How do we handle cocktail effects of chemicals?

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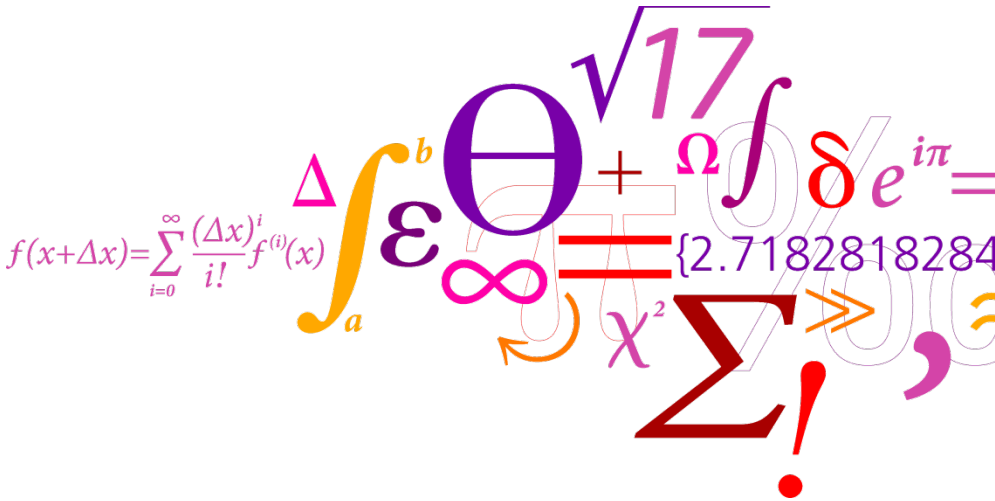
19th March 2015

