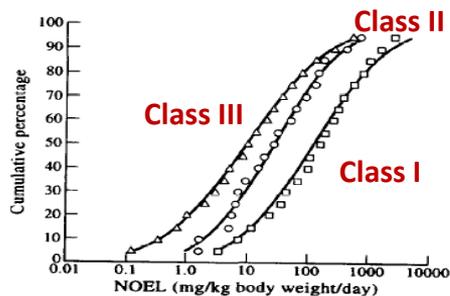
### *Regulatory*

#### Correlation of Structural Class with No-Observed-Effect Levels: A Proposal for Establishing a Threshold of Concern

I. C. MUNRO, R. A. FORD\*, E. KENNEPOHL† and J. G. SPRENGER  
CanTox Inc., 2233 Argentia Road, Suite 308, Mississauga, Ontario, Canada L5N 2X7 and \*Research  
Institute for Fragrance Materials, Inc., Two University Plaza, Suite 408, Hackensack, NJ 07601, USA

- Division of the database into the three classes developed by Cramer and colleagues (1978)
  - Cramer Class I: chemicals of simple structure, with efficient modes of metabolism, suggesting low oral toxicity
  - Cramer Class II: chemicals with structures less innocuous than Cramer Class I but without features suggesting significant toxicity
  - Cramer Class III: chemicals with structures suggesting significant toxicity or which did not permit any strong initial presumption of safety

# 1990-1996: Development of the TTC concept by Munro and colleagues



- Derivation of human threshold values by

1. Taking the lower 5<sup>th</sup> percentile value of the distribution of NOELs for the substances in each of the three Cramer structural classes
2. Multiplying by 60 to convert the values expressed as mg/kg bw per day into mg/person per day
3. Dividing by a factor of 100 to ensure a margin of safety.

Cramer Structural Class	Fifth percentile NOEL (mg/kg bw per day)	Human exposure threshold (mg/person per day)
I	3.0	1.8
II	0.91	0.54
III	0.15	0.09

# Next step: refinement of the TTC



ELSEVIER

Food and Chemical Toxicology 42 (2004) 65–83



Food and Chemical  
Toxicology

[www.elsevier.com/locate/foodchemtox](http://www.elsevier.com/locate/foodchemtox)

## Structure-based thresholds of toxicological concern (TTC): guidance for application to substances present at low levels in the diet

R. Kroes<sup>a</sup>, A.G. Renwick<sup>b</sup>, M. Cheeseman<sup>c</sup>, J. Kleiner<sup>d,\*</sup>, I. Mangelsdorf<sup>e</sup>,  
A. Piersma<sup>f</sup>, B. Schilter<sup>g</sup>, J. Schlatter<sup>h</sup>, F. van Schothorst<sup>e</sup>, J.G. Vos<sup>f</sup>, G. Würtzen<sup>i</sup>

- Decision-tree approach for the application of TTC
- Substance exclusion criteria
  - polyhalogenated-dibenzodioxins, -dibenzofurans and -biphenyls
  - non-essential metals in elemental, ionic or organic forms and other inorganic substances
  - proteins
  - aflatoxin-like, azoxy- and N-nitroso- compounds
- Introduction of separate threshold values for
  - organophosphates (TTC value of 18 µg/person per day)
  - compounds with structural alerts for genotoxicity (TTC value of 0.15 µg/person per day)

# TTC as a Tool for Safety Assessment: First uses

- ❖ 1995: JECFA
  - Considered for the evaluation of **flavourings** by the JECFA
  - TTC approach used in the evaluation of ~2000 flavourings
- ❖ 1996: Scientific Committee on Food
  - First discussions on concept of 'threshold of concern'
  - The concept of TTC was considered rational, pragmatic and scientifically valid'
- ❖ 1999: Scientific Committee on Food
  - Opinion on a programme for the evaluation of flavourings.
  - The JECFA procedure seen as reasonable and pragmatic approach that could be used for flavourings
  - Use of Cramer's three structural classes (I, II, III) and the corresponding TTC values for the risk assessment of flavourings

# Use of TTC by EFSA

- Since 2004: Use of the JECFA procedure (slightly modified) for the evaluation of **flavourings** by EFSA.



