The threshold of toxicological concern (TTC)
-
a suitable tool for mixture risk assessment and ranking?

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This is about the TTC concept

- as a tool for mixture toxicity assessment, prioritisation and management, it's possibilities, options and limitations.
- as a general concept for data-free risk assessment and management of chemicals

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This is not about

- Problems and issues relating to (cumulative) exposure assessment
- General issues, pitfalls, shortcomings in chemical risk assessment

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The Threshold of Toxicological Concern (TTC)

Generic human exposure threshold value, below which "the probability of adverse effects on human health is considered to be very low. "

(Draft Scientific Opinion, EFSA)

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The Threshold of Toxicological Concern (TTC)

- Distribution based approach

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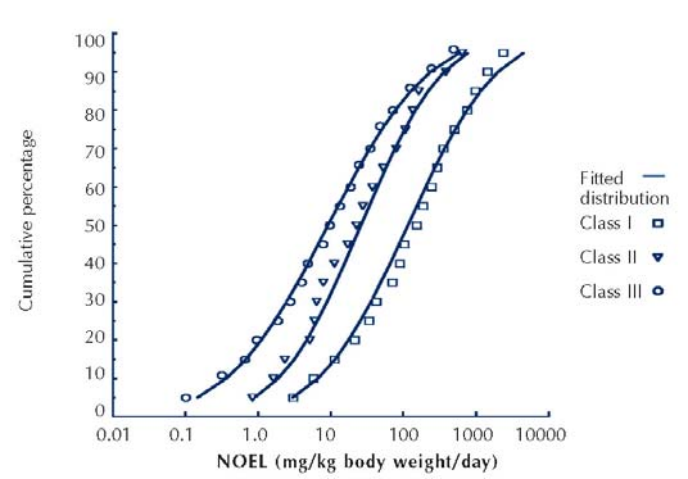
The Threshold of Toxicological Concern (TTC)



S. Barlow, Threshold of Toxicological Concern, ISLI Monograph Series, 2005.
After: Munro IC, et al.; Food Chem Tox , 34. 829-867, 1996

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The Threshold of Toxicological Concern

- Distribution based approach.
- Lower 5% percentile divided by an Assessment Factor of 100.
- Distinction of 3 main chemical groups (Cramer Classes).

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TTC: Cramer Classes

Structural classes for chemicals in the TTC approach

Class I	Substances with simple chemical structures and for which efficient modes of metabolism exist, suggesting a low order of oral toxicity.
Class II	Substances which possess structures that are less innocuous than class I substances, but do not contain structural features suggestive of toxicity like those substances in class III.
Class III	Substances with chemical structures that permit no strong initial presumption of safety or may even suggest significant toxicity or have reactive functional groups.

(Draft Scientific Opinion on TTCs, EFSA)

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Excluded compounds

- Heavy metals
- Bioaccumulative compounds (e.g. polyhalogenated dibenzo-p-dioxins, polyhalogenated dibenzofurans and biphenyls, chocolate)
- Endocrine disrupting compounds
- Polymers
- Proteins
- Nanomaterials
- Specific consideration of carcinogenic compounds

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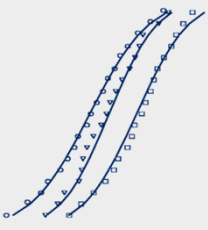
TTCs for the three Cramer Classes

Class I: 1800 µg/person day

Class II: 540 µg/person day

Class III: 90 µg/person day



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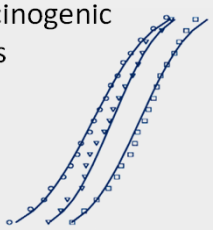
The Threshold of Toxicological Concern

- Distribution based approach.
- Lower 5% percentile divided by an Assessment Factor of 100.
- Distinction of 3 main chemical groups (Cramer Classes).
- Extended ruleset (extended Cramer rulebase, TTC decision tree)
- Specific analysis of endocrine disrupters, carcinogenic compounds (0.15 µg/day), organophosphates (18 µg/day)