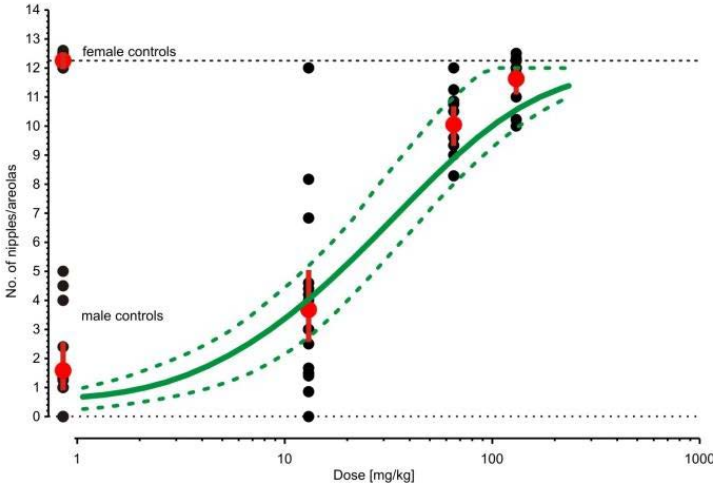


DTU Food
National Food Institute

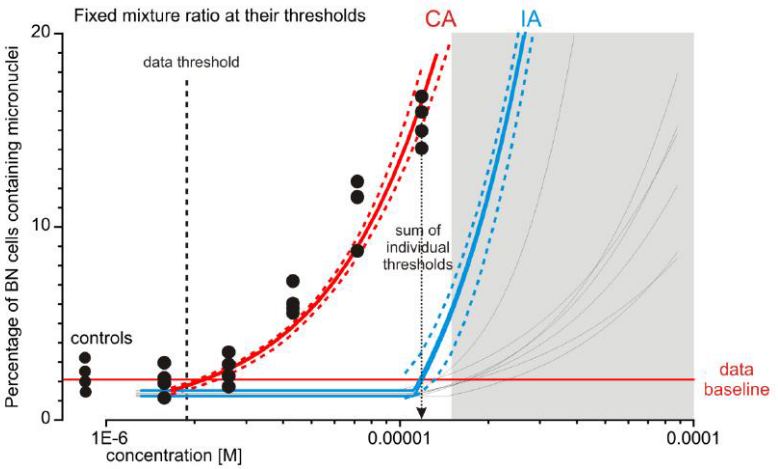
Prediction of cocktail effects

Dose addition provides good approximations of observed effects

