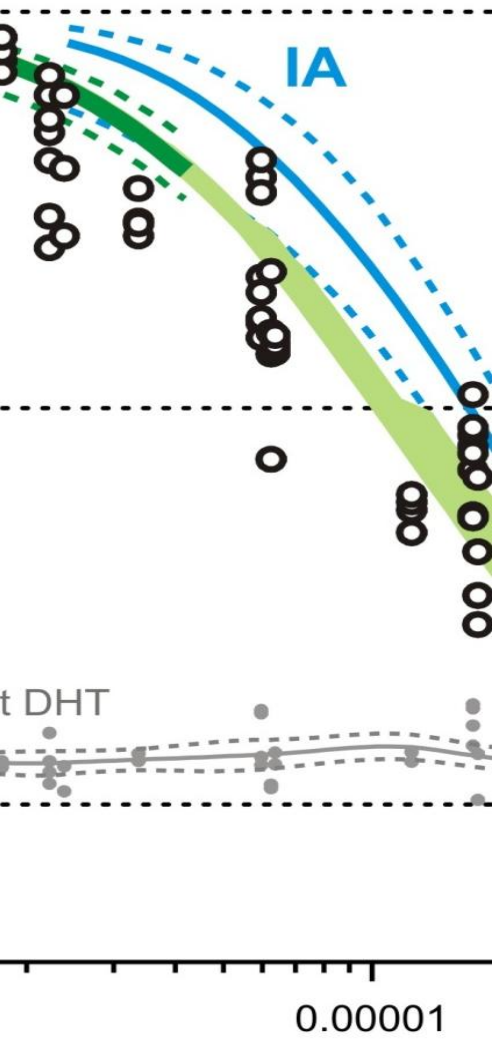
Solutions Norman Prioritisation Workshop



Mixture effects and prioritisation schemes

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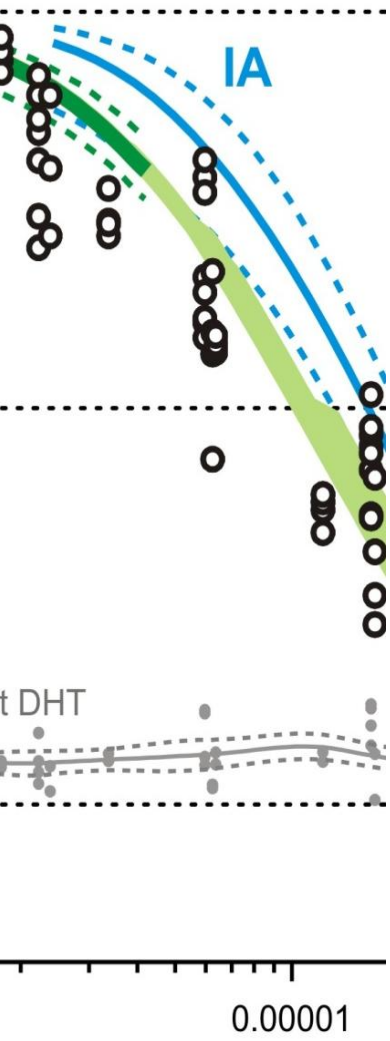
Paris 24 June 2014

