



National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

Risk management challenges ahead in mixtures and cumulative environmental assessments

Theo Traas
Charles Bodar
Dick Sijm

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Introduction

- Exposure to mixtures is common; e.g.
 - Environmental exposure to brominated flame retardants
 - Agricultural worker exposure to carbamates
 - Environmental and human health exposure to dioxins (TEF / TEQ – approaches)
- In this presentation, focus on environmental assessment.
- There is a multitude of mixtures out there; many different chemicals (EINECS list > 100.000 chemicals, ~30.000 marketed in EU > 1 tpa)
 - ‘study combination of all chemicals everywhere’ doesn’t work, neither at the notification stage nor at the risk assessment/ monitoring stage



Continued

- Risk-driven priority setting
 - Is it possible in exposure assessment to zoom in on the relevant mixtures and substances in it, to prevent an expensive 'one precautionary approach solves all'?
- Would we need to adapt (EU) legislation to cover possible effects due to combination effects? And how? Focus on possibilities under REACH.



Hazard assessment

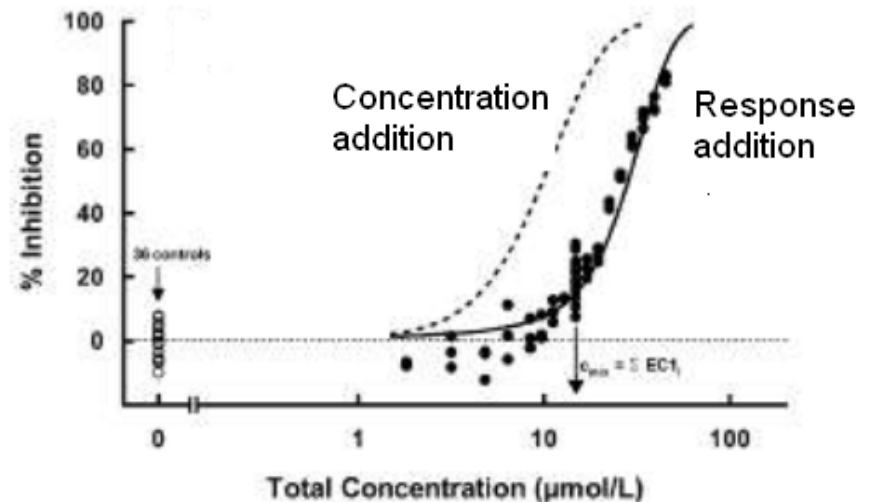
- Toxicity of mixtures, recognised long ago (e.g., Könemann 1981, Hermens et al, 1984), remains a cause for concern, to name a few:
 - Consumer exposure to several phthalates (DK restriction proposal under REACH)
 - Environmental and human health exposure to various chromates
- Two main concepts:
 - Concentration Addition
 - › Every chemical (at any concentration) adds up to the toxicity of the mixture
 - Response Addition or Independent Action
 - › Effects are statistically independent, zero effects (below threshold) do not contribute to joint effect of mixture



CA as a default

- Several studies with mixtures of chemicals with similar and dissimilar modes of action have confirmed that concentration addition (CA) is a conservative estimator of the toxicological effect of mixtures.

Faust et al 2003, effect of 16 dissimilarly acting chemicals on Algae



Due to this - in most cases relatively modest - over prediction, CA be used in risk assessment as the default approach (cf. SETAC Symposium feb. 2011, Kortenkamp this symposium)