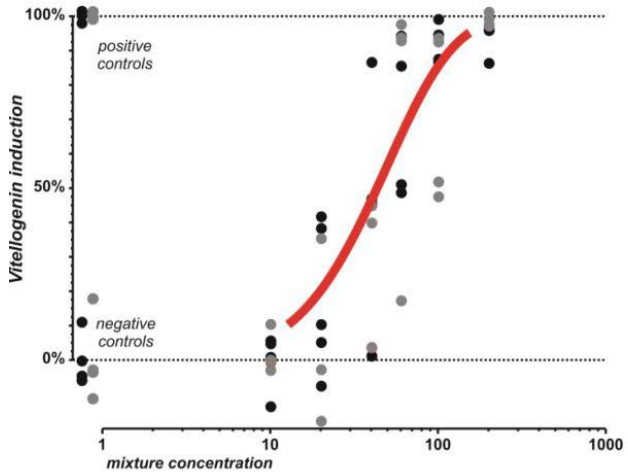
Retained nipples



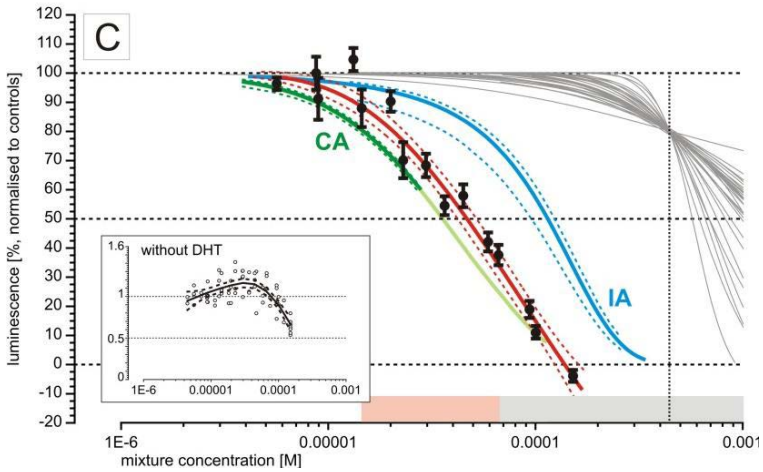
Micronuclei



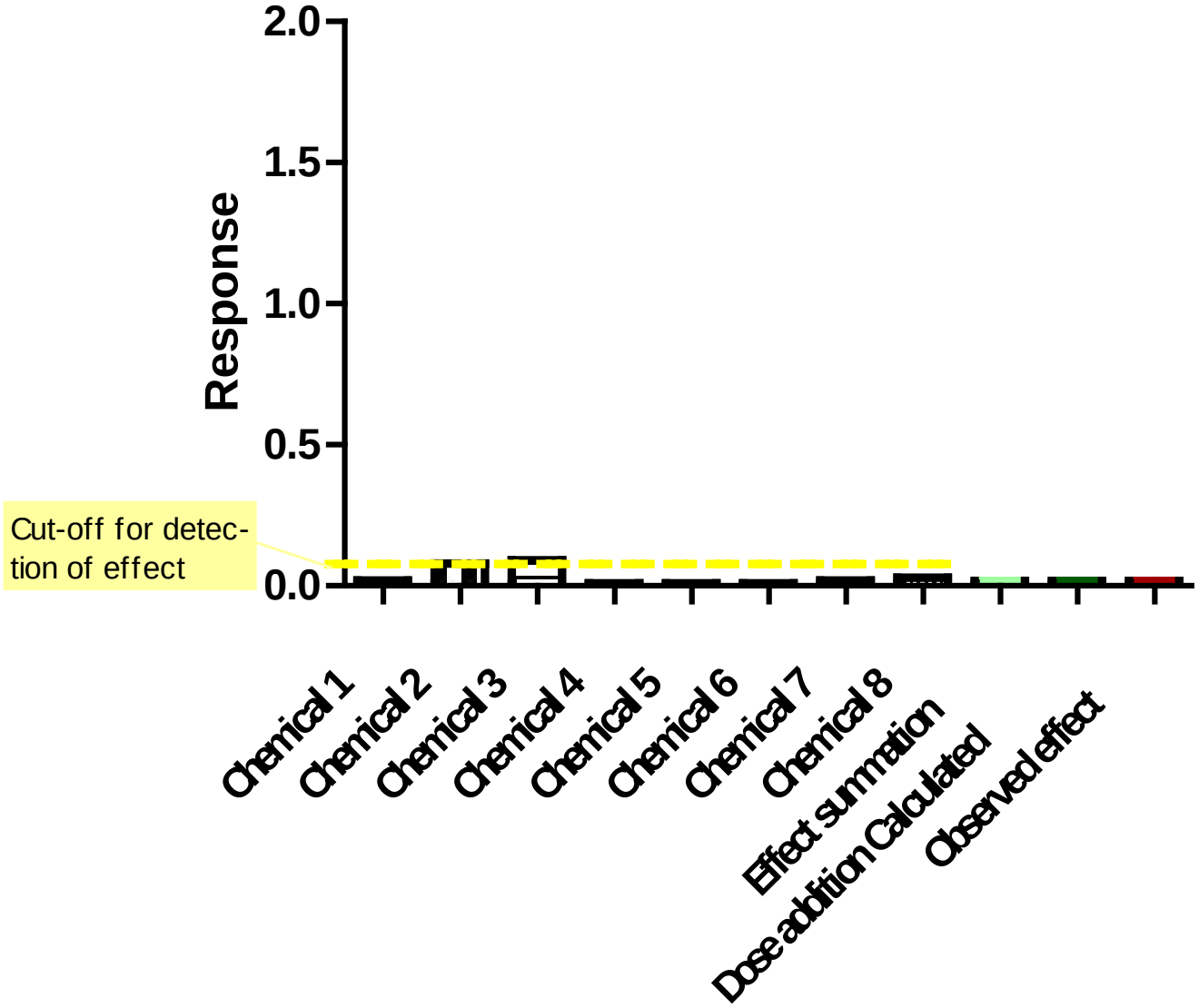
Vtg induction (fish)



