EFSA/WHO TTC Stakeholder Day, Brussels

The Utility of the Threshold of Toxicological Concern Concept in the Agrochemical Industry

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Outline

- **Robustness of TTC values**
- **Regulatory approaches**
- **Toxicologically-derived endpoints in comparison to TTC thresholds**
- **Use of TTC values in practise**
  - Assessment of impurities
  - Assessment of plant/livestock metabolites
  - Non-relevant metabolites in ground and drinking water
- **Conclusions**

The TTC Approach
delivers health based limit values

- A threshold of toxicological concern (TTC) value is a human exposure threshold value for a chemical of unknown toxicity, below which there is no appreciable risk to health following oral exposure for a life-time

- Application of the TTC approach requires knowledge of the structure of the chemical and adequate human exposure estimates

- The use of the TTC principle eliminates the necessity of extensive toxicity testing and safety evaluations, when human intakes of a chemical are below a certain level of concern

- The oral TTC values for non-genotoxic compounds are considered to cover* …
  - long term effects
  - Reproductive toxicological / developmental effects
  - adverse effects with endocrine mode of action (except for steroids)

Are the TTC values obtained by Munro et al., 1996 reliable and robust?

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- **Derivation of TTC values, when using other repeated dose toxicity databases**
  - RepDose oral data base: around 600 substances (Escher & Mangelsdorf, 2009)
  - 861 industrial chemicals: 28- and 90-day studies (Kalkhof et al., 2012)

Database	5th percentile NOAELs [mmol/kg bw/day or mg/kg bw/day}	
	Cramer class I	Cramer class III
Munro et al., 1996	0.0115 mmol/kg bw/day	0.0005 mmol/kg bw/day
Repdose, 2009	0.0357 mmol/kg bw/day	0.0016 mmol/kg bw/day
Munro et al., 1996	3.0 mg/kg bw/day	0.15 mg/kg bw/day
Kalkhof et al., 2012	2.5 mg/kg bw/day* 24.5 mg/kg bw/day**	1.6 mg/kg bw/day* 1.0 mg/kg bw/day**

***based on 28-day studies **based on 90-day studies**

- **Similar values obtained when using different databases**

Do the Cramer class thresholds cover all relevant toxicological endpoints

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Reproduction toxicity

- Fertility and teratogenicity endpoints were not lower than NOAELs used for TTC (Kroes, 2004)
- 91 chemicals and 507 pharmaceuticals were evaluated (Bernauer, 2008)
  - TTCs of 60 and 90 µg/person/day were derived, however using an **uncertainty factor of 1000**
- Developmental toxicity studies in rats of 93 chemicals (van Ravenzwaay et al., 2011)
  - TTCs of 480 µg/person/day, **uncertainty factor of 500**)
- Developmental toxicity studies in rabbits of 104 active ingredients (van Ravenzwaay et al., 2012)
  - TTC of 240 µg/person/day, **uncertainty factor of 500**)
- Developmental and reproduction toxicity studies of 300 substances (Laufersweiler et al., 2011)
  - TTCs of 8520, 1122, 186 µg/person/day for Cramer 1, II, III compounds with an **uncertainty factor of 100**

Regulatory approaches

- REACH Guidance Chapter R. 7c pages (Appendix R.7-1)
  - “alternatively, a toxicological threshold may also be based on the statistical analysis of the toxicological data of a broad range of structurally-related ... chemicals...”
- Food contact materials (US-FDA, EFSA)
- Flavourings and food additives (FAO/WHO, EFSA)
- Pharmaceuticals – genotoxic impurities (EMEA)
- Contaminants in ground and drinking water (Sanco Guidance)
  - Generic TTC value of 1.5 µg/person/day included
- Assessment of plant and livestock metabolites (EFSA Scientific Opinion)
  - Cramer class values (I and III considered)

TTC values are usually lower than compound-specific thresholds

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Laabs et al., Water Res. Mgmt, submitted.

Example I

Distribution of DW Guidance values derived from real data

- Health based values derived for AI's
  → all (375 AI's*)
  Min: 0.2 µg/L
  → EU approved (264 AI's*)
  Min: 0.6 µg/L
  → EU appr. & non-hazard (195 AI's*)
  Min: 1.95 µg/L

- Health-based values derived for non-relevant metabolites (**TTC: 4.5 µg/L**)
  → 56 nr-metabolites (from 35 AI's)
  → Minimum: 10.5 µg/L
  → 10th perc: 106 µg/L
  → Median: 1025 µg/L

