Threshold of Toxicological Concern (TTC)

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American® Chemistry Council

Threshold of Toxicological Concern (TTC)

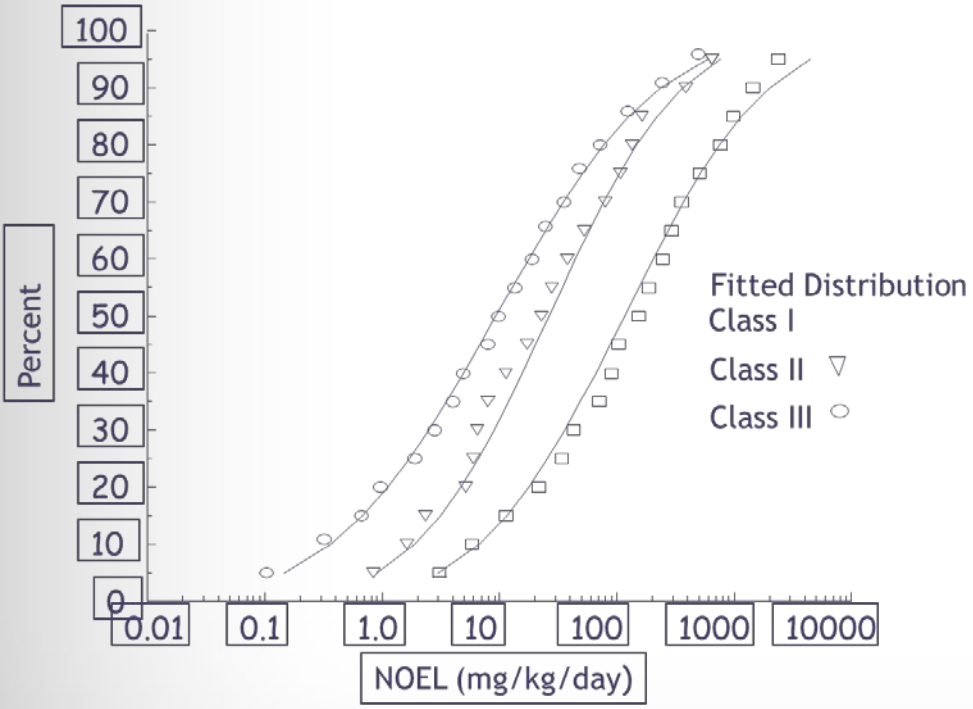
What is the TTC?

Potential uses of the TTC

Recommendations for exploring utility of TTC as a NAM within safety evaluation programs

Threshold of Toxicological Concern (TTC)

TTC is based on frequency distributions (5th percentile) of NOAELs of systemic toxicants



- TTC: a health protective human exposure reference value for daily exposure over a lifetime below which there would be no appreciable risk to human health (similar to an reference dose)
- TTC – based on accumulated data & knowledge regarding the distribution of potencies of relevant classes of chemicals for which solid toxicity data exist