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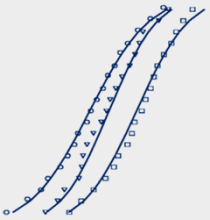
Required Data for applying the TTC concept

- Chemical Structure, in order to classify the compound in question into a Cramer Class
- Exposure

- But NO TOXICITY DATA for the substance in question



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Current use of TTCs

- UN Joint Expert Committee on Food Additives (JECFA)
- US FDA for deciding on whether toxstudies are needed for food additives ("threshold of regulation" for food contact material is 0.5 ppb)
- Genotoxic impurities in pharmaceuticals for human use (EMEA guideline on the limits of genotoxic impurities, 2006)
- Environmental risk assessment of pharmaceuticals ("action limit" of 0.1 µg/L)

- Currently explored: cosmetic ingredients (sponsored by COLIPA, European Cosmetic Toiletry and Perfumery Association)

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Critical issues

- In violation of the "no data, no market" philosophy of REACH.
- No novel toxicological knowledge is generated, despite the fact that new compounds are constantly put on the market.
- Questionable quality, quantity and transparency of the initial data for deriving the toxicity-distributions.
- Based on NOELs, a seriously limited approach for describing low-dose effects of chemicals.

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TTC and mixture risk assessment

- TTC as surrogates for experimental low-dose data (NOELs)
- Exposure at or below TTC as a decision criterion whether a mixture risk assessment is needed

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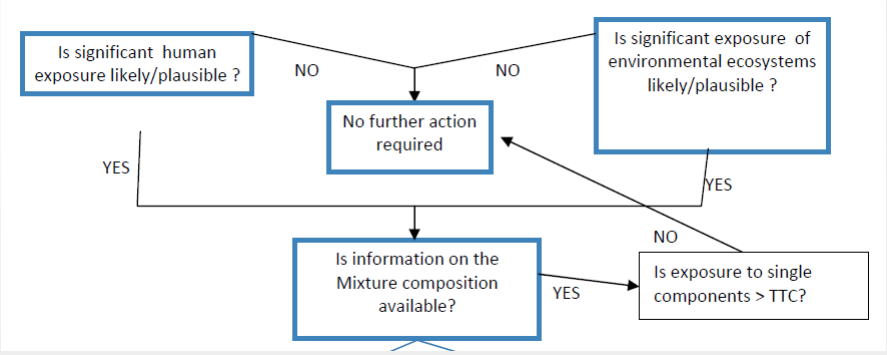
TTCs and mixture risk assessment



*(**Draft** Scientific Opinion on Mixture Toxicity Assessment, SCHER, SCENIHR, SCCS)*

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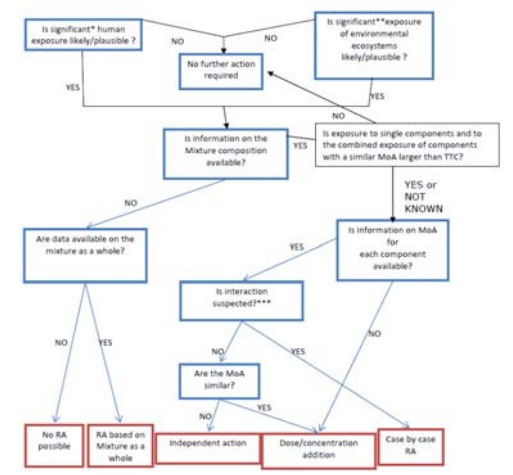
Suggested use of the TTC concept in mixture risk assessment



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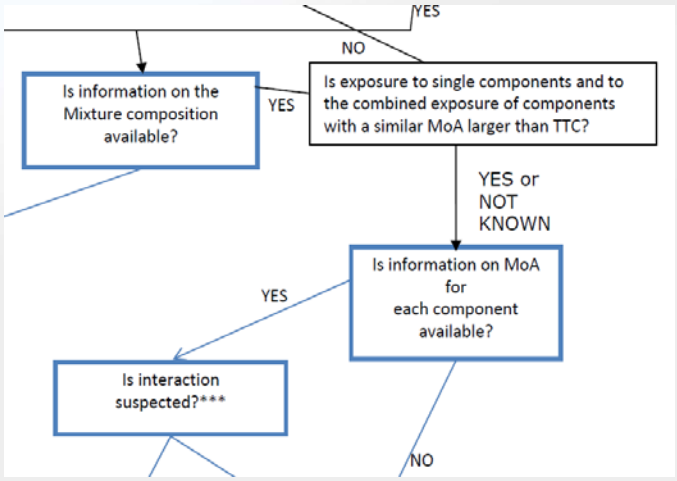