Technical guidance for EQS

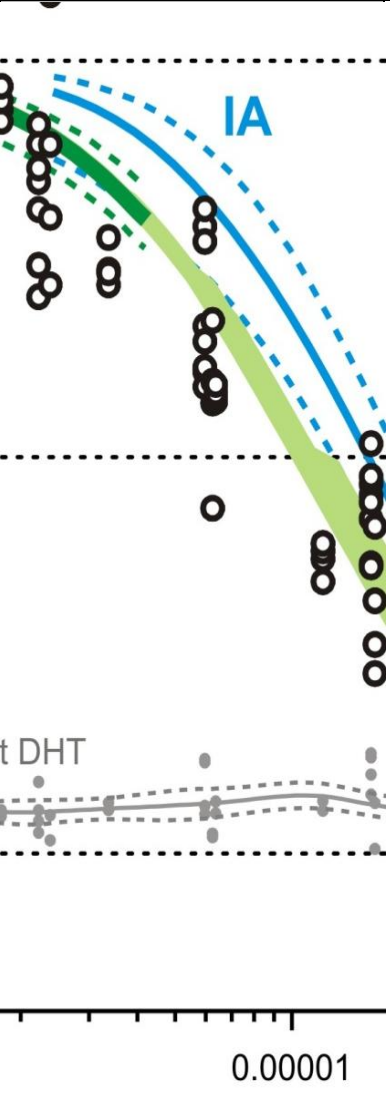


For **well-defined mixtures**, ie those with a well defined qualitative and quantitative composition, the toxic unit (TU) approach (e.g. Altenburger and Greco 2009) may be used to calculate the EQS.

EQSs may be defined for **grouped** substances that **exert a similar mode of action** and may be expressed according to the concept of Toxic Equivalent [TEQ] concentrations in environmental samples.

Guidance Document No: 27 Technical Guidance For Deriving Environmental Quality Standards, p 117

Why a similar mode of action?



- Effects can be predicted by using ***dose (concentration) addition*** or ***independent action***
- Concepts have been allied with modes of action: ***dose addition – similar action***; ***independent action – dissimilar action***

Independent action

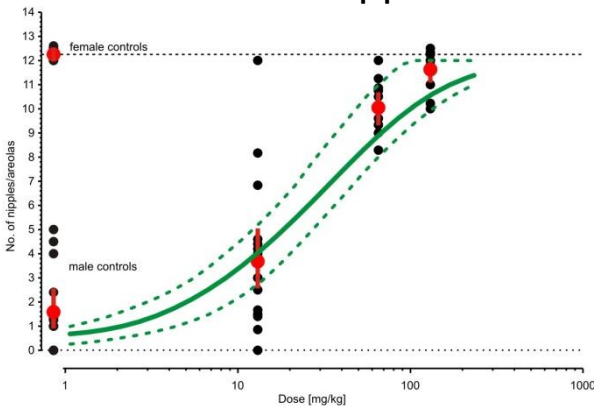
- Stochastic principles
- Additivity expectation: effect multiplication
- Simultaneous exposure: stochastic principles only fulfilled when components show **different modes of action** in inducing the **same effect**

Dose addition

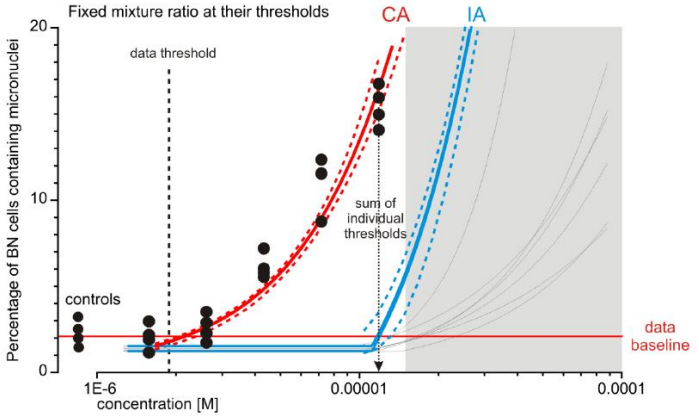
- Agents behave like “dilutions” of each other
- Contribute to joint effect in proportion to their dose
- **Additivity expectation**: addition of equi-effective doses
- Applied to combinations of **similarly acting** chemicals

Dose addition – examples of "similar action"