EFSA Journal 2010; 8(6):1623

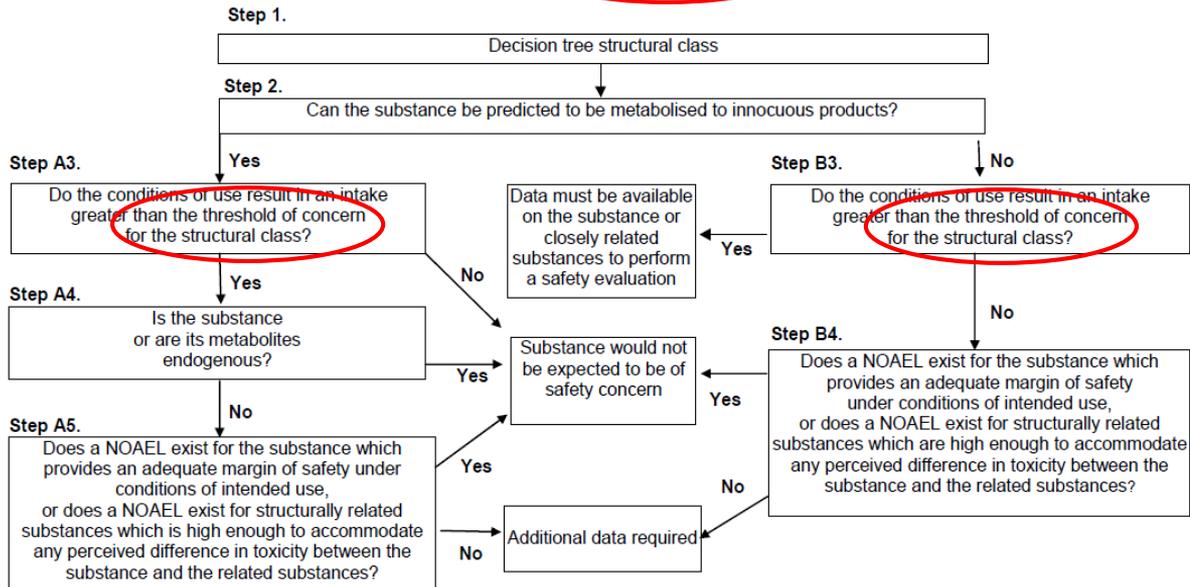
## SCIENTIFIC OPINION

**Guidance on the data required  
for the risk assessment of flavourings to be used in or on foods<sup>1</sup>**

**EFSA Panel on Food Contact Materials,  
Enzymes, Flavourings and Processing Aids<sup>2,3</sup>**

European Food Safety Authority (EFSA), Parma, Italy

## Procedure for safety evaluation of chemically defined flavouring substances



Note: BMDL may be used instead of NOAEL.

## SCIENTIFIC OPINION

### **Scientific Opinion on Exploring options for providing advice about possible human health risks based on the concept of Threshold of Toxicological Concern (TTC)<sup>1</sup>**

**EFSA Scientific Committee<sup>2,3</sup>**

European Food Safety Authority (EFSA), Parma, Italy

*'[T]he TTC approach can be recommended as a useful screening tool either for priority setting or for deciding whether exposure to a substance is so low that the probability of adverse health effects is low and that no further data are necessary.'*

**Review of the Threshold of Toxicological Concern (TTC)  
approach and development of new TTC decision tree**  
**European Food Safety Authority and World Health Organization**

## Rationale

- ❑ To continue (joint) validation and (consistent) implementation of **harmonised methods for chemical risk assessment** such as TTC, read-across, omics etc.
- ❑ To introduce **improvements in the scientific substantiation of the TTC approach** where needed.
- ❑ To meet TTC experts worldwide **to stimulate a proper implementation of the approach internationally.**