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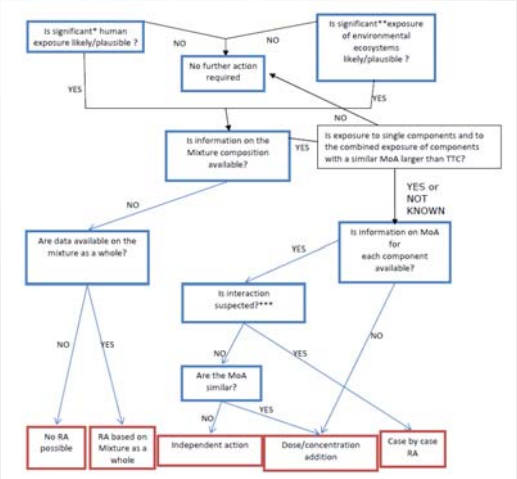

(Final Scientific Opinion on Mixture Toxicity Assessment, SCHER, SCENIHR, SCCS)

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Mixture toxicity concepts

Similarly acting substances: Concentration Addition

$$ECx_{(Mix)} = \left(\sum_{i=1}^{n} \frac{p_i}{ECx_i} \right)^{-1}$$

c_i = Concentration of component *i* in the mixture (*i = 1...n*)

ECx_i = Concentration of substance *i* provoking a certain effect *x* when applied alone

$ECx_{(Mix)}$ = Predicted total concentration of the mixture, that provokes x% effect.

pi = relative fraction of component *i* in the mixture

Dissimilarly acting substances: Independent Action

$$E_{Mix} = 1 - \prod_{i=1}^{n} (1 - E_i)$$

E_{Mix} = Effect of the mixture of *n* compounds

E_i = Effect of substance *i*, when applied singly

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Concentration Addition (CA)

$$ECx_{(Mix)} = \left(\sum_{i=1}^{n} \frac{p_i}{ECx_i} \right)^{-1}$$

$$EC50_{Mix} = \left(\frac{p_1}{EC50_1} + \frac{p_2}{EC50_2} \right)^{-1}$$

$$NOEL_{Mix} = \left(\frac{p_1}{NOEL_1} + \frac{p_2}{NOEL_2} \right)^{-1}$$

$$DNEL_{Mix} = \left(\frac{p_1}{DNEL_1} + \frac{p_2}{DNEL_2} \right)^{-1}$$

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Mixture toxicity concepts

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TTC and IA

$$E_{Mix} = 1 - \prod_{i=1}^{n} (1 - E_i)$$

$$E_{Mix} = E_1 + E_2 - E_1 \times E_2$$

If $E_1=0$ AND $E_2=0$ then $E_{Mix}=0$,

Ergo: $TTC_{Mix} = \min\left(\frac{TTC_i}{p_i}\right)$

Price et al. Risk Analysis, 2009

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TTC and IA and some pitfalls

- TTC must actually describe a true zero effect concentration if IA is supposed to safeguard against unwanted mixture effects

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Implications of IA

Careful differentiation between true ZERO effects and SMALL effects is crucial:

Example:

Number of mixture components *n*	Individual effect $E(c_i)$	Expected joint effect $E(c_{mix})$
70	0 % each	0 %
70	1 % each	50 %

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NOELs and the hypothesis of IA

- NOEL values denote the highest tested concentration at and below which the response of exposed organisms does not depart significantly (in a statistical sense) from untreated controls.
- **NOELs are no true zero effect levels:**
  below the NOECLtoxicity may be absent or may be present but undetected, due to a limited sensitivity of the experimental protocol.
- As a consequence, the assumption of IA does not exclude the possibility for occurrence of significant joint effects from individual concentrations ≤ NOEL.