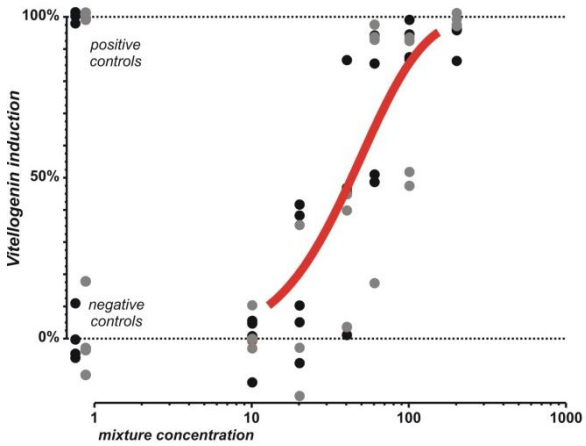
Retained nipples



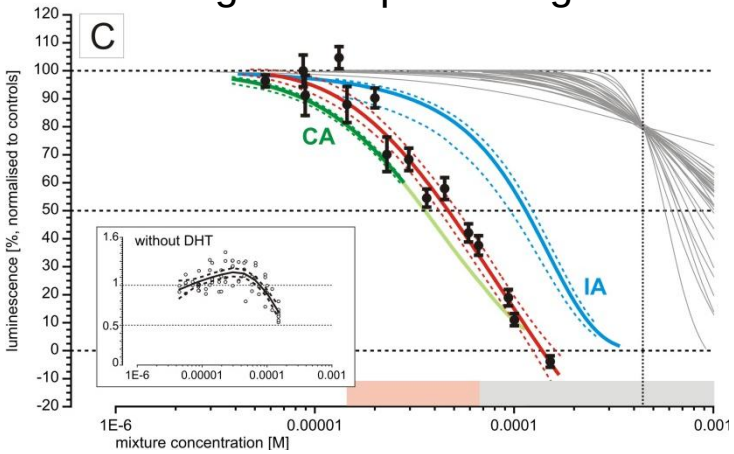
Micronuclei



Vtg induction (fish)