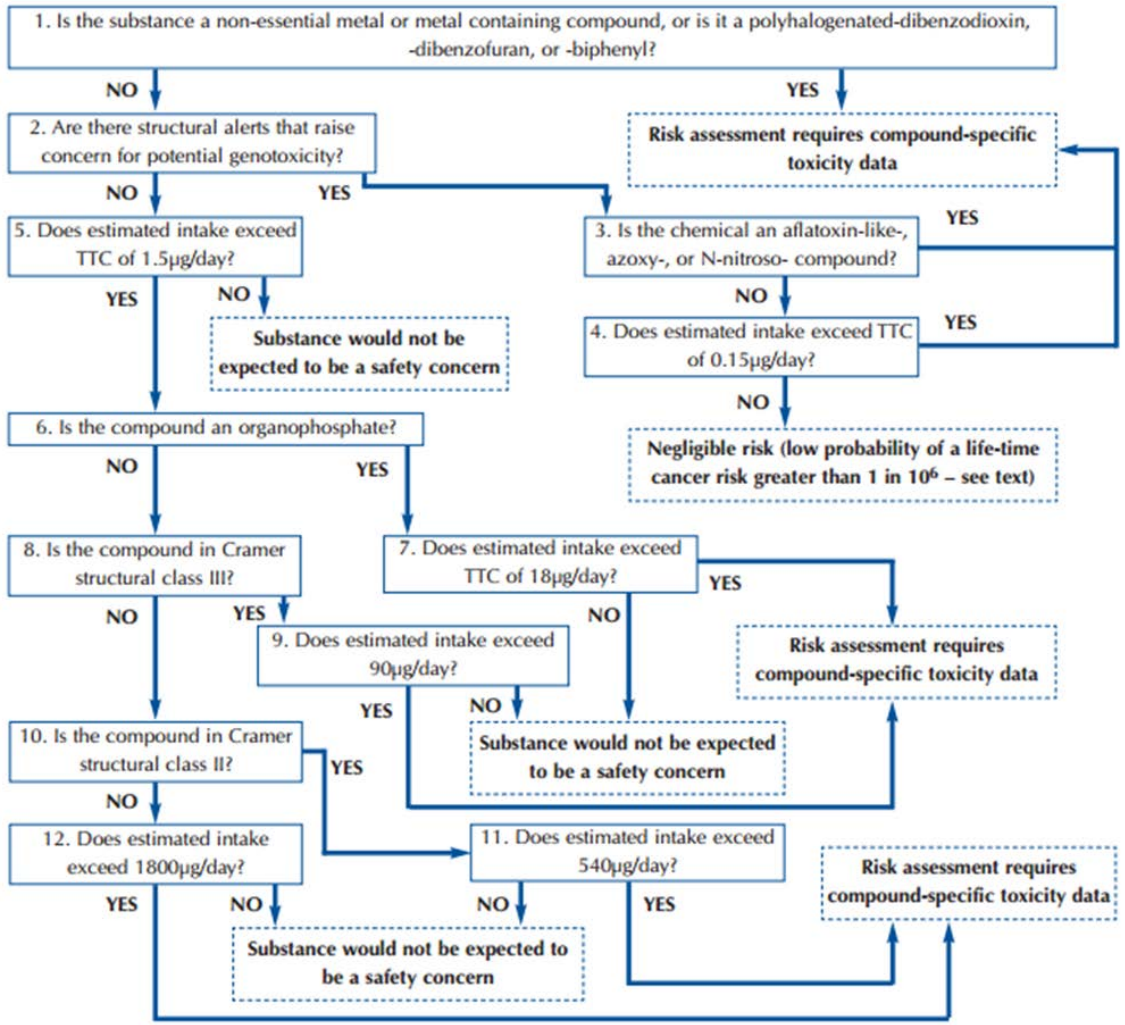
Threshold of Toxicological Concern (TTC)

Type of substance	TTC µg/person/day (µg/kg-day 60 kg adult)
Alerts for potential genotoxic carcinogenicity	Kroes: 0.15 (0.0025 µg/kg-day) ICH: 1.5 (0.025 µg/kg-day)
Acetylcholinesterase inhibitors (AChEI) Organophosphate/carbamate	18 (0.3 µg/kg-day)
Cramer Class III	90 (1.5 µg/kg-day)
Cramer Class II	540 (9.0 µg/kg-day)
Cramer Class I	1800 (30 µg/kg-day)

Exclusions: Aflatoxin-like, Azo-compounds, Nitroso-compounds, Benzidines, Metals and Organometallics, Proteins, Steroids, Substances with a potential for bioaccumulation, Nanomaterials, Radioactive substances, Mixtures of substances containing unknown chemical structures

Threshold of Toxicological Concern (TTC)

Kroes et al (2004)



In a safety evaluation, use the TTC in the same manner as a Reference Dose

$$\text{Margin of Safety} = \frac{\text{TTC}}{\text{Predicted (or measured) Exposure}}$$