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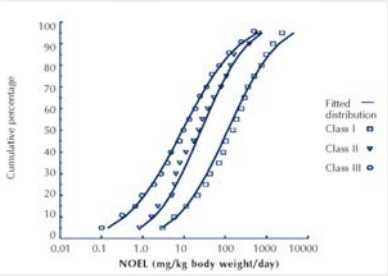
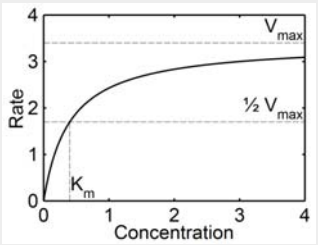
TTCs and the hypothesis of IA

- TTCs are the lower 5% percentile of NOEL distributions divided by 100
- **Do TTCs equate to true zero effect levels?**



$$v = \frac{V_{\max} \times [c]}{K_M + [c]}$$



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TTC and IA and some pitfalls

- TTC must actually describe a true zero effect concentration, AND
- compounds must be completely independently acting

… if IA is supposed to safeguard against unwanted mixture effects

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Independent Action

Bliss, 1939:

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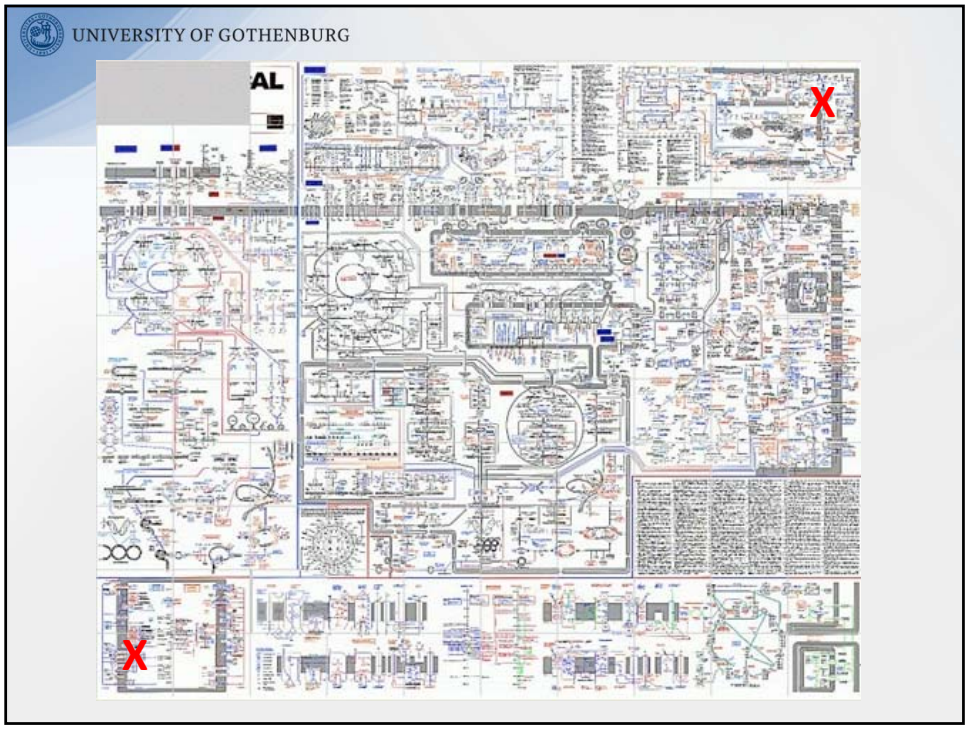
Independent Action