AR antagonism



Chemicals with no effect individually can give rise to a marked cocktail effect



Hazard Index

$$HI = \sum_{i=1}^{n} \frac{EL_i}{AL_i}$$

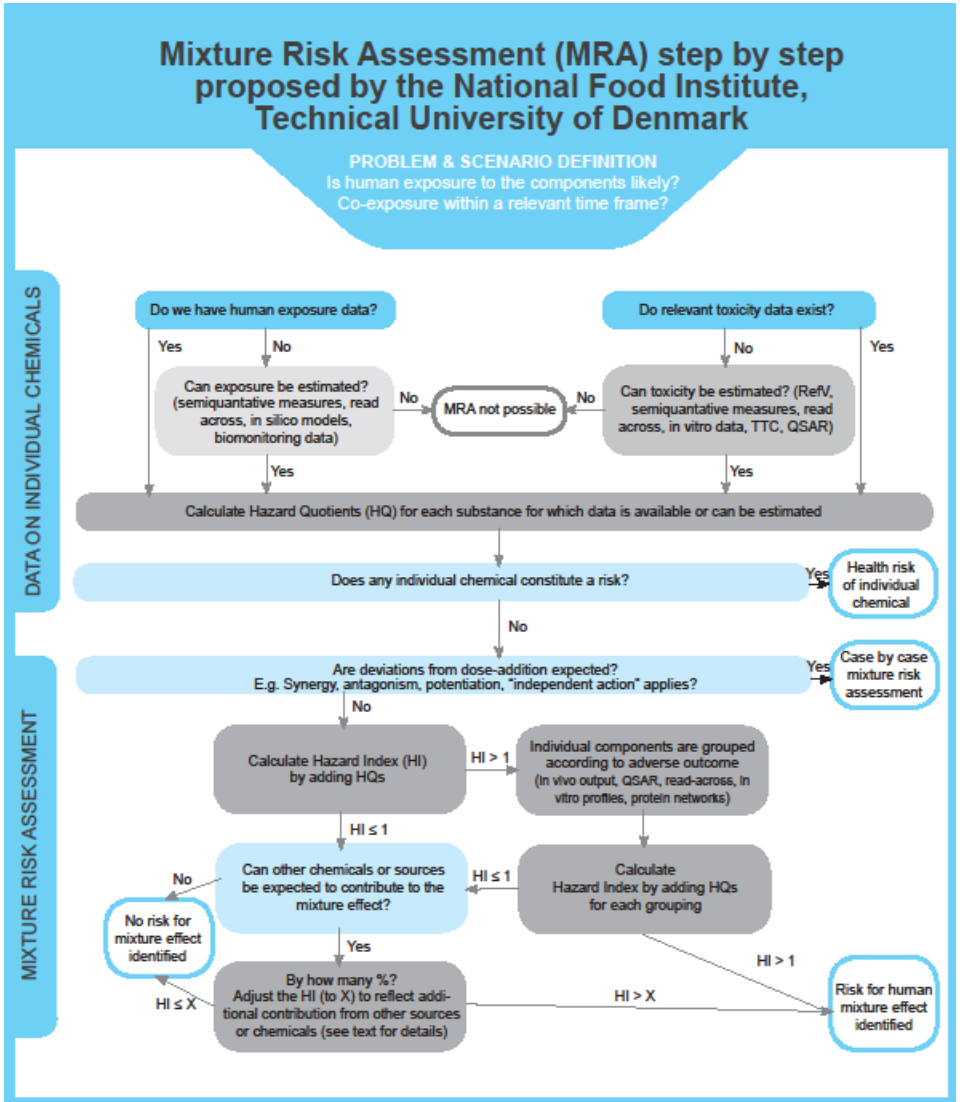
EL: Exposure level

AL: Acceptable level