# Use of TTC by EFSA

- Flavouring substances in food (EFSA, 2010)
- Impurities, metabolites and degradation products of food additives (EFSA, 2012)
- Pharmacologically active substances present in food of animal origin (EFSA, 2018)
- Some metabolites and degradation products of plant protection products in the context of residue definition for risk assessment (EFSA, 2016)
- The derivation of 'maximum acceptable feed concentrations' for flavouring additives based on default values for feed consumption (EFSA, 2017)
- The development of the criteria for the safety evaluation of mechanical processes to produce recycled poly(ethylene terephthalate) (PET) intended to be used for manufacture of materials and articles in contact with food (EFSA, 2011)
- Chemical mixtures (EFSA, 2018 – in preparation)

## GUIDANCE DOCUMENT



ADOPTED: date

doi:10.2903/j.efsa.20YY.NNNN

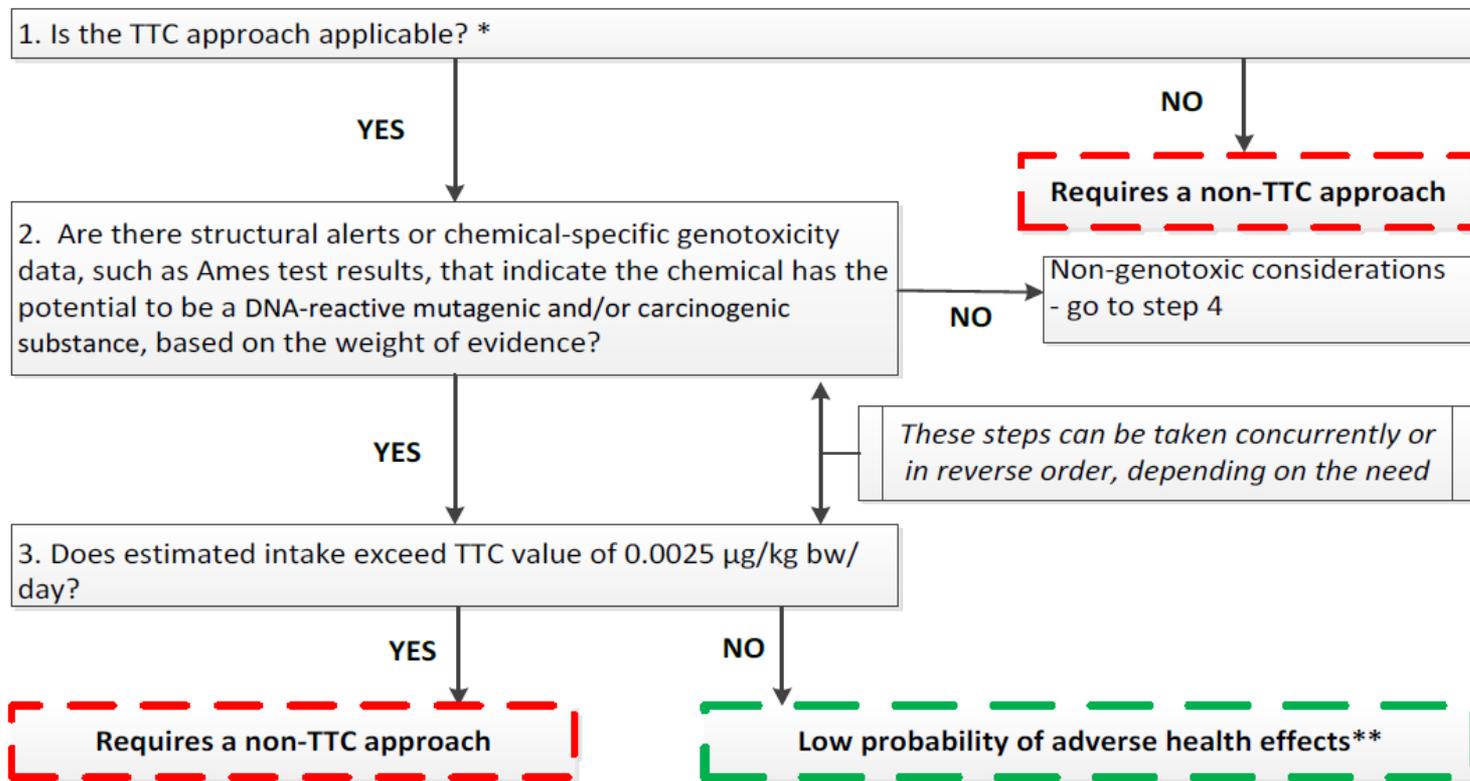
1                   **Guidance on the use of the Threshold of Toxicological**  
2                   **Concern approach in food safety assessment**