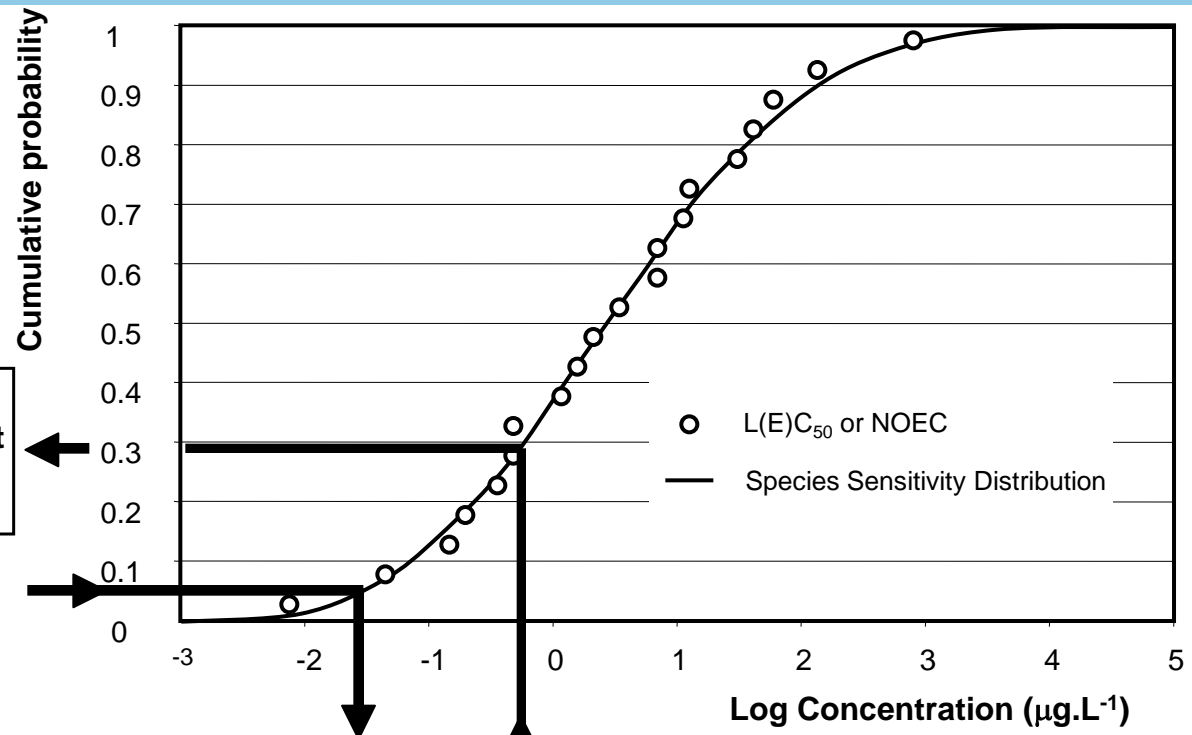
Expressing mixture toxicity

- Sum of Toxic Units (scaled on EC50 values)
- The sum of risk quotients per chemical: (exposure divided by ecological quality standards per chemical)
- Toxic equivalent concentration, e.g., for estrogen or dioxin-like compounds

$$TU = \sum \frac{C_i}{EC50_i}$$

$$HQ = \sum \frac{C_i}{EQS_i}$$

$$TEQ = \sum TEF_i \cdot C_i$$



Risk Assessment
↓
PAF

EQC ⇒ HC₅

- Ms-PAF, the fraction of species in the ecosystem that is potentially affected due to the mixture (ms-PAF), based on statistical species sensitivity distributions
- (Traas et al., 2002)

Sum 'toxic units' (NOEC based)