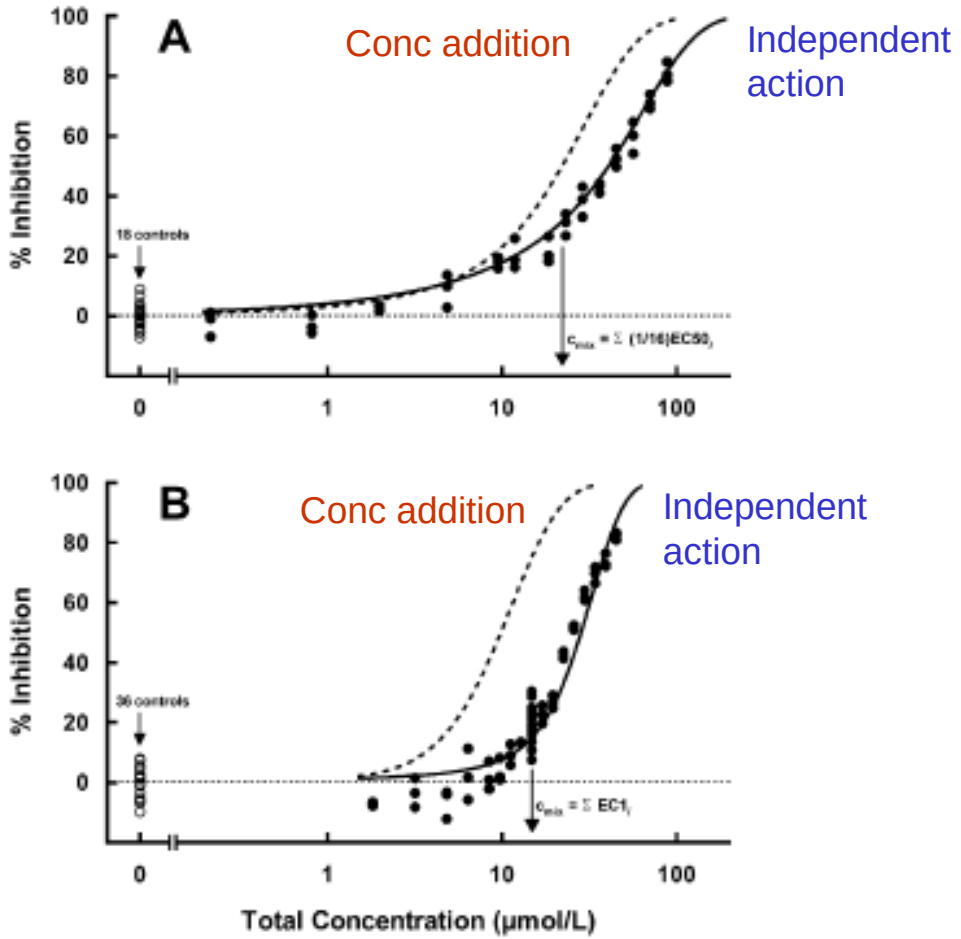
Androgen receptor antagonism



Algal toxicity of 16 dissimilarly acting toxicants

Faust *et al.* (2003) Aquat Toxicol **63**, 43

- Aclonifen
- 8-Azaguanine
- Azaserine
- CCCP
- Chloramphenicol
- DTMAC
- Fenfuram
- Kresoxim-methyl
- Metalaxyl
- Metazachlor
- Metsulfuron-methyl
- Nalidixic acid
- Norflurazon
- Paraquat
- Terbutylazim
- Triadimenol



Dose addition or independent action?

- **Are hypotheses about modes of action a reliable basis for declaring “similar action”?**

Mixtures of anticancer drugs

Phul *et al.* (in prep)

