



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

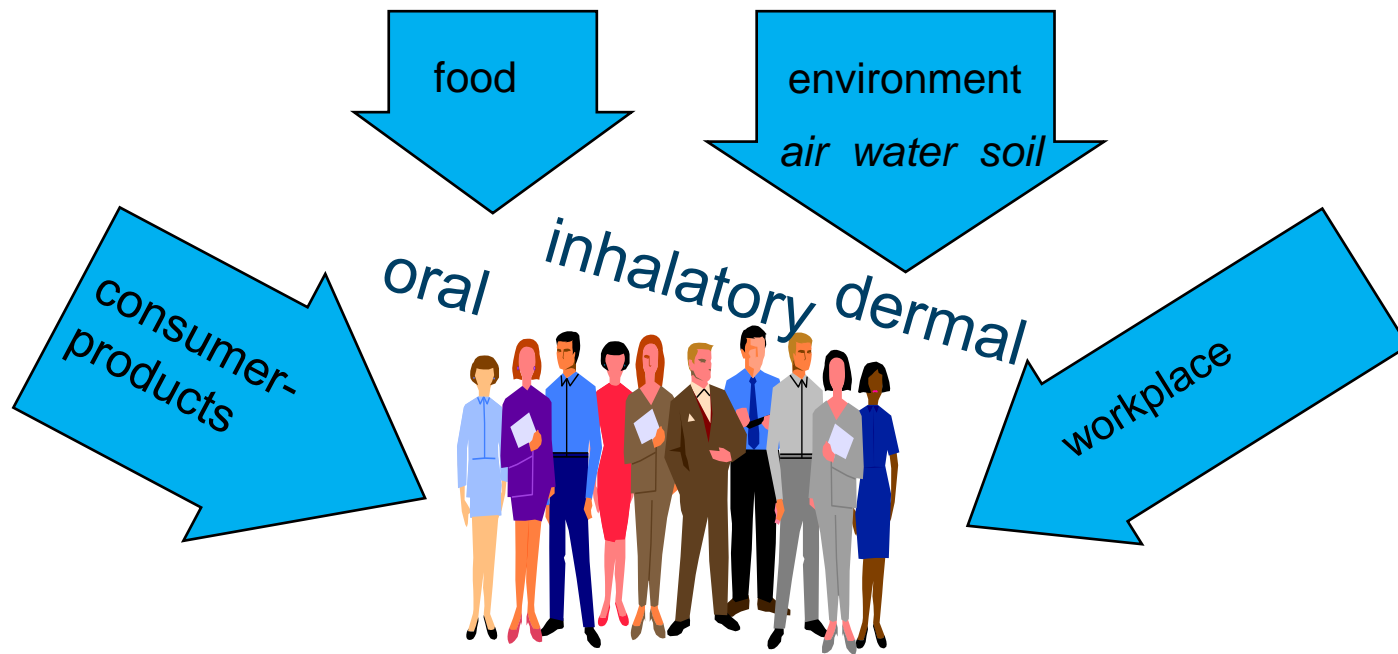
# Mixture toxicity Introduction

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# Introduction





## Concerns

- Increasing concern about exposure to chemicals (and other stressors) alone and in combination
  - REACH
  - Regulated substances (*e.g.*, pesticides, biocides, cosmetics)
  - Unintentional mixtures
- For consumers, workers and regulators
  - Need to consider combined exposures is mandated or recommended in some regulations
  - Combined exposure is priority in the European Chemical Strategy for Sustainability (to be incorporated in relevant legislation by 2022)
- There is a sound scientific rationale for considering at least some exposure combinations together
- Combined exposure (mixtures) can be defined very broadly