$$PAF_{TMOA} = \frac{1}{1 + e^{\frac{\log(\sum HU_{TMOA})}{\beta_{TMOA}}}}$$

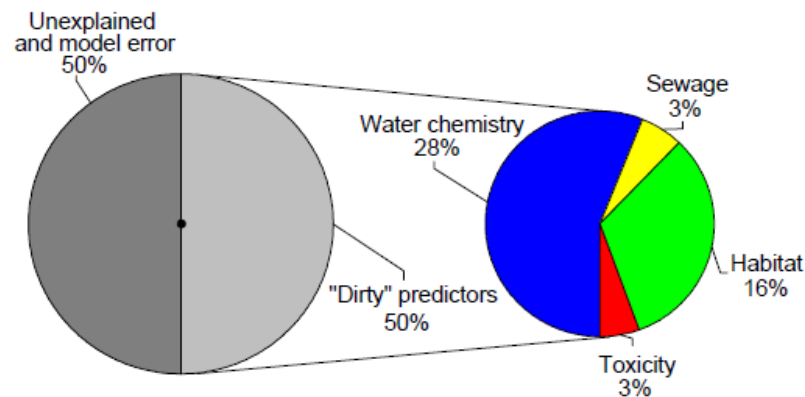


Challenge

- Expressing mixture effects for risk assessment purposes
- Simple, policy approach (but scientifically challenged when using different assessment factors) using quality standards:

risk controlled $HQ < 1$

- More refined but more data-hungry and still needs further field validation: ms-PAF (De Zwart et al., 2006)





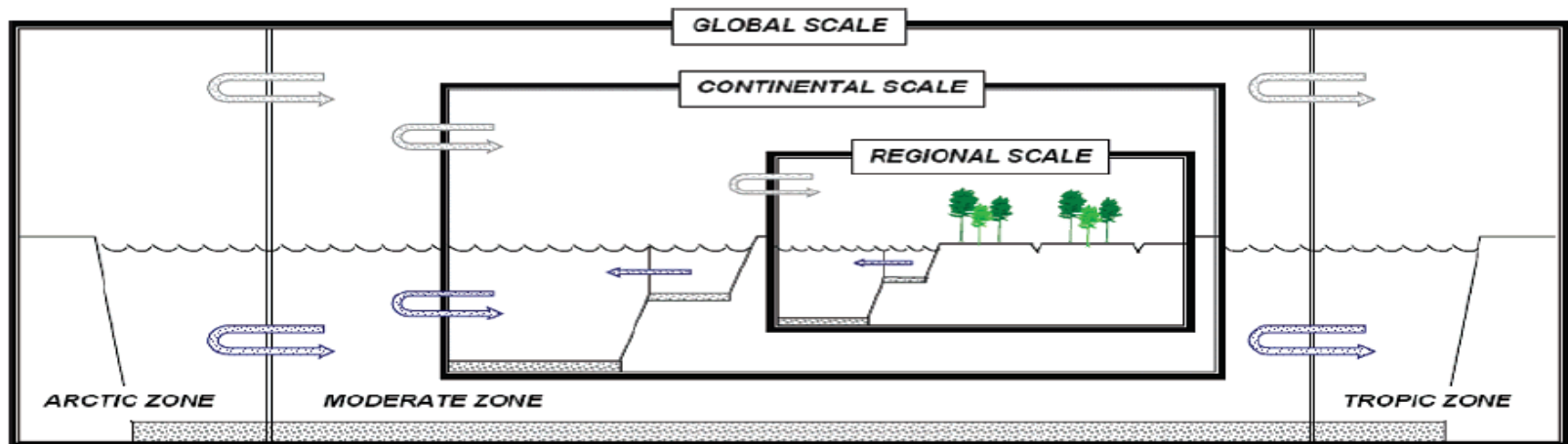
Exposure assessment of mixtures

- Are we facing very complex assessments?
 - In principle yes, but from field experience complexity can be reduced
 - > as < 10 chemicals dominate overall toxicity
 - > i.e., challenge is to focus on most relevant substances!
 - > focus is needed on relevant sites (with highest overall toxicity)
 - > using Toxicity Identification Evaluation (TIE) to zoom in
- Case studies
 - Modelling of statistical measure of overall toxicity (msPAF) on coastal North Sea waters
 - Biomonitoring data from Dutch surface waters