Etoposide

Melphalan

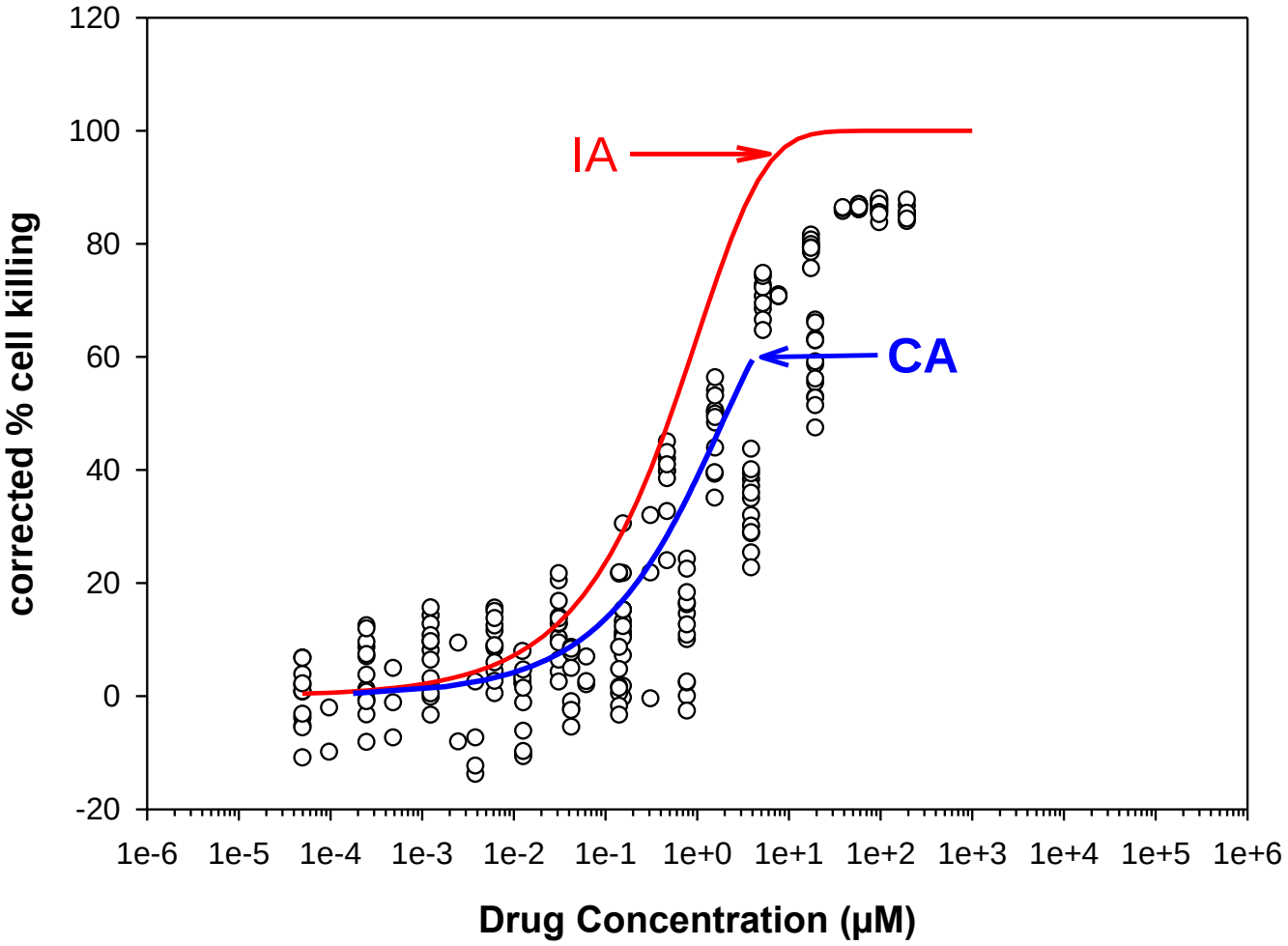
Doxorubicin

5 FU

Vincristine

Cis-Pt

Cyclophosphamide



Mixtures of aneugens and clastogens

Ermler *et al.* Arch Tox (2013)

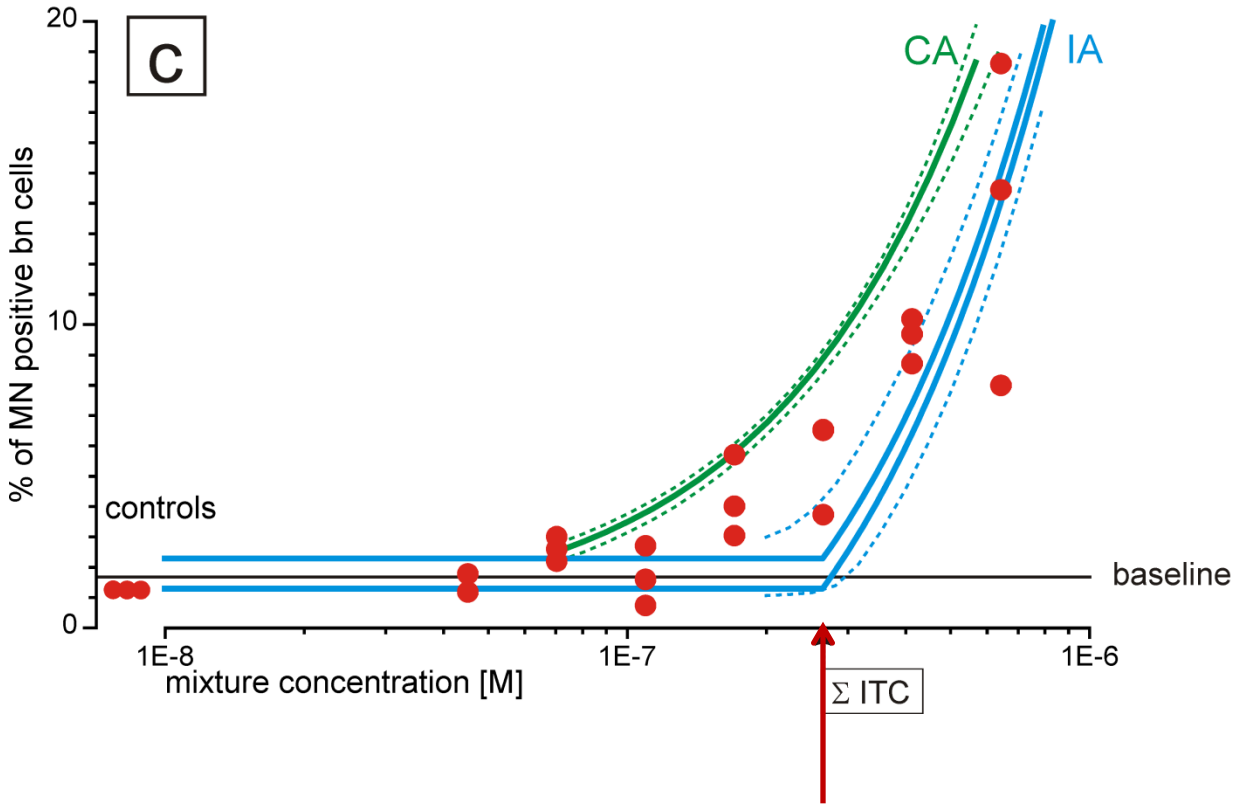
Flubendazole

Doxorubicin

Etoposide

Melphalan

Mitomycin C



How then should we group?