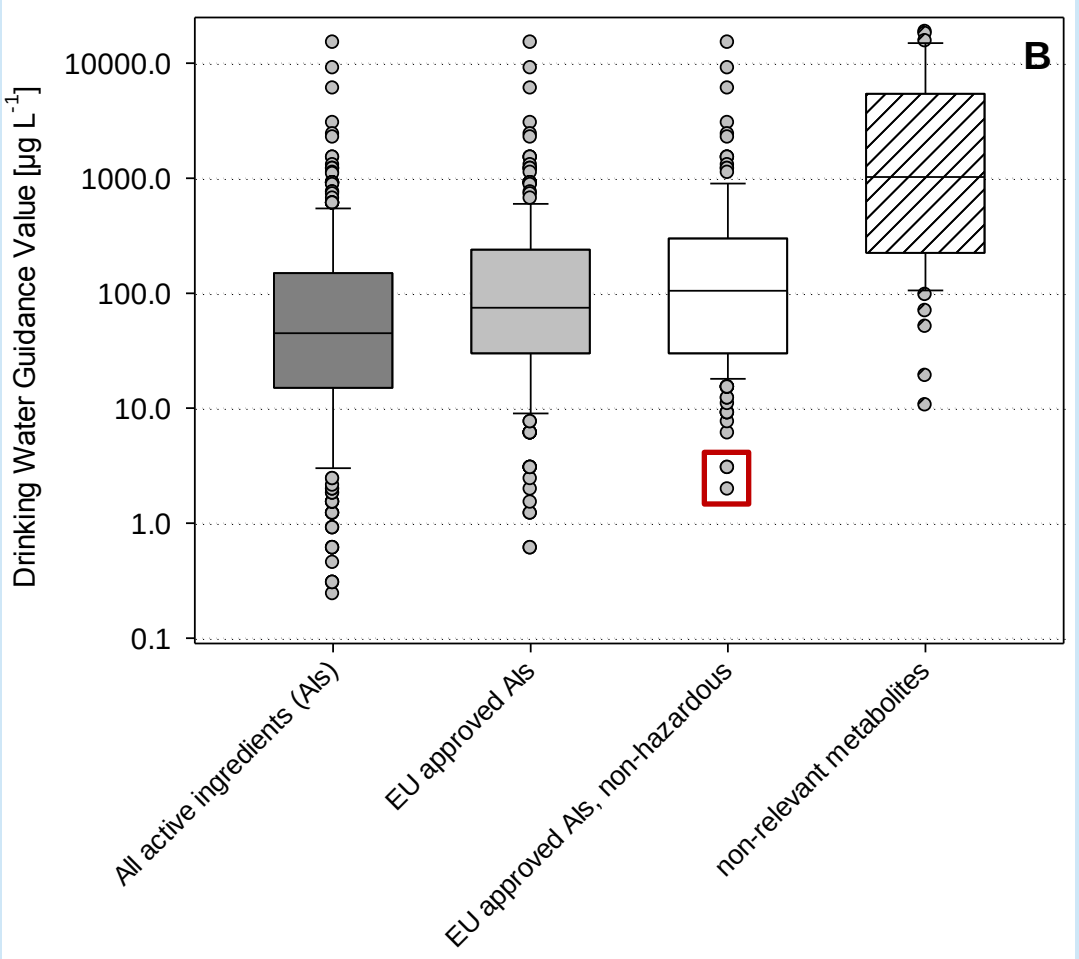

Figure: Drinking water guidance values
(WHO standard methodology, 10% ADI allocation)

** EU data base: http://ec.europa.eu/sanco_pesticides/public/*

TTC values are usually lower than compound-specific thresholds

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Example II

Characterizing the Noncancer Toxicity of Mixtures Using Concepts from the TTC and Quantitative Models of Uncertainty in Mixture Toxicity

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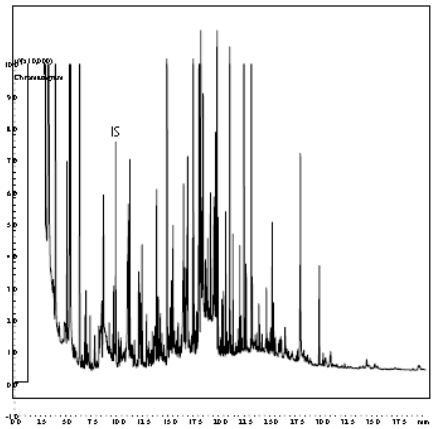
Table VII. Impact of the Use of Cramer Class to Estimate Mixture Toxicity (mg/(kg d))