One toxicant does not influence the toxicity of another one.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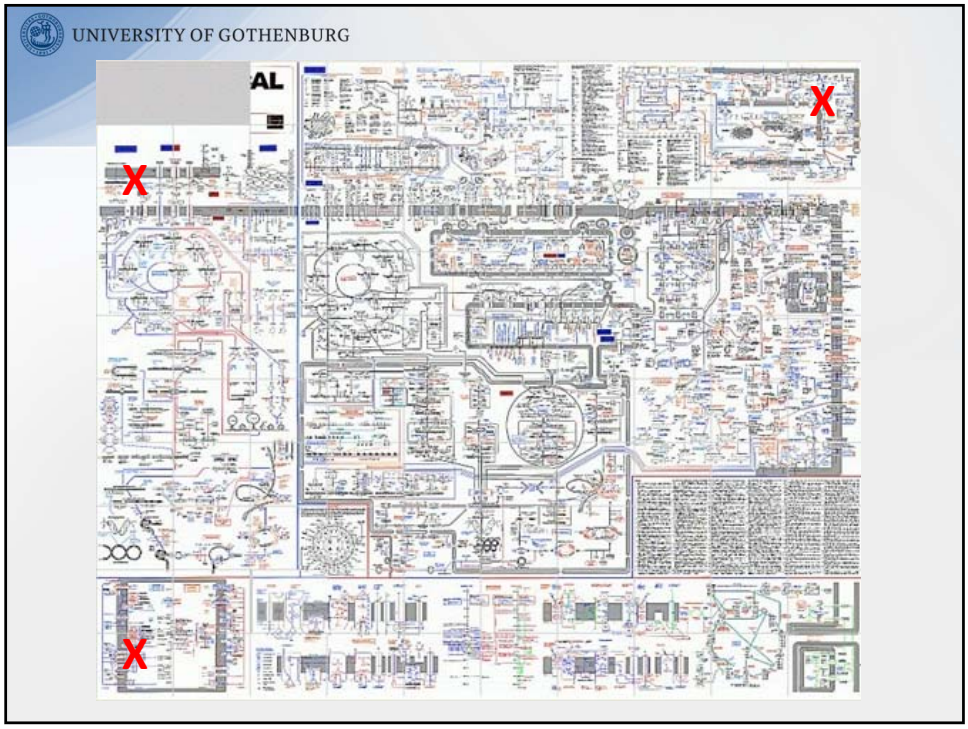
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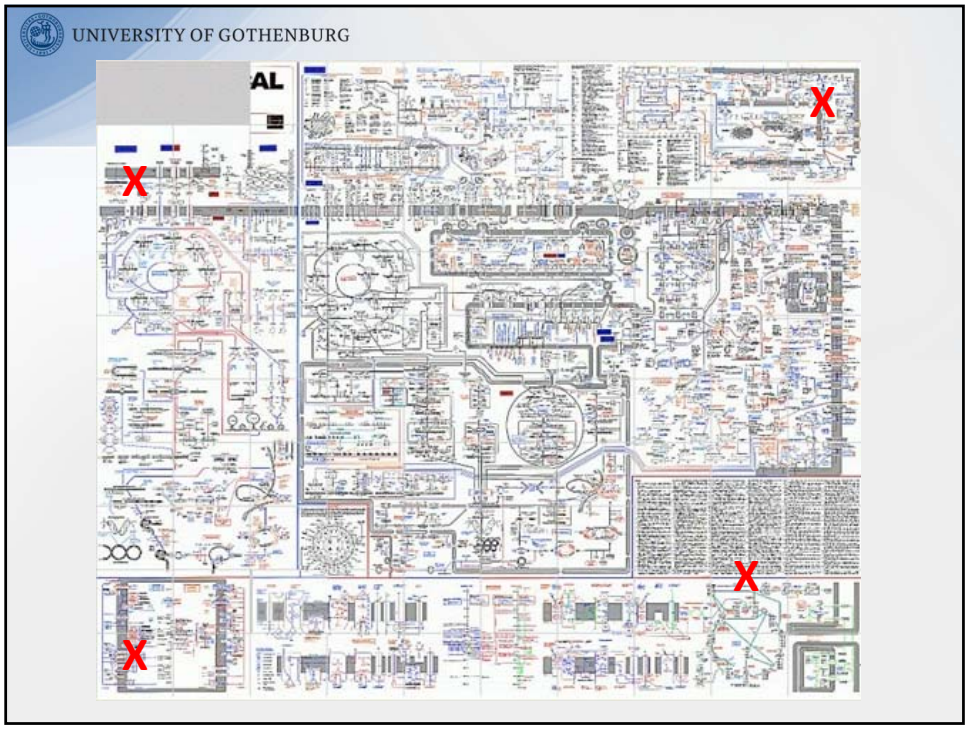