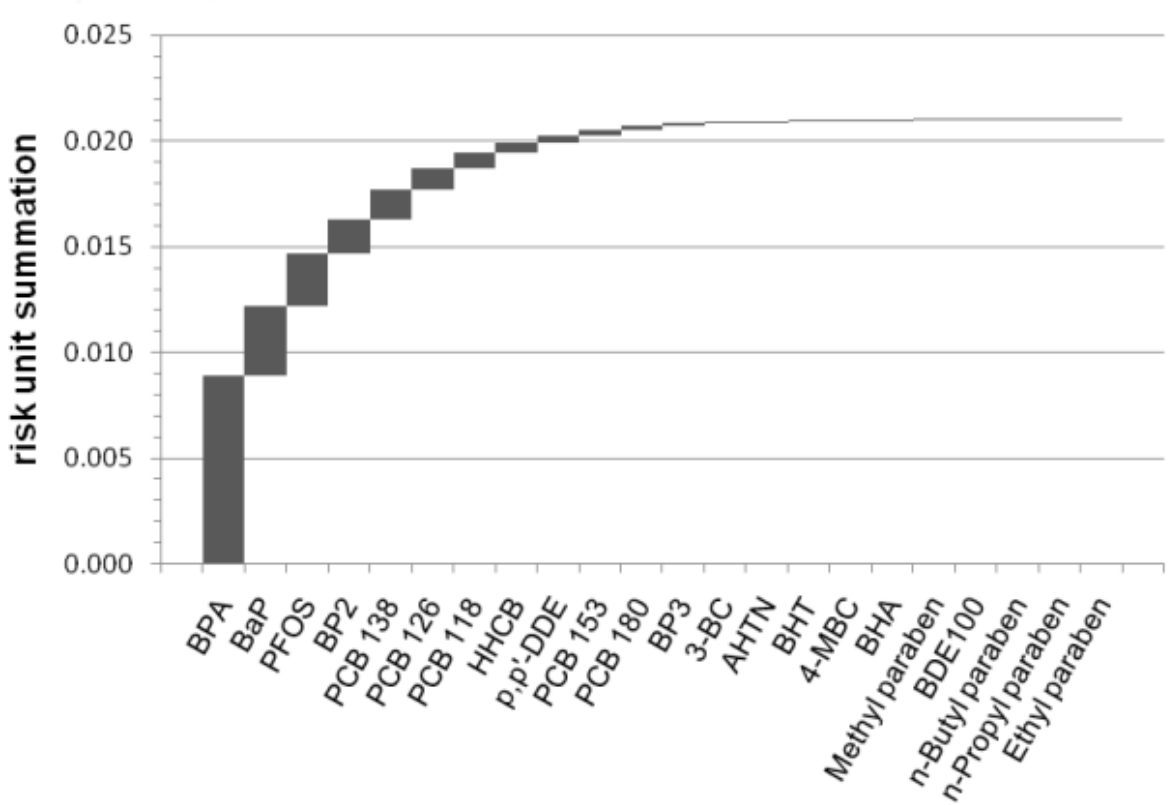
- US EPA: **Common mechanisms** – similar chemical structures
- US National Acad of Sciences (2008): Similar structures too narrow - **common adverse outcomes**
- Mechanisms: an **unreliable grouping criterion** – information often not available
- **Common adverse outcomes** irrespective of mechanisms