- DNEL, TDI, ADI (uncertainty factor included)
- NOAEL, RefV, BMDL

Cut-off for HI is by default 1

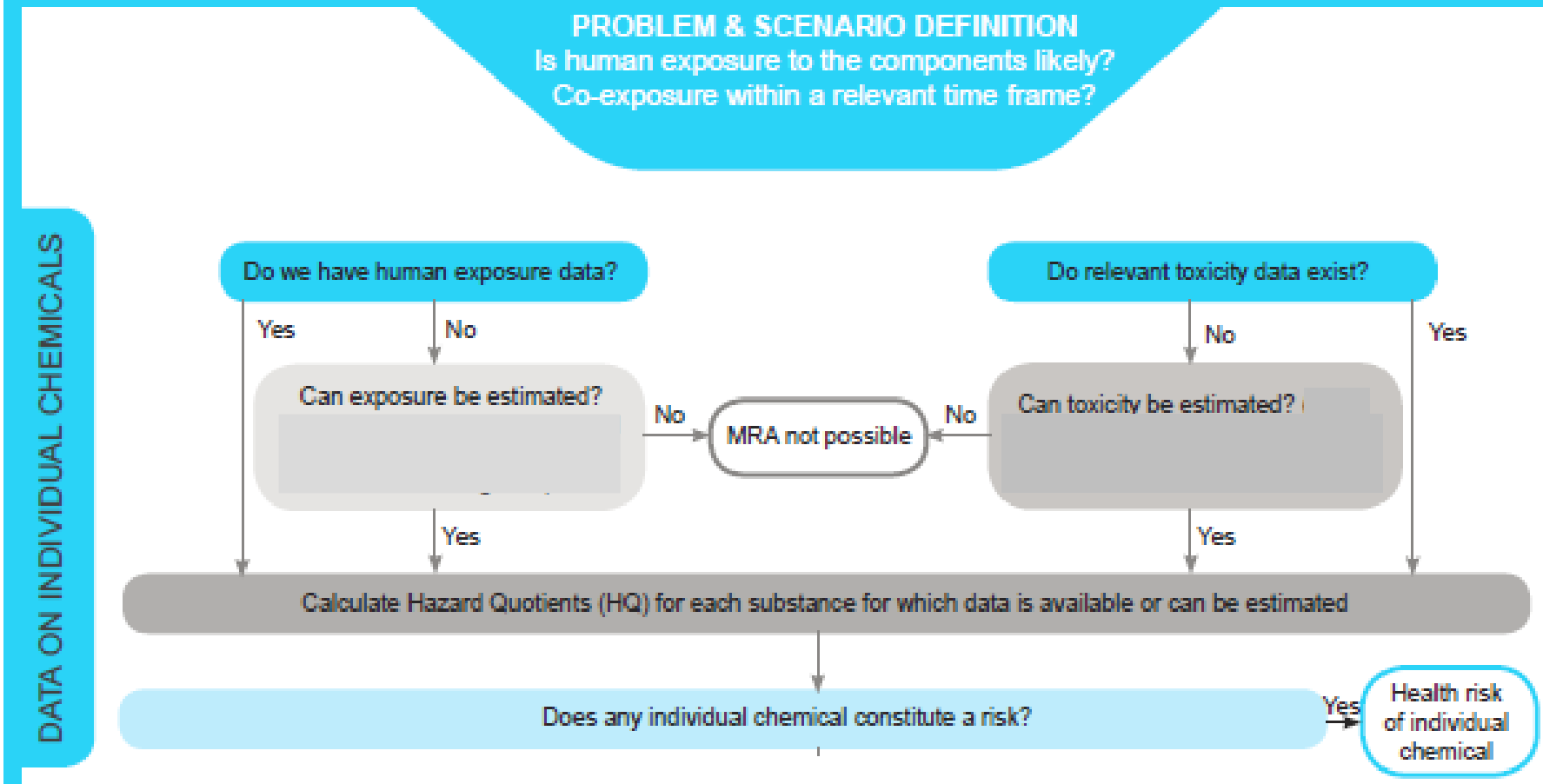
Mixture Risk Assessment (MRA) step by step proposed by the National Food Institute, Technical University of Denmark