3                   EFSA Scientific Committee

4                   Simon J. More, Vasileios Bampidis, Diane Benford, Jos Boester, Claude Bragard, Thorhallur I  
5                   Halldorsson, Antonio F Hernández-Jerez, Susanne Houliard Bennekou, Konstantinos P  
6                   Koutsoumanis, Hanspeter Naegeli, Søren S Nielsen, Josef R Schlatter, Dieter Schrenk,  
7                   Vittorio Silano, Dominique Turck, Maged Younes, Ursula Gundert-Remy, George E N Kass,  
8                   Juliane Kleiner, Daniela Maurigi, Anna Maria Rossi, Rositsa Serafimova, Linda Reilly and  
9                   Hilary M Wallace

Public consultation  
9 November - 1 January

# The new EFSA TTC Decision Tree (I)



# The new EFSA TTC Decision Tree (II)

4. Is the compound an organophosphate or carbamate?

NO

6. Is the compound in the Cramer class III ?

YES

5. Does estimated intake exceed TTC value of 0.3  $\mu\text{g}/\text{kg bw}/\text{day}$ ?

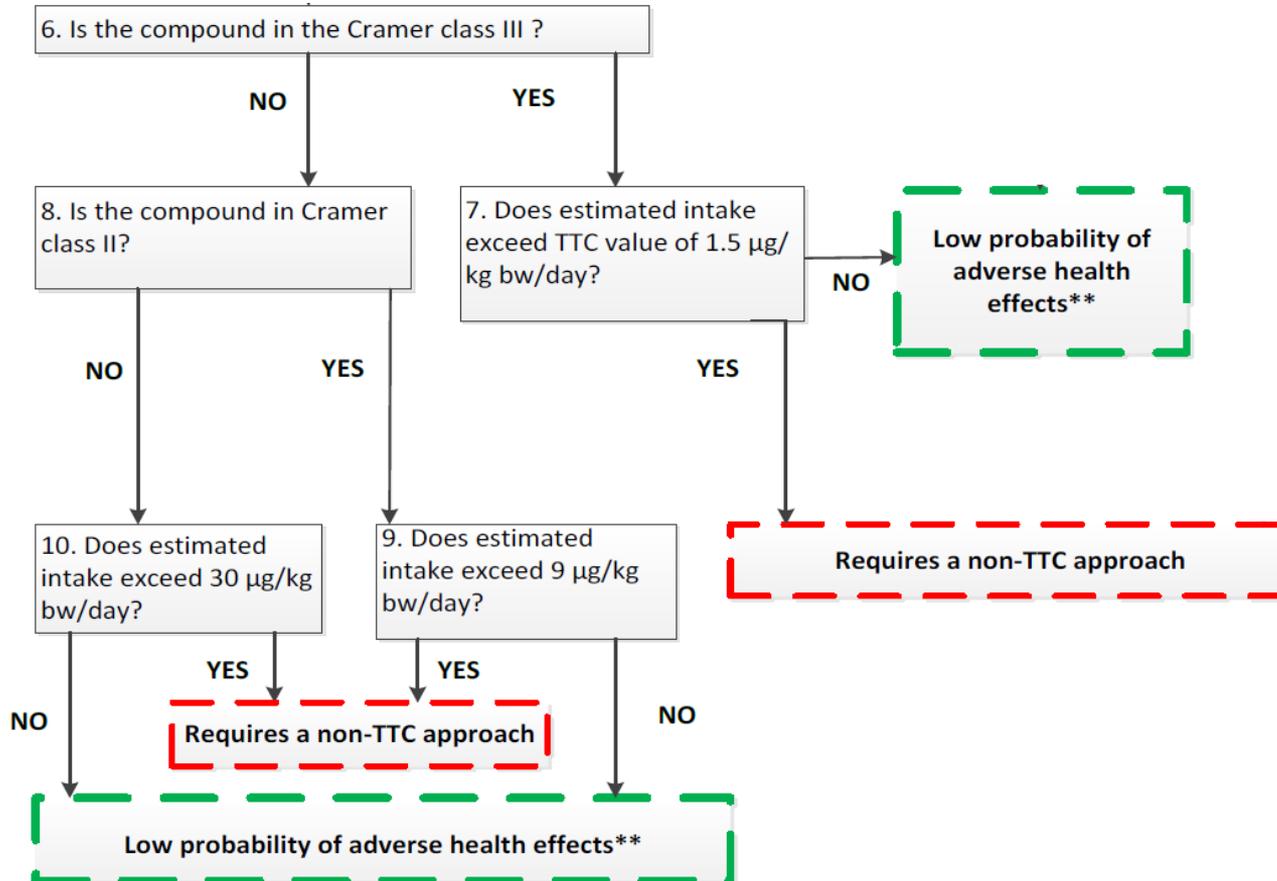
NO

YES

Low probability of adverse health effects\*\*

Requires a non-TTC approach

# The new EFSA TTC Decision Tree (III)



# Critics of the TTC



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## News Press Release

**Latest Press Releases** 30th August 2011  
**Press Release Archive** Brussels

**PAN Europe in the news** Food Authority EFSA embraces industry proposal to stop safety testing of chemicals

**Contact** European food watchdog EFSA proposes to substitute the actual testing of chemicals with a fixed exposure figure[1]. An adult can – according to EFSA – for most chemicals[2] safely eat 90 microgrammes (µg) of a single chemical every day for his or her entire life, called the TTC (Threshold of Toxicological Concern). The TTC is a proposal developed by the pesticide industry and is far from safe.