# 'Some' Activities

- **USEPA (2002)** Guidance on cumulative risk assessment of pesticide chemicals that have common mechanisms of toxicity. Washington DC; 2002
- **WHO/IPCS** (2011) Meek MEB, Boobis AR, Crofton KM, Heinemeyer G, Raaj M, Vickers C. Risk assessment of combined exposure to multiple chemicals: a framework. Regul Toxicol Pharmacol. 2011; 60:S1.
- **European Commission** 2012: Commission Communication on the combination effects of chemicals/chemical mixtures (COM(2012) 252 final). In this Communication, several areas that need to be further addressed and data gaps have been identified.
- **JRC** (2015) Scientific methodologies for the combined effects of chemicals – a survey and literature review; EUR 27471 EN; doi:10.2788/093511.
- **SCHER, SCCS, SCENIHR**. Toxicity and assessment of chemical mixtures. European Union Commission; 2012. DOI: 10.2772/21444.
- **EFSA** Panel on Plant Protection Products and their Residues. Scientific opinion on the identification of pesticides to be included in cumulative assessment groups on the basis of their toxicological profile. EFSA Journal. 2013; 11(7):3293. DOI: 10.2903/j.efsa.2013.3293.
- **EFSA** Guidance on harmonised methodologies for human health, animal health and ecological risk assessment of combined exposure to multiple chemicals. EFSA Journal 2019;17(3):5634
- **RISK21**. ILSI Health and Environmental Science Institute; 2015 (<http://www.risk21.org/>).
- **EuroMix**. National Institute for Public Health and the Environment. (<https://www.euromixproject.eu/>).
- **OECD**: TFHA and TFEA
- **EU** Chemical Strategy for Sustainability



# Definitions

## Unintentional mixtures

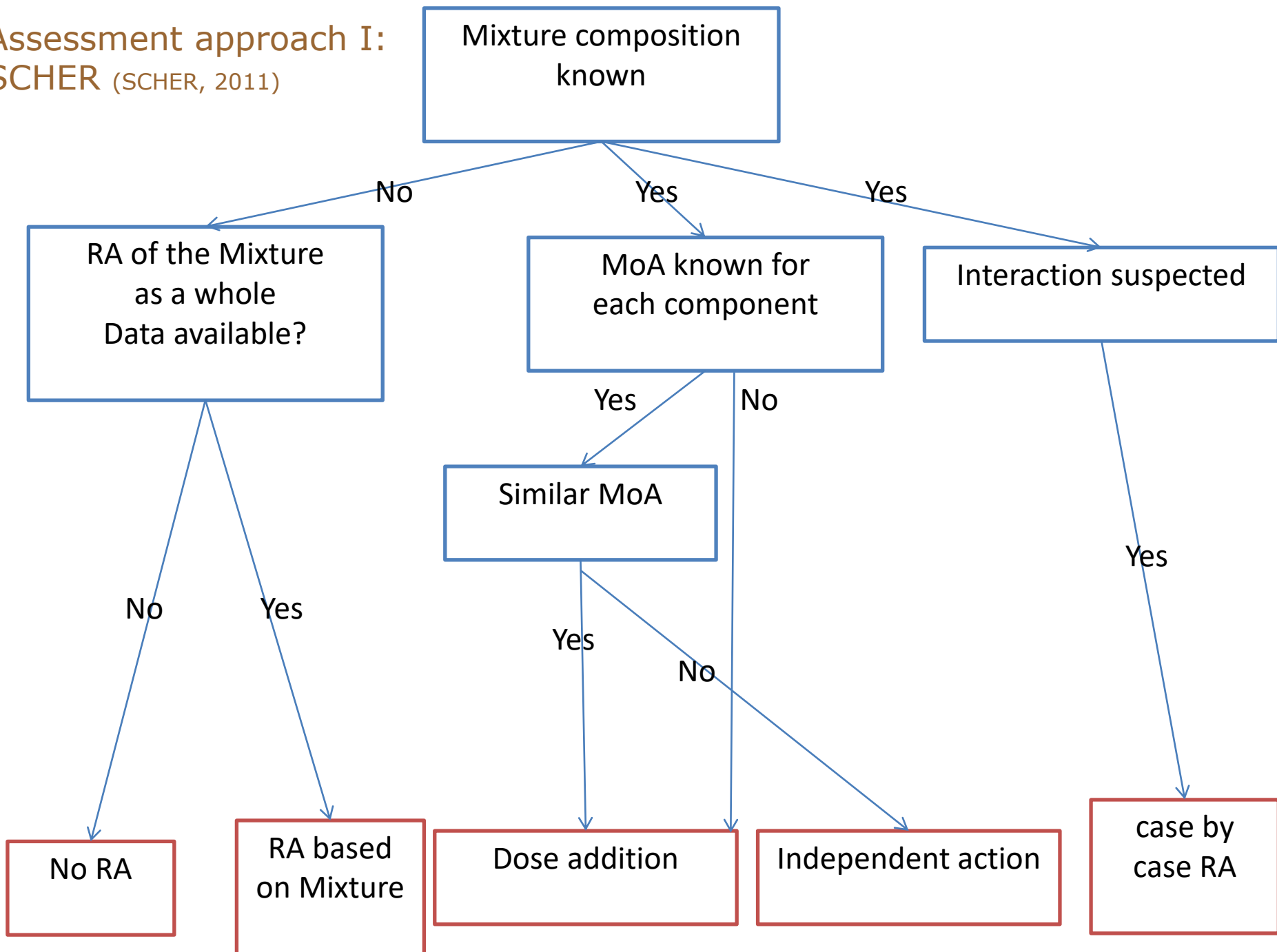
- Aggregate exposure: single chemical, all routes
- Combined exposure: multiple chemicals/stressors, single or multiple routes
  - > Dose/concentration addition (similar action)
  - > Independent action (dissimilar action, response/effect addition)