Modelling study by Habers et al. 2006

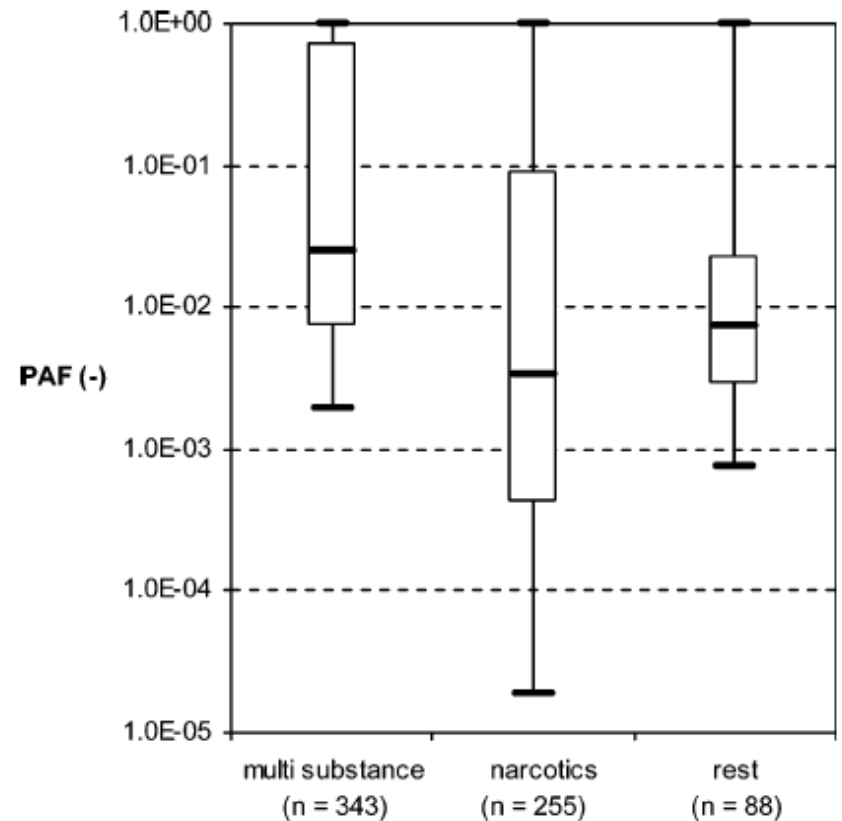
- quantifies toxic pressure of mixture of HPVCs in North Sea
- hazard: SSDs for each compound → msPAF
- exposure: production volumes, emission rates and fate assessment (box model) for each compound
- Risk: probability and magnitude of ecological effects in the aquatic ecosystems for cumulated emissions of all substances





Results

- Combined msPAF (EC50-based) of all 343 chemicals is 0.025 (2.5% of the species are exposed > EC50)
- Gross ranking of chemicals in categories:
 - With 95% confidence, 283 of the 343 chemicals (83%) contribute negligibly (less than 0.1%) to overall toxic pressure,
 - ‘only’ 60 (17%) need further consideration





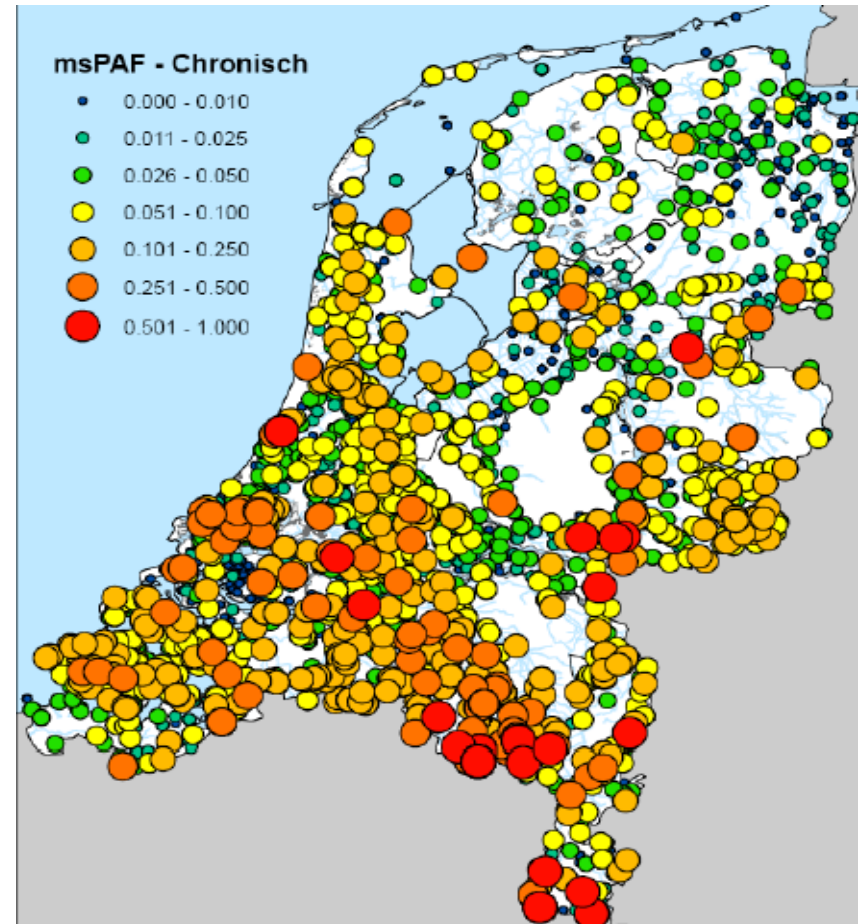
Conclusions from case study Habers et al.