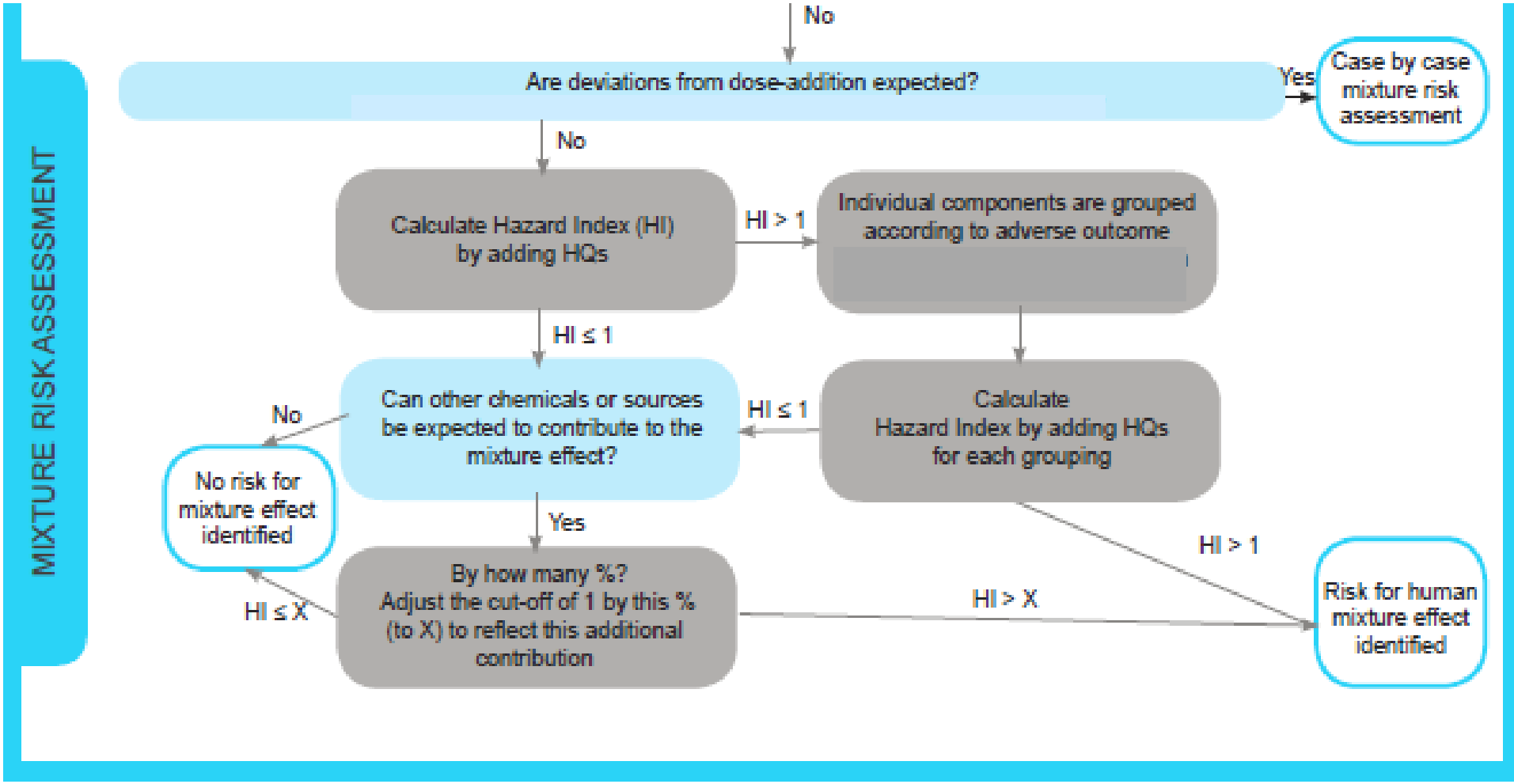


Assumptions, guidance and abbreviations:

The mixture composition is assumed being known.
Toxicity information of the entire mixture is assumed not being available. If this is the case,the mixture is risk assessed as one compound.
If exposure is based on food intake only, and exposure via other sources is likely, the percentage of the HI that is allowed being occupied by the actual mixture is estimated.
RefV: reference value based on ADI, TDI, DNEL etc
MRA: Mixture Risk Assessment;
HI: An interpretation of the Hazard Index actual value should be based on an expert judgment and uncertainties taken into account;
HQ: Hazard Quotient
TTC: Threshold of toxicological concern

Mixture Risk Assessment (MRA) step by step proposed by the National Food Institute, Technical University of Denmark




MIXTURE RISK ASSESSMENT
No
Are deviations from dose-addition expected?
Yes
Case by case mixture risk assessment
No
Calculate Hazard Index (HI) by adding HQs
HI > 1
Individual components are grouped according to adverse outcome
HI ≤ 1
Can other chemicals or sources be expected to contribute to the mixture effect?
No
No risk for mixture effect identified
HI ≤ 1
Calculate Hazard Index by adding HQs for each grouping
Yes
By how many %? Adjust the cut-off of 1 by this % (to X) to reflect this additional contribution
HI ≤ X
HI > X
HI > 1
Risk for human mixture effect identified

CASE: Exposure to a phthalate mixture

Phthalate	Estimated exposure from food (97.5th percentile, µg/kg bw/day)	Acceptable level (µg/kg bw/day)	Hazard Quotient (based on 97.5th percentiles)
DEHP	9.9	35	0.28
DBP	1	6.7	0.15
DiBP	2.7	420	0.006
BBP	1.3	500	0.003
Total Hazard Index			**0.44**

$$HI = HQ1 + HQ2 + HQ3 + HQ4 = \frac{exposure1}{AL1} + \frac{exposure2}{AL2} + \frac{exposure3}{AL3} + \frac{exposure4}{AL4}$$

CASE: Exposure to a phthalate mixture

DEHP, DBP, DiBP and BBP from various sources	Hazard Index (based on 97.5th percentiles)
Food	0.44
Articles	0.14
Dust	0.72
Indoor air	0.06
Total Hazard Index	**1.36**

Tool box for mixture risk assessment

- Tools for **Grouping of chemicals** (QSAR, integrative systems biology, metabolomics)
- **Flow diagram** for Hazard Index calculation
- **Software: 'Cocktail Effect Calculator'** containing:

  Module 1: Toxicity and exposure information for important chemicals

  Module 2: HI calculator

  Module 3: Mathematical modeling of effects

Take home messages

- Additive effects => cocktail effects can be predicted based on information on single chemicals
- Low doses of many chemicals can have a marked negative effect
- Grouping of chemicals by computational tools & metabolomics
- New methods for identifying problematic compounds in foods and food packaging developed
- Pragmatic approach for risk assessing cocktails developed
- Significant progress, but still many unresolved issues to be addressed