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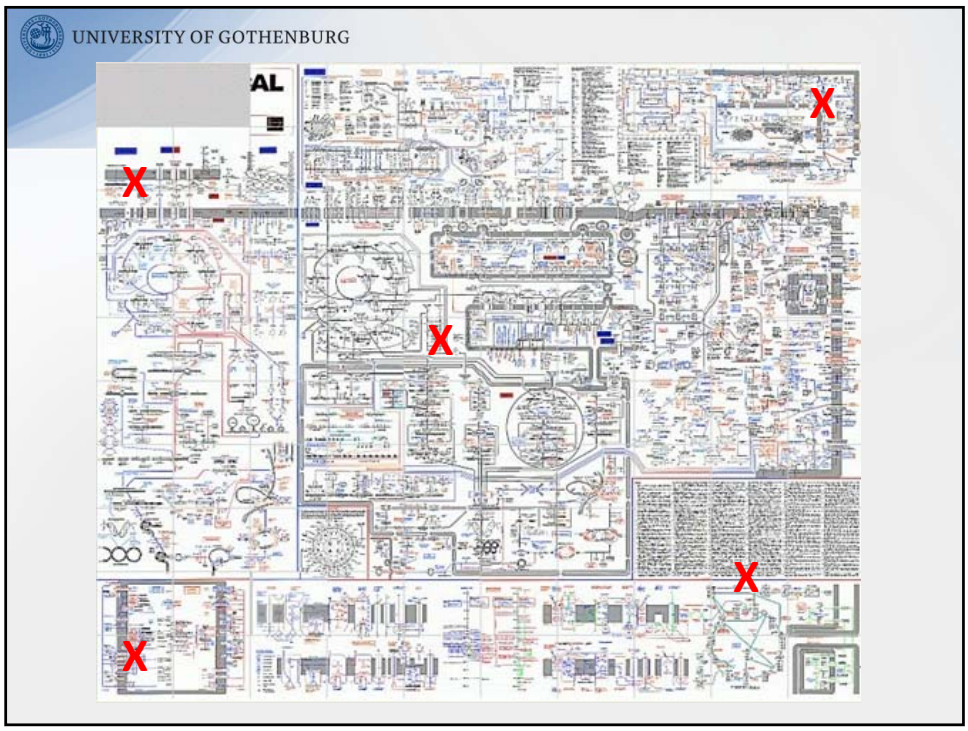
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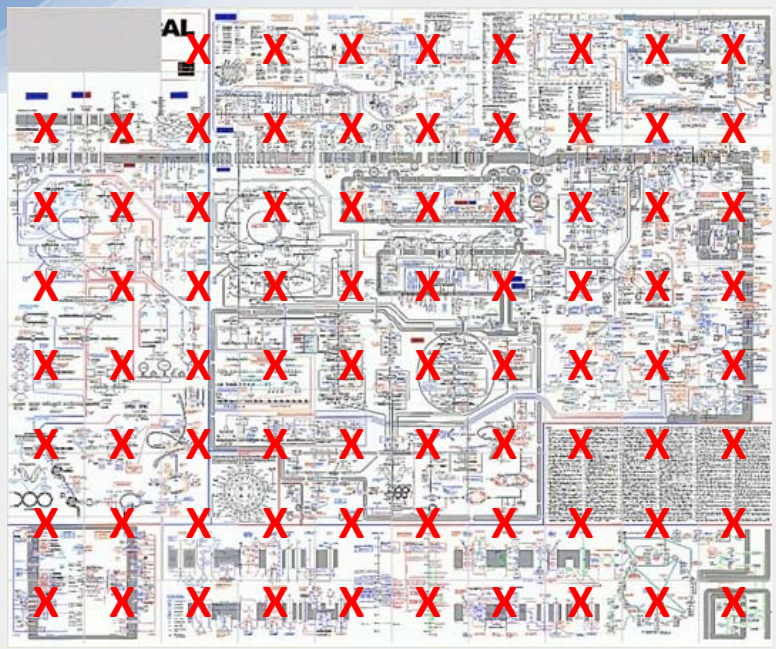