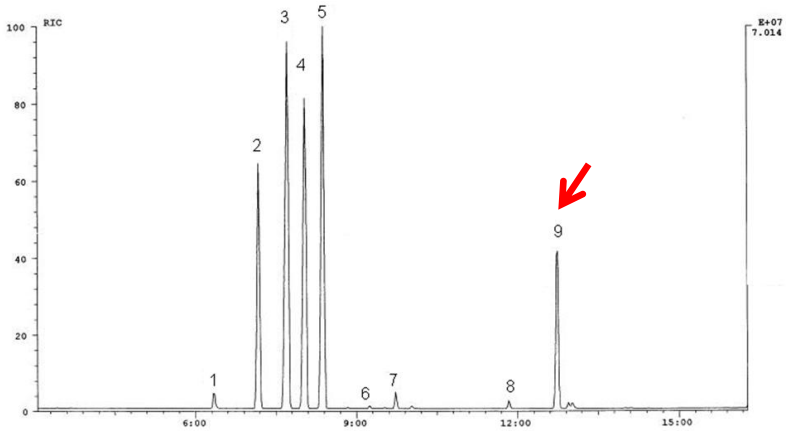
$mDNEL_A$ Based on Compound-Specific Toxicity Data	$mDNEL_A$ Based on Cramer Class	Ratio of the Two Approaches
2.70E-02	6.30E-03	4
4.80E-02	3.10E-03	16
6.30E-02	5.10E-03	12
6.40E-02	4.50E-03	14
2.10E-01	2.40E-03	88
2.70E-01	1.50E-02	18
3.30E-01	1.40E-02	23
3.40E-01	1.50E-03	230
3.90E-01	1.10E-02	36
6.40E-01	1.60E-02	39
9.70E-01	6.30E-03	150
1.20E+00	7.20E-03	170
1.40E+00	4.00E-03	340
1.60E+00	4.90E-03	330
8.80E+00	1.50E-03	5,900

Practical uses



- Impurities
- Plant and livestock metabolites

Example: Assessment of plant metabolites



Identified plant metabolites

- QSAR / DEREK
- ToxTree

Any genotoxic alert

Consider potential neurotox

Cramer class III

Allowed human exposures:

0.0025 µg/kg bw/day	0.3 µg/kg bw/day	1.5 µg/kg bw/day

Example: continued

- **If modeled human exposure is > 0.0025 µg/kg bw/day and an alert for genotoxicity**
  - Conduct genotoxicity testing
- **If modeled human exposure is > 0.3 µg/kg bw/day and a structural alert for neurotoxicity**
- **If modeled human exposure is > 1.5 µg/kg bw/day**
  - Conduct specific hazard and risk assessment with the metabolite

Applicability to define health-based water limits for non-relevant metabolites

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ECPA Position

Thresholds of Toxicological Concern (TTCs)				
	Historical TTC value	Cramer class III	Cramer class II	Cramer class I
TTC value [µg/person/d]	1.5	90	540	1800
TTC value for water* [µg/L]	0.75 **	4.5	27.0	90.0

* Calculation basis: person of 60 kg, consumption of 2 L water/day (= WHO); 10% contribution of drinking water to ADI

** 100% contribution of drinking water to ADI

Conclusions

- TTC concept is a useful tool to predict safe human thresholds for oral systemic exposure
- TTC concept is a useful tool to prioritize further (animal) testing
- TTC thresholds derived by Munro et al., 1996, refined by Kroes et al., 2004 are robust
- Relevant toxicological endpoints are covered
- TTC thresholds are usually lower than respective specific toxicologically derived endpoints
- TTC thresholds can be used for safety assessment of substances with expected very low human oral exposure

Thank you for your attention!

References

Bernauer U, Heinemeyer G, heinrich-Hirsch B, Ulbrich B, Gundert-Remy U (2008) Exposure-triggered reproductive toxicity testing under the REACH legislation: A proposal to define significant/relevant exposure. Toxicology Letters 176, 68 - 76

Dekant, W., Melching-Kollmuß, S., Kalberlah, F. 2010 Toxicity assessment strategies, data requirements, and risk assessment approaches to derive health based guidance values for non-relevant metabolites of plant protection products. Regul. Toxicol. Pharmacol. 56:135-142.

EFSA Scientific Opinion on Exploring options for providing advice about possible human health risks based on the concept of threshold of toxicological concern (TTC)., EFSA Journal 2012, 10(7), 2750

EFSA Scientific Opinion on Evaluation of the toxicological relevance of pesticide metabolites for dietary risk assessment, EFSA Journal 2012, 10(7), 2799

Kalkhof H, Herzler M, Stahlmann R, Gundert-Remy U (2012) Threshold of toxicological concern values for non-gentoxic effects in industrial chemicals: re-evaluation of the Cramer classification. Arch Toxicol, 86, 17-25

Laabs, V., Leake, C., Botham, P., and Melching-Kollmuß, S. (submitted) Regulation of non-relevant metabolites of plant protection products in drinking and groundwater in the EU: Current status and way forward. Water Res. Mgmt. submitted in April 2014.