The TTC is based on old, outdated company data which EFSA has not checked because the original studies are non-retrievable. The TTC is calculated by excluding the most toxic (5th percentile) chemicals of the database. This means many chemicals in the industry database itself show toxic effects below this "safe" TTC derived level. The pesticide Dieldrin is 30 times more toxic than the TTC derived level.

By way of this manipulation, TTC is set at an extremely high level of exposure, allowing all kind of untested chemicals easy market access. In addition, infants, which are known to be more vulnerable, are not protected by the TTC and mixtures of chemicals are not calculated. The TTC is scientifically unjustifiable, artificially puts TTC at an extremely high level, puts adults, babies and children at great risk and only serves to get unlimited market access for chemicals.

The findings of independent (non-industry) scientific literature were not taken into account in setting the TTC. PAN Europe could easily falsify the extremely high TTC threshold with such independent scientific data. For endocrine disrupting chemicals, doses that are lower than the TTC

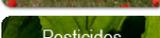


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## News Press Release

**Latest Press Releases** 19th December 2012  
**Press Release Archive** Brussels

**PAN Europe in the news** Network of industry agents uncovered in Food Authority EFSA

**Contact** A new PAN Europe report reveals that 10 out of 13 members of the EFSA working group on TTC (Threshold of Toxicological Concern, a method to decide on the health impacts of chemicals), have a conflict of interest. TTC is an industry-driven approach and these members have been developing or promoting this method in the past jointly with industry. The interlinking of these people shows they are operating as a network.