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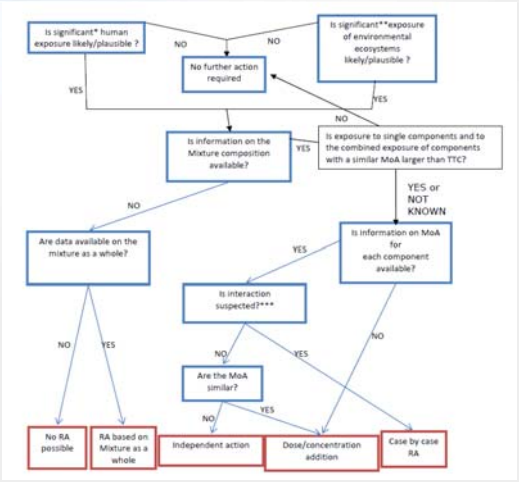
Suggested use of the TTC concept in mixture risk assessment



(Final Scientific Opinion on Mixture Toxicity Assessment, SCHER, SCENIHR, SCCS)

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EXCLUSIVE

515 chemicals a day on a woman's face

By JANE HAMILTON

Published: 19 Nov 2009

Add a comment (2)

WOMEN slap 515 chemicals on their face and body every day - and many could be harmful.

Beauty-conscious girls use up to 13 products, most containing more than 20 ingredients, a new study found.

Some of the additives have been linked to cancer, hormone problems, skin conditions and allergies.

Slip, slap, stop ... women should be wary of the creams and lotions they apply every day

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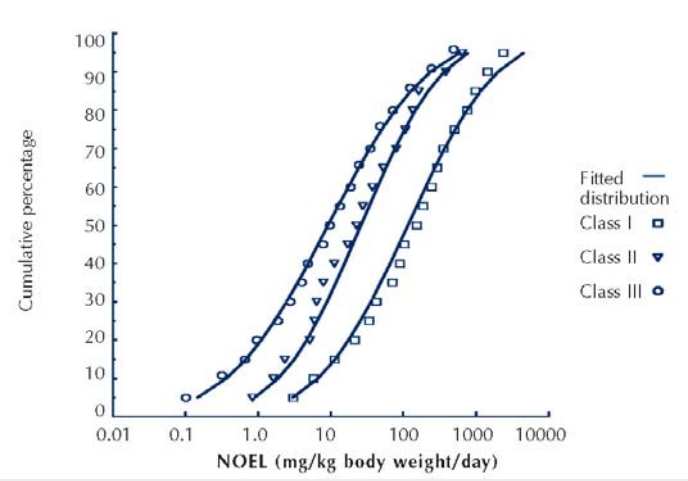
Only a very few Cramer Classes!



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After: Munro IC, et al.; Food Chem Tox , 34. 829-867, 1996

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TTC and Concentration Addition