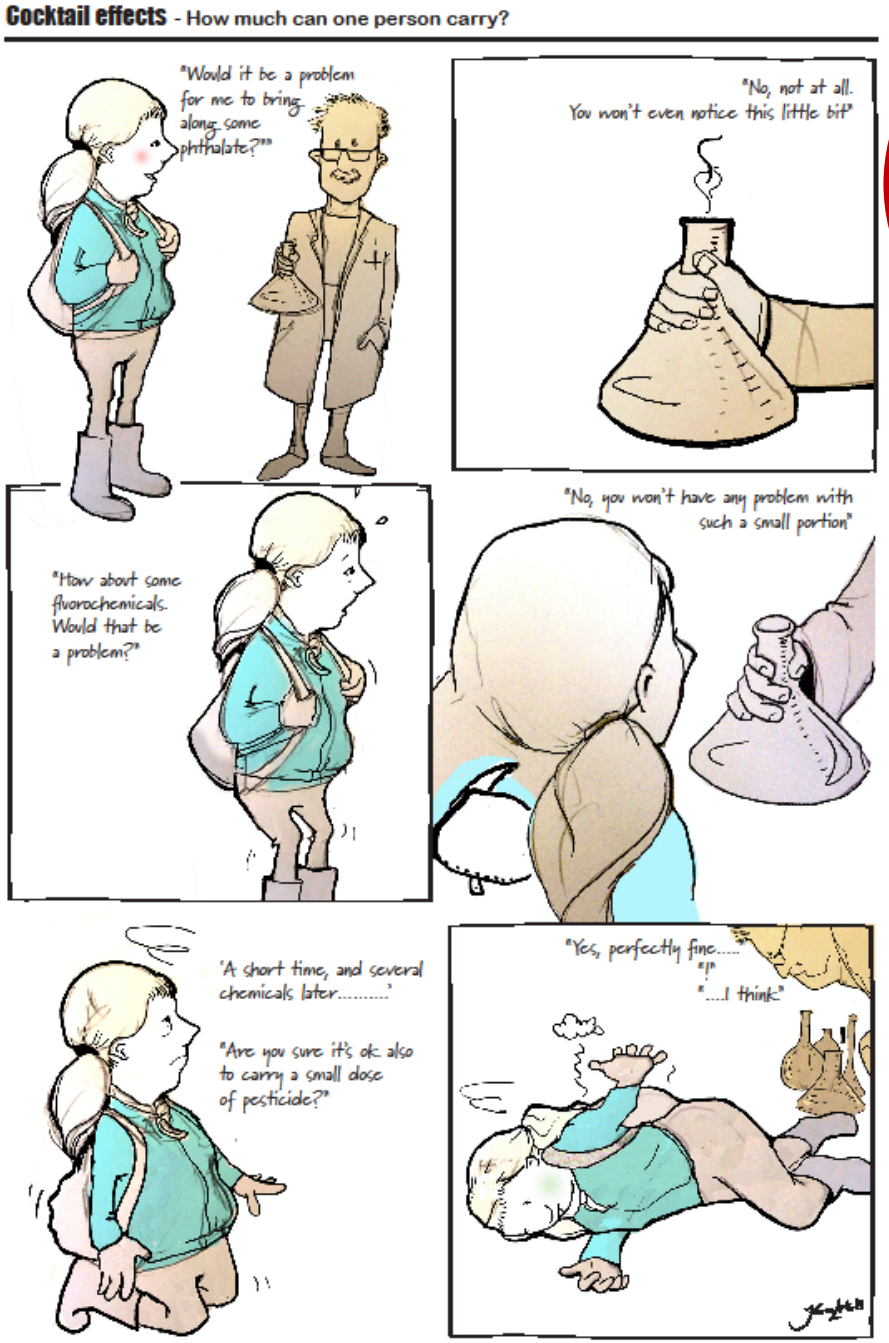
Perspectives

- Bottleneck: data gap on single chemicals
- Alternative ways of risk assessing chemicals
- Effects caused by ‘real-world’ mixtures
- Development and refinement of the tools for mixture risk assessment

Acknowledgements

- Ministry of Food, Agriculture and Fisheries of Denmark
- Danish Veterinary and Food Administration
- DTU Food
- DTU Systems Biology
- DTU Management
- Brunel University, UK
- University of Alberta, CA
- Environmental Protection Agency, USA
- The Food and Environment Agency, UK
- University of Rennes, FR

Thank you!



Cocktail effects – how much can a person carry?