Laufersweiler MC, Gadagbui B, Baskerville-Abraham IM, Maier A, Willis A, Scialli AR, Carr GJ, Felter SP, Blackburn K, Daston G (2012) Correlation of chemical strucuture with reproductive and developemtnal toxicity as it relates to the use of the threshold of toxicological concern. RegToxPharm, 62, 160 - 182

Melching-Kollmuß, S., Dekant, W., Kalberlah, F. 2010 Application of the "threshold of toxicological concern" to derive tolerable concentrations of "non-relevant metabolites" formed from plant protection products in ground and drinking water. Regul. Toxicol. Pharmacol. 56 :126–134.

Munro, I.C., Ford, R.A., Kennepohl, E., Sprenger, J.G. 1996 Correlation of structural class with no-observed-effect levels: a proposal for establisheing a threshold of concern. Food Chem. Toxicol. 34:829-867.

Ravenzwaay, B. van, Damman, M., Buesen, R., Schneider, S. 2011 The threshold of toxicological concern for prenatal developmental toxicity. Regul. Toxicol. Pharmacol. 59:81-90.

Ravenzwaay B van, Dammann M, Buesen R, Flick B, Schneider S 2012 The threshold of toxicological concern for prenatal developmental toxicity in rabbits and a comparison to TTC values in rats. Regul. Toxicol. Pharmacol. 64, 1-8

Backup
Applicability of TTC concept

Substances excluded from TTC

- High potency carcinogens (aflatoxin-like, azoxy- or N-nitroso compounds)
- Inorganic substances
- Metals
- Proteins
- Substances known or predicted to bioaccumulate
- Substances with structures not adequately represented in original databases (nanomaterials, radioactive substances)
- Substances likely to have potential for local effects (e.g. corrosiveness, acidity)

The TTC Approach

Defining structural substance classes

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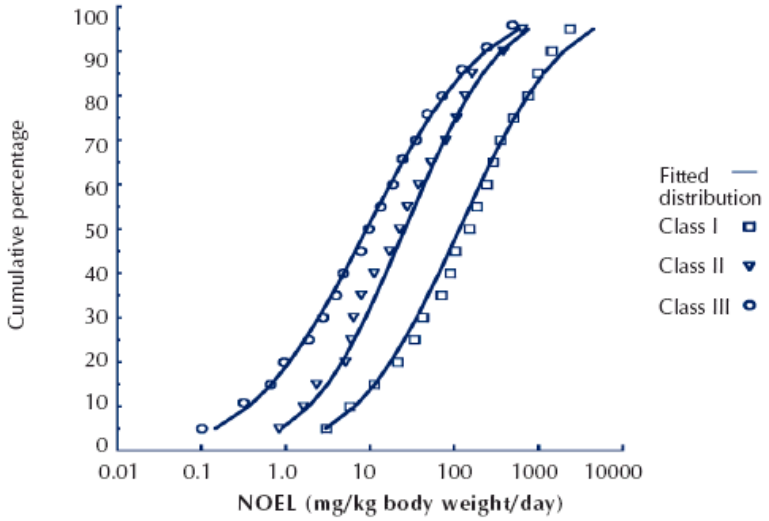
Cramer classes (evaluated for 613 chemical substances with tox data)

- **Cramer I:** simple structures, efficiently metabolised, low potential for toxicity (137)
- **Cramer II:** between Cramer I and III (28)
- **Cramer III:** structural features that may suggest toxicity (448)

Principle of threshold value determination:

The lowest NOAEL from a number of different studies was selected for each chemical and the cumulative percentage plotted within each structure class.



The TTC Approach

Defining TTCs for substance classes

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- Based on the Cramer class NOAEL distribution, the 5th percentile NOAEL was selected and divided by a safety factor of 100: This value is then converted into a daily intake per person.
- Chronic NOAELs have been used in most cases (an additional safety factor of 3 was applied in case of subchronic NOAELs)
- The TTCs only apply to substances with defined chemical structures, for which there is no evidence of genotoxic carcinogenicity and no structural alerts for genotoxicity.

Generic TTCs: Derivation of human exposure thresholds from toxicity data

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

* The human exposure threshold was calculated by multiplying the fifth percentile NOEL by 60 (assuming an individual weighs 60 kg) and dividing by a safety factor of 100.