$$TTC_{Mix} = \left(\frac{p_1}{TTC_1} + \frac{p_2}{TTC_2} \right)^{-1}$$

$$E(Mix)_{CA} \leq E_{TTC}$$

$$\text{if} \quad c_i \leq \left(\frac{TTC_i}{n} \right)$$

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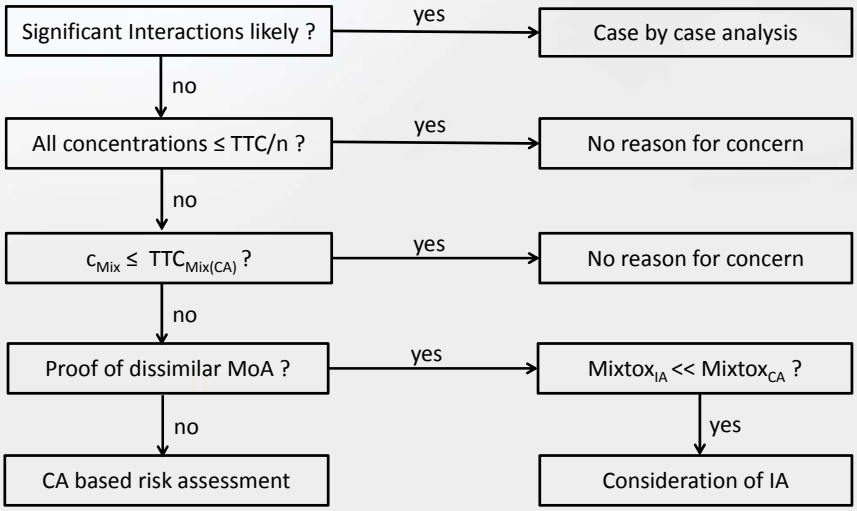
Suggested use of TTC for mixture risk assessment



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Summary and conclusions

- TTCs are based on a distribution analysis of a sample of toxicity data, thought to represent all chemicals
- Lower 5% percentile, divided by an Assessment Factor of 100
- Some critical issues include
  - Stagnation of toxicological knowledge
  - Quality and quantity of input data, transparency
  - Use of NOELs

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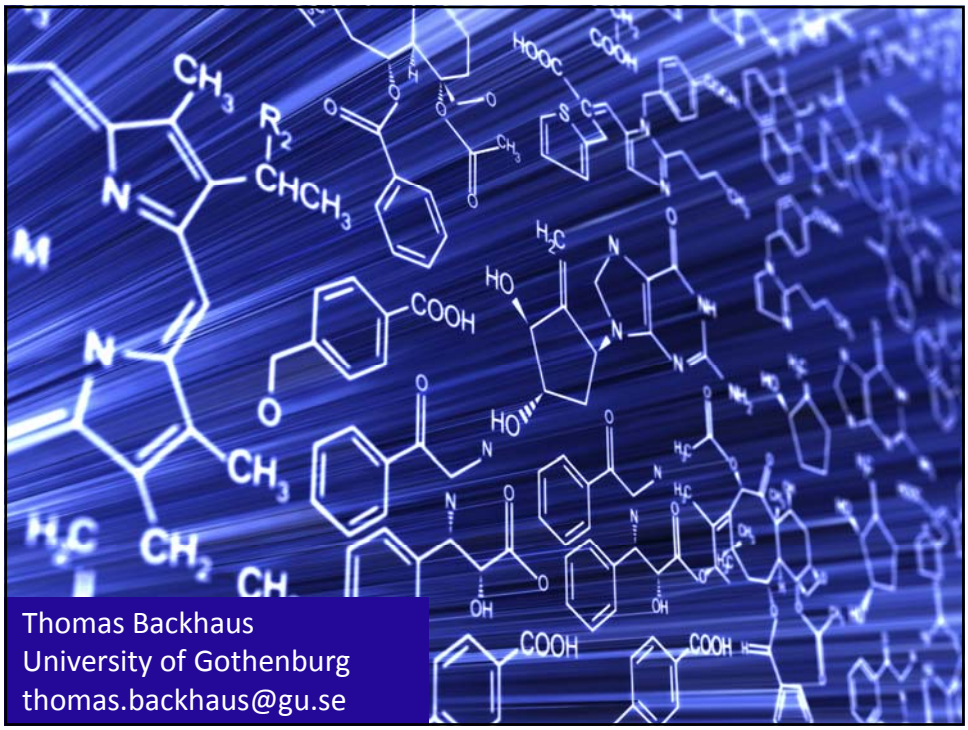
Summary and conclusions

- Independent Action for mixture risk assessment is of very limited use
- In particular: the assumption of IA does not allow the conclusion that mixture effects are absent at low doses
- Use CA for estimating the mixture TTC
- Incorporation into a tiered approach



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