Ranking according to toxic units

Kortenkamp *et al.* (2014), Reproduction

"Real world" mixture of AR antagonists

…after having made a grouping decision



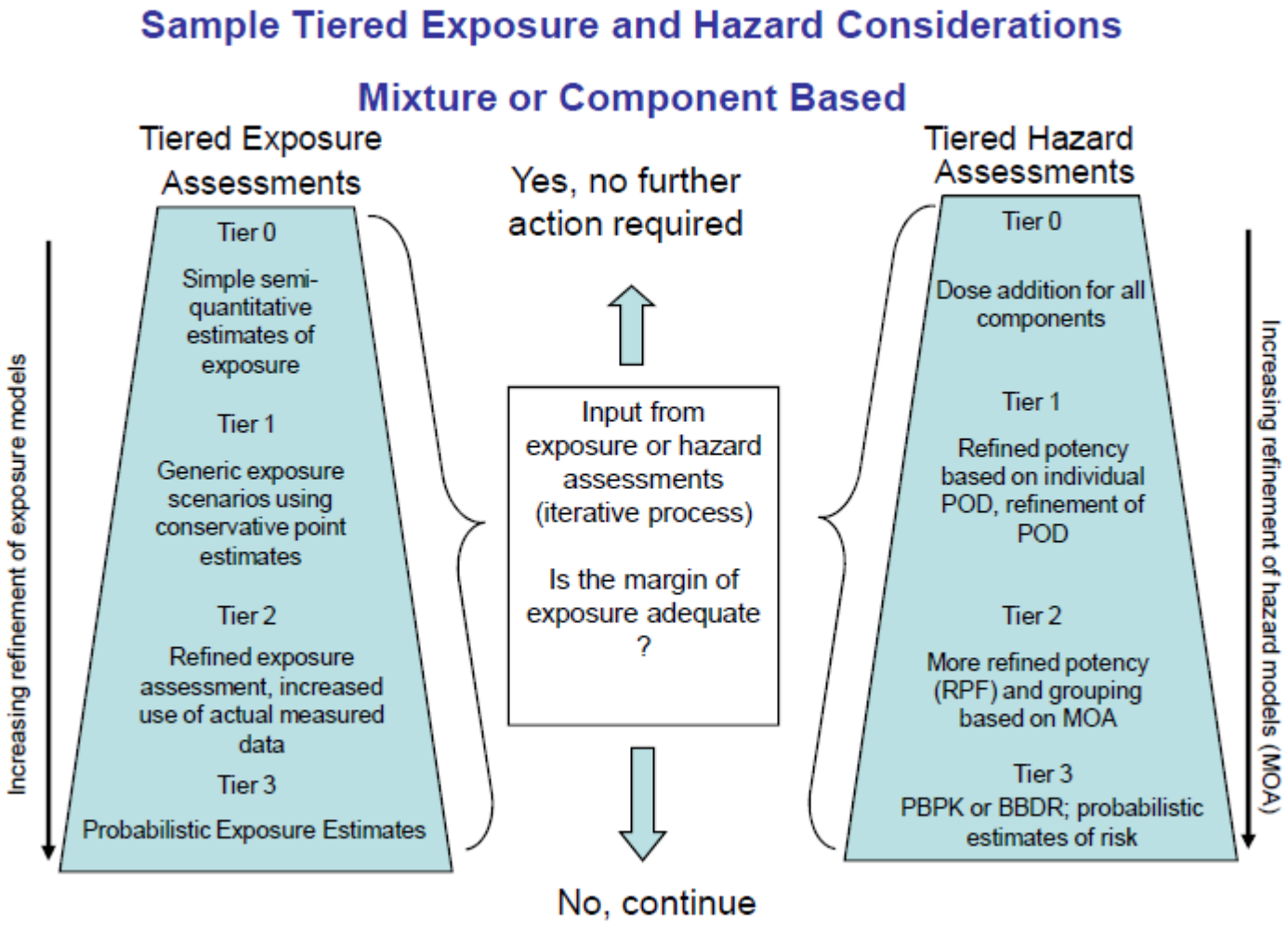
Pareto's 20:80 rule

Ranking affected by:

- Toxicity endpoint
- Grouping decision
- Data availability (only possible if data for risk quotients available)

Tiered approaches – bypassing the grouping issue?

WHO / IPCS 2009



Mixture risk assessment factors

$$\frac{\text{Intake}_1}{\text{Tolerable Daily Intake}_1} + \frac{\text{Intake}_2}{\text{Tolerable Daily Intake}_2} < 1$$

If every component is present at **TDI / n** the mixture effect is equal to an effect associated with TDI (the hope: 0)

MAF = n

Thank you