Some TTC References

- I.C. Munro, A.G. Renwick, B. Danielewska-Nikiel. The Threshold of Toxicological Concern (TTC) in risk assessment. Toxicol. Lett., 180 (2008), pp. 151-156, 10.1016/j.toxlet.2008.05.006
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- Health Canada, Science Approach Document Threshold of Toxicological Concern (TTC)-based Approach for Certain Substances Health Canada. https://www.ec.gc.ca/ese-ees/326E3E17-730A-4878-BC25-D07303A4DC13/HC%20TTC%20SciAD%20EN%202017-03-23.pdf, 2016 (accessed 21 January 2018)
- S. Felter, R.W. Lane, M.E. Latulippe, G.C. Llewellyn, S.S. Olin, J.A. Scimeca, T.D. Trautman. Refining the threshold of toxicological concern (TTC) for risk prioritization of trace chemicals in food. Food Chem. Toxicol., 47 (2009), pp. 2236-2245, 10.1016/j.fct.2009.06.018
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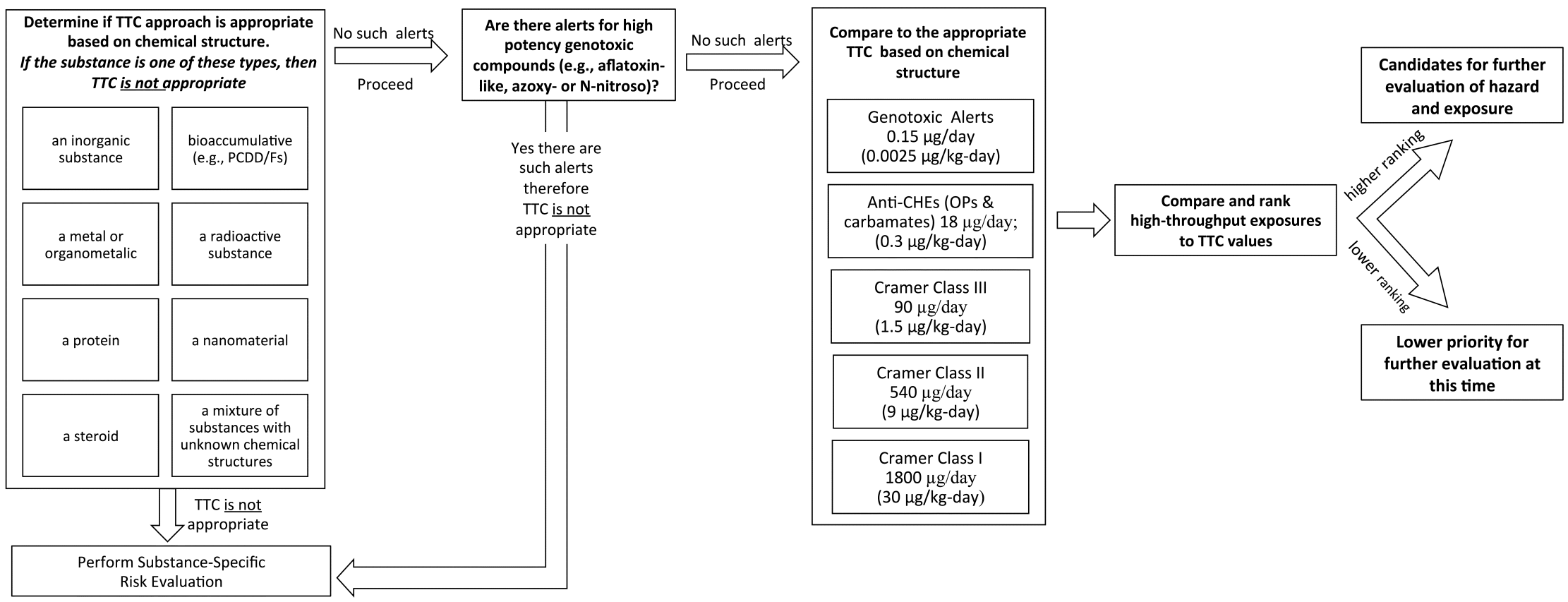
- EFSA & WHO. Review of the Threshold of Toxicological Concern (TTC) approach and development of new TTC decision tree 2016. https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/sp.efsa.2016.EN-1006