- It is possible to hypothesize which are the relevant ones, based on available and updated information from notification/ registration (and a LARGE number of assumptions)
- A fairly limited number of substances causes most of the toxicity
- Couldn't we reduce the toxicity by further assessing the 60 chemicals identified, i.e. on a case by case basis?
 - > What if 30.000 chemicals were to be assessed?
- This is a regional steady state assessment and spatio-temporal issues probably still exist
 - > Also scope to further explore local and dynamic models



Monitoring study by de Nijs et al. (2008)

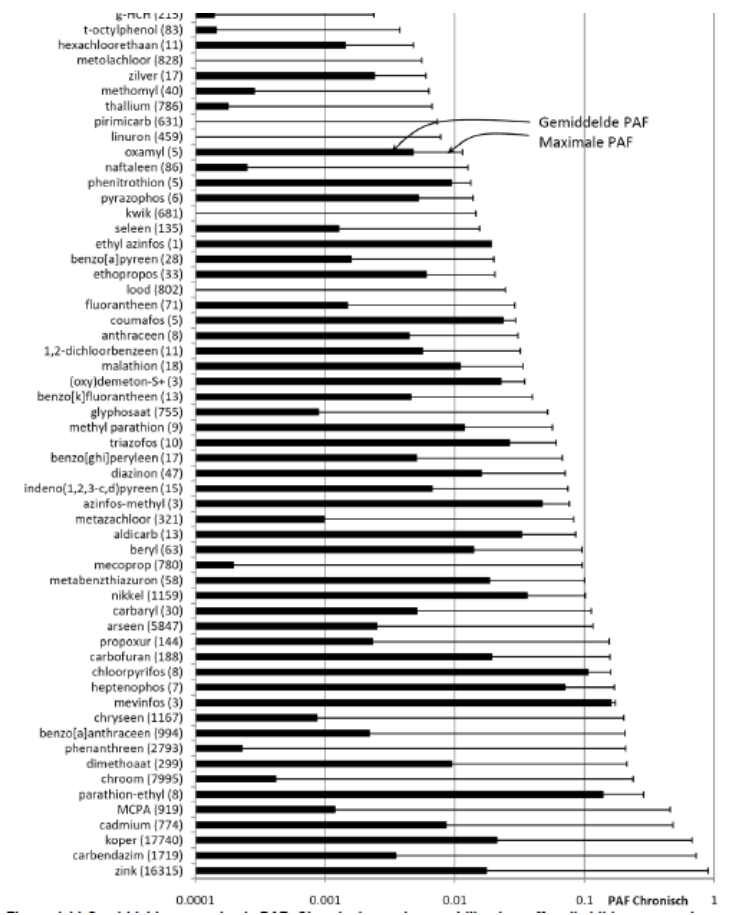
- Monitoring data were used from 2005 and 2006.
- The toxicity is expressed as msPAF, based on NOEC data
- The method allows to identify hotspots (percentile values of the effect distribution)





Selection of priority chemicals

- Metals : zinc, copper, cadmium, chrome, nickel, arsenic
- PAHs: benzo(a)anthracene
- PPP: carbofurane, carbendazim, dimethoate





Conclusions from de Nijs et al.