Whole mixtures (intentional): acts as single component, composition unchanged

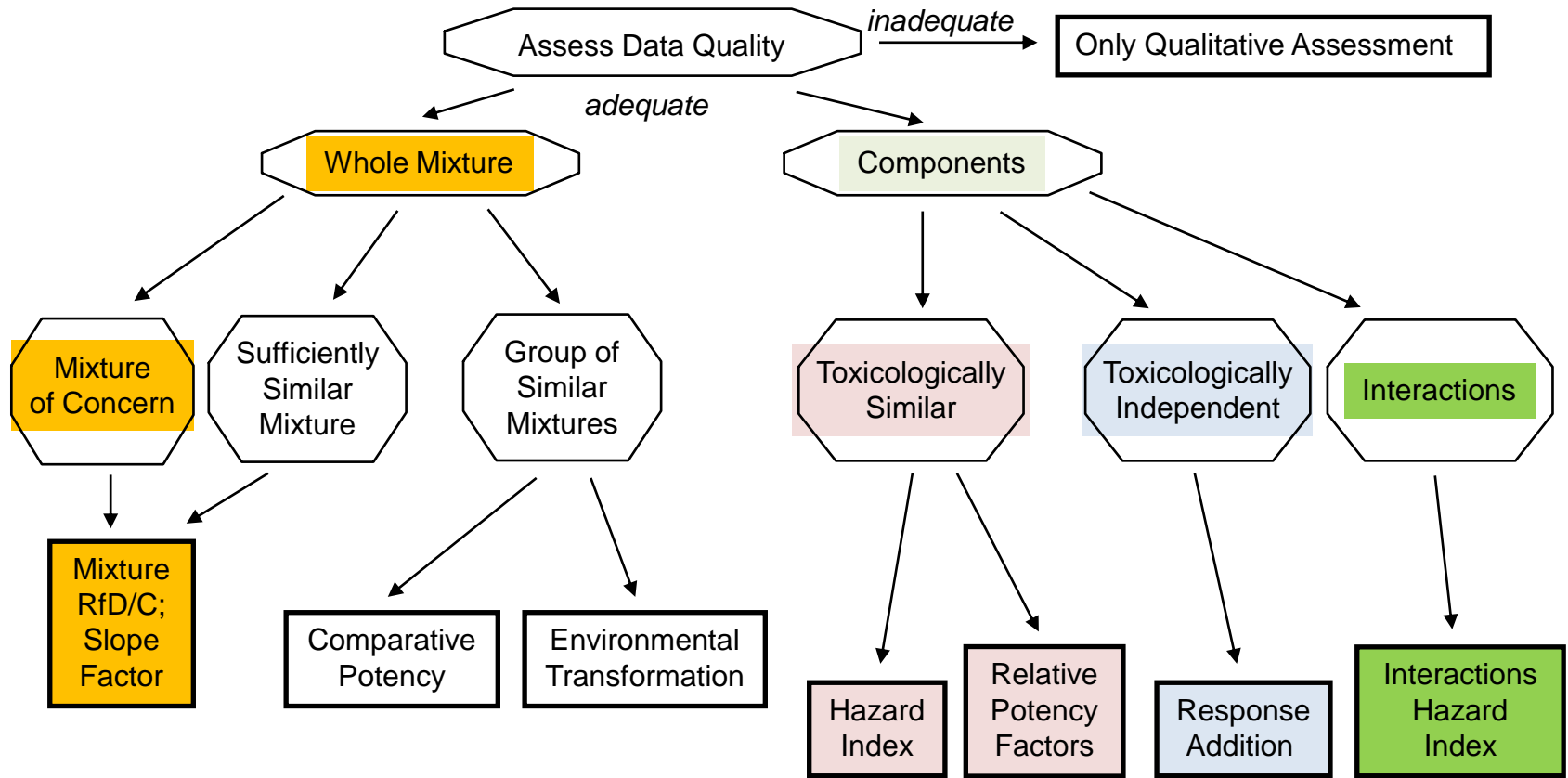
- Interaction: synergism or antagonism



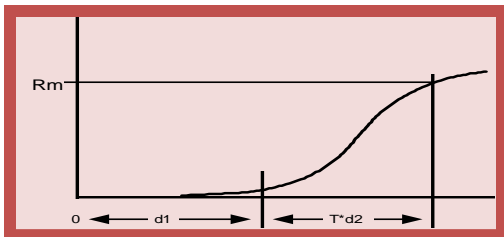
Assessment approach I:  
SCHER (SCHER, 2011)



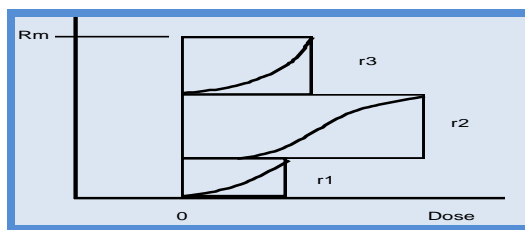
# Assessment approach II (US-EPA)



**Dose Addition**



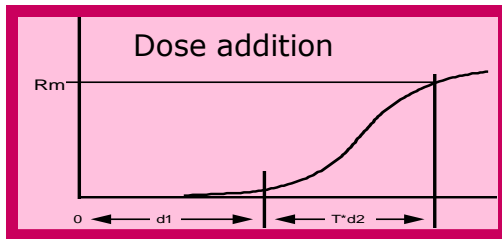
**Independent Joint Action**



**Interaction (> or < dose addition)**

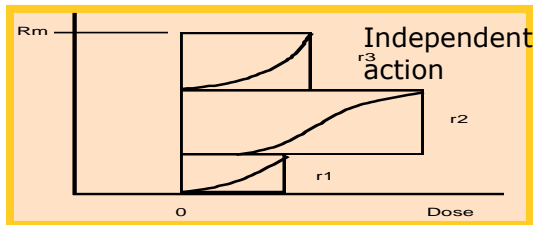


## Assessment approach to mixture toxicity III



$$HI = \sum_{i=1}^n \frac{\text{estimated intake}_i \text{ or } c_i}{HBGV_i}$$

Other approaches: Reference Point Index, Point of Departure Index, Relative Potency Factor/Toxicological Equivalency Factor