Uses of the TTC

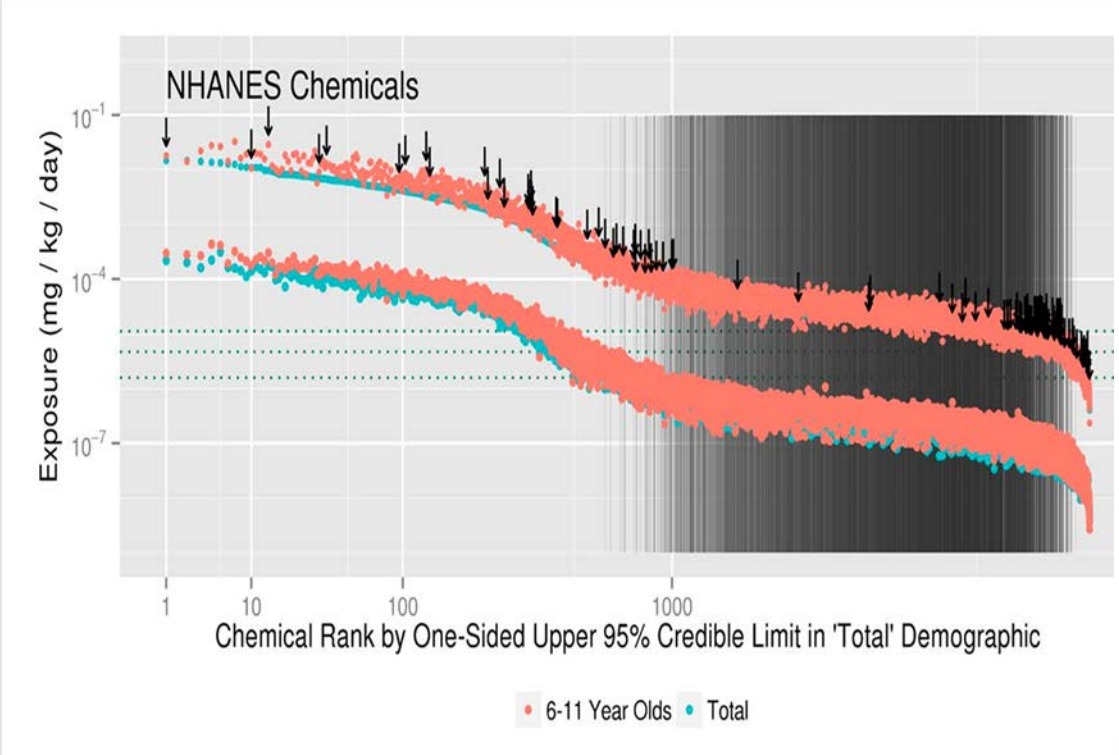
Risk-Based Priority Setting

Patlewicz et al. 2018. Utilizing Threshold of Toxicological Concern (TTC) with high throughput exposure predictions (HTE) as a risk-based prioritization approach for thousands of chemicals Comp Toxicology 7: 58-67, 2016.



Uses of the TTC

Risk-Based Priority Setting



Wambaugh and colleagues (2014) developed a rapid heuristic high throughput exposure (HTE) model that enables prediction of potential human exposure to thousands of substances for which little or no empirical exposure data are available

Patlewicz et al. 2018. Utilizing Threshold of Toxicological Concern (TTC) with high throughput exposure predictions (HTE) as a risk-based prioritization approach for thousands of chemicals Comp Toxicology 7: 58-67, 2016.

TTC category	# of chemicals
Total dataset	7968
Dataset with available structures	7699
TTC is not appropriate	904
TTC is appropriate	6795
Genotox alerts	1853
AChEIs	102
Cramer class III	3214
Cramer class II	332
Cramer class I	1294

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TTC category	Number of chemicals	TTC (µg/kg-day for 60 kg adult)	Percentage of Substances Exceeding the TTC	
			UCI Exposure Value (number of chemicals)	Median Exposure Value (number of chemicals)
Cramer class III	3214	1.5 µg/kg-day	2% (58)[a]	0
Cramer class II	332	9.0 µg/kg-day	0	0
Cramer class I	1294	30 µg/kg-day	0	0
AChEIs	102	0.3 µg/kg-day	1% (1)	0
Genotoxic alerts	1853	Kroes 0.0025 µg/kg-day	94% (1740)	4% (79)
		ICH 0.025 µg/kg-day	18% (333)	1% (19)

Uses of the TTC

Filling a Toxicity Data Need

Hartung 2017. ALTEX 34(3), 2017

Tab. 1: Current regulatory use of TTC

Area	Authority	Reference
Food packaging migrants and flavoring agents	US FDA, JECFA, WHO	FDA, 1995, 2001; JECFA, 1998; WHO, 2000
Food flavorings and pesticide metabolites in groundwater; *Under discussion for:* food contact materials; impurities and breakdown/reaction products in food and feed additives; plant metabolites and degradants of pesticides; metabolites of feed additives; technological feed additives; flavoring substances in feed	EFSA	EFSA, 2012, 2016
Genotoxic impurities in (veterinary and human) pharmaceutical preparations and genotoxic constituents in herbal substances and preparations	EMEA, EMA	EMEA, 2004; FDA, 2008; EMA, 2006, 2013
Genotoxic and carcinogenic impurities in drugs	US FDA	McGovern and Jacobson-Kram, 2006; ICH guidance M5, 2015[a]
Within REACH registrations for industrial chemicals	ECHA	ECHA, 2016

[a] https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM347725.pdf

[1] https://www.kvcv.be/index.php/en/food-contact-materials

Recommendations

TTC was featured in EPA OPPT's draft strategic plan, but is inexplicably absent in the final doc "Alternative Test Methods and Strategies to Reduce Vertebrate Animal Testing"

"EPA believes that exploration and potential implementation of the toxicological threshold of concern approach, at least for some chemical structural classes, is an important possible avenue for making some TSCA decisions. EPA is considering this topic as part of collaborative efforts…"

https://www.epa.gov/sites/production/files/2018-06/documents/epa_alt_strat_plan_6-20-18_clean_final.pdf

Let's start the collaboration!! and include TTC as part of the ICCVAM / NICEATM set of activities