Not surprisingly, the 'independent' assessment by EFSA of the usefulness of TTC was very positive. It is like asking Coca Cola to do an independent assessment of Coca Cola products. Industry's interest can be explained by the massive cost reductions TTC will bring if chemicals of unknown toxicity will be deemed safe below a certain exposure threshold. In these cases, expensive safety testing will not be needed anymore and market access is granted quickly.

The analysis made by PAN Europe shows that the 10 EFSA working group members all have ties to industry or industry lobby club ILSI (International Life Science Institute) by direct contracts, formal positions or joint publications. This means that EFSA does not take her self-declared independency seriously. Even EFSA staff is part of an ILSI taskforce. In addition, only three members of the working group are actively publishing scientists which raises serious questions about the scientific quality of the EFSA opinion.



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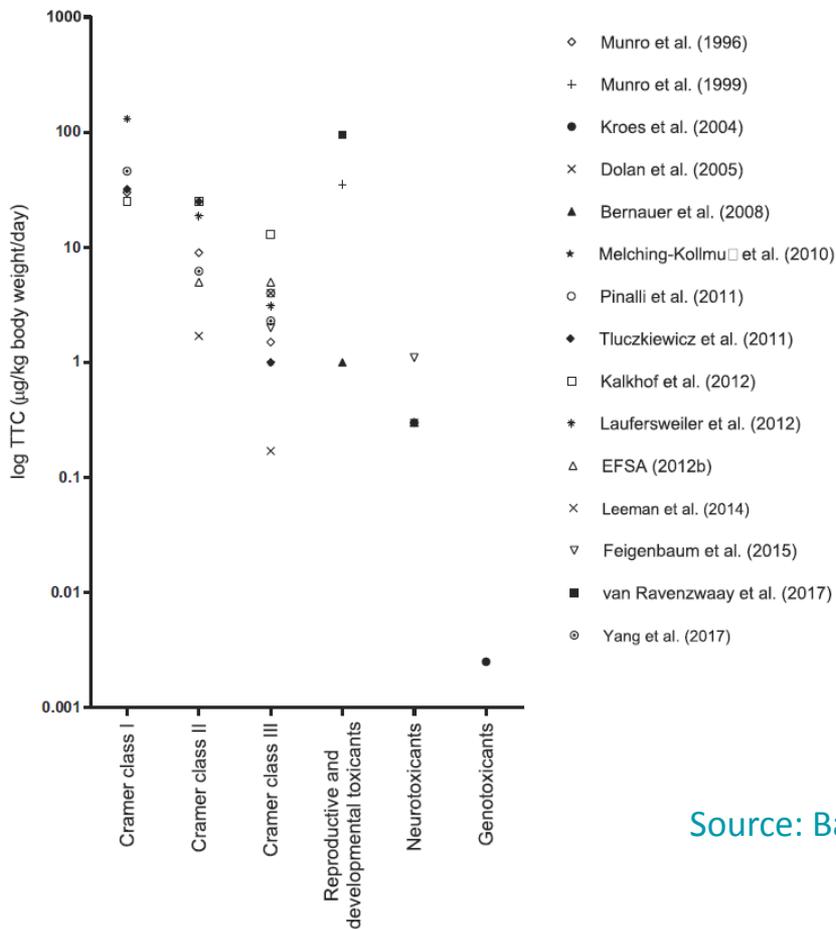
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# Validation of the TTC values



Source: Baken et al. *Envir. Int.* 118, 293-303, 2018

# Summary and Conclusions

1. The TTC approach is a conservative screening and prioritization tool for the safety assessment of chemicals
  - when hazard data are incomplete
  - when human exposure can be estimated and is very low
  - when the identity of the chemical is fully known
  - when the chemical is within the application domain of the TTC
  - when EU legislation **does not** request sector-specific toxicity data
2. TTC approach recognised as such by different organisations, e.g.
  - WHO (International Programme on Chemical Safety (IPCS))
  - JECFA
  - EFSA
  - FDA
  - EMA

# どうもありがとうございました