- Monitoring data can be used to calculate mixture toxicity effects
- Statistical analysis of the data allows to identify substances that contribute most to the overall toxicity
- There is a strong correlation (> 0.8) between number of substances in the mixture and msPAF; i.e. mixture toxicity plays an important part in the field
- It was shown that national quality criteria for some priority chemicals were not met! i.e. there is scope for improvement via single toxicity-based measures.
- *Challenges exist in the area of fate, bioavailability and representativeness of the monitoring data*



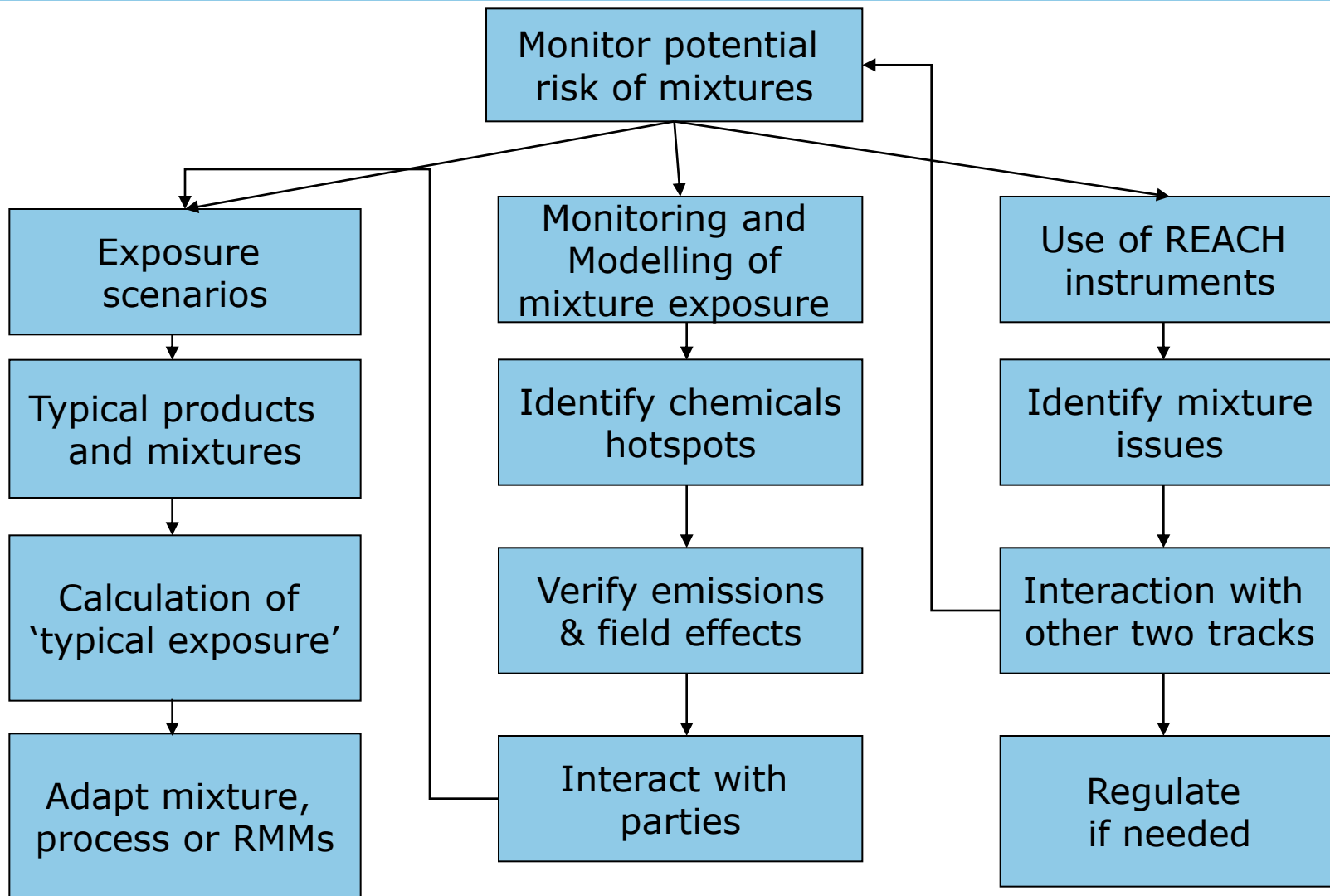
Way forward for exposure

- (Houston) we have a problem indeed. But we need to better define when single substance approaches are not protective.
- Can we address mixture exposure and ensuing risks in current risk assessments?
 - From a scientific point it seems we can, even though exposure to mixtures is still not easy to characterise quickly and completely
 - From a practical point of view, it is possible to prioritise and zoom in on substances that dominate overall toxicity
- Priority setting needs to be done by both Industry and Authorities to identify the most relevant mixtures and (groups of) chemicals
- This may need an extension of single chemical exposure scenarios into relevant 'mixture exposure patterns'. Information on use and emissions in the supply chain will greatly increase over the next 10 years. From this, we should be able to determine priorities.



Three pronged attack

- Extension of Industries activities to develop exposure scenarios and to measure or estimate emissions and exposure of relevant mixtures
- Modelling and monitoring activities of Authorities to identify hotspots, problem chemicals or groups
- Use of legislative instruments to manage risks emissions of mixtures to safe levels, e.g.
 - focus on exposure and hazard assessment under REACH registrations (NEW, by Industry)
 - focus on authorisation under REACH (TO BE FURTHER DEVELOPED, by Authorities)
 - focus on market and use restrictions under REACH or WFD (TO BE FURTHER DEVELOPED, by Authorities)





Challenges for authorities

- Authorities have a responsibility to push the barrier and try to adapt REACH for mixture toxicity
- Identify triggers for further assessments for relevant emissions when:
 - toxicological similarity of products with
 - > equal function
 - > multiple applications of (similar) chemicals for consumer / worker populations, e.g. the DK phthalate restriction proposal
- Prioritise the efforts based on most relevant chemicals and exposure patterns.



Challenges for authorities (2)

- Do modelling studies based on information from notification / registration and modelling chain
- Analysis of monitoring data
- Water Framework Directive can be used to measure overall effect (across regulations/ directives) on ecosystem quality.



Challenges for industry (REACH inspired)

- Take combination effects into account in exposure estimation,
 - more knowledge on DU use is becoming available (via REACH)
 - Prioritise based on overall mixture toxicity
- Triggers should be based on
 - > 'typical' products or product groups
 - > multiple uses of similar compounds, e.g. plasticizers, solvents
 - > defined sets of 'standard chemicals' in regular industrial or consumer products, i.e. rethink single chemical exposure scenarios into 'mixture exposure patterns'
- Monitoring responsibility, e.g.
 - Effluent / emission monitoring
 - Combined exposure calculations; e.g. the overall SIEF tonnage
 - Improvement of emission estimates under REACH



Cooperation needed

- Authorities and Industry can make this work if
 - Sufficient emission and exposure information is provided in the registrations, allowing for mixture toxicity assessments
 - The supply chain is pro-active in identifying mixture toxicity issues and use this information
 - They cooperate in developing the appropriate tools to address the mixture toxicity issues in exposure scenarios and the related exposure estimation
 - Agreement can be reached on how to prioritise our efforts.





Thank you for your attention!

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Contact: theo.traas@rivm.nl