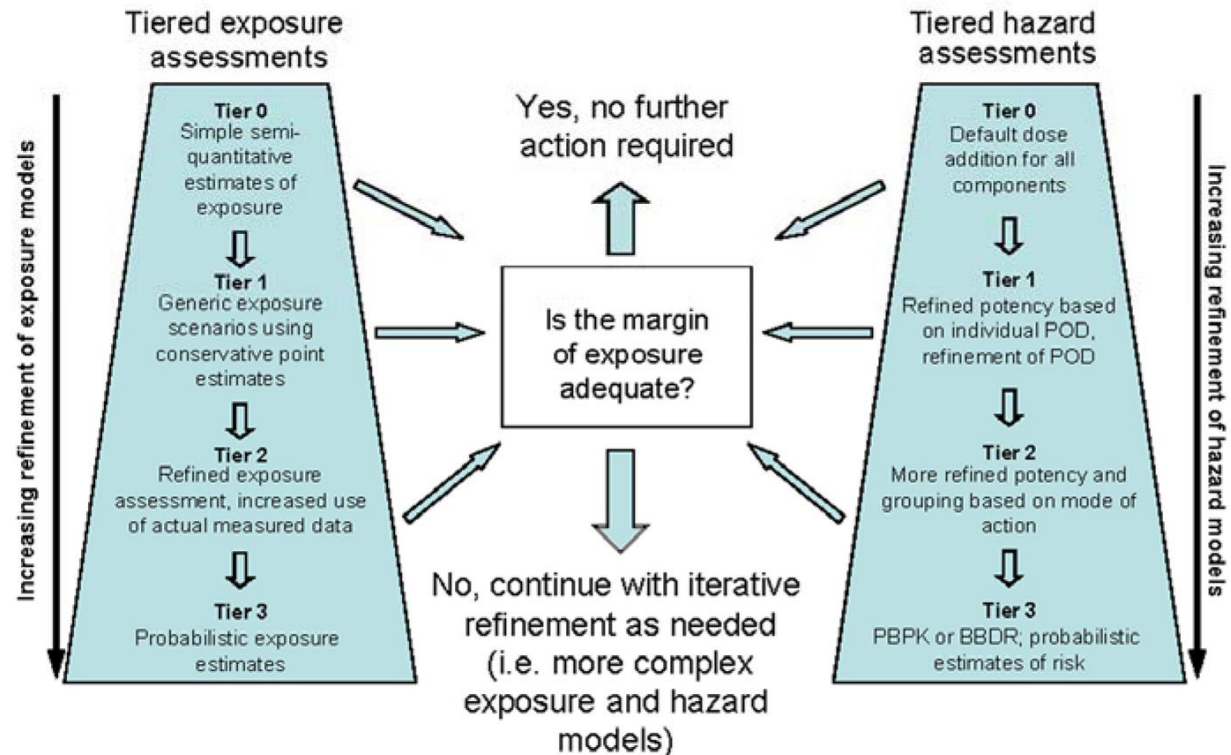
$$E(C_{\text{mix}}) = 1 - \prod_{i=1}^n (1 - E(C_i))$$

## Problem Formulation for Combined Exposure Assessment

- *What is the nature of exposure?*
- *Is exposure likely, taking into account the context?*
- *Is there a likelihood of co-exposure within a relevant timeframe?*
- *What is the rationale for considering compounds in an assessment group?*



### Example Tiered Exposure and Hazard Considerations: Mixture or Component Based



WHO-  
framework  
for risk  
assessment  
of  
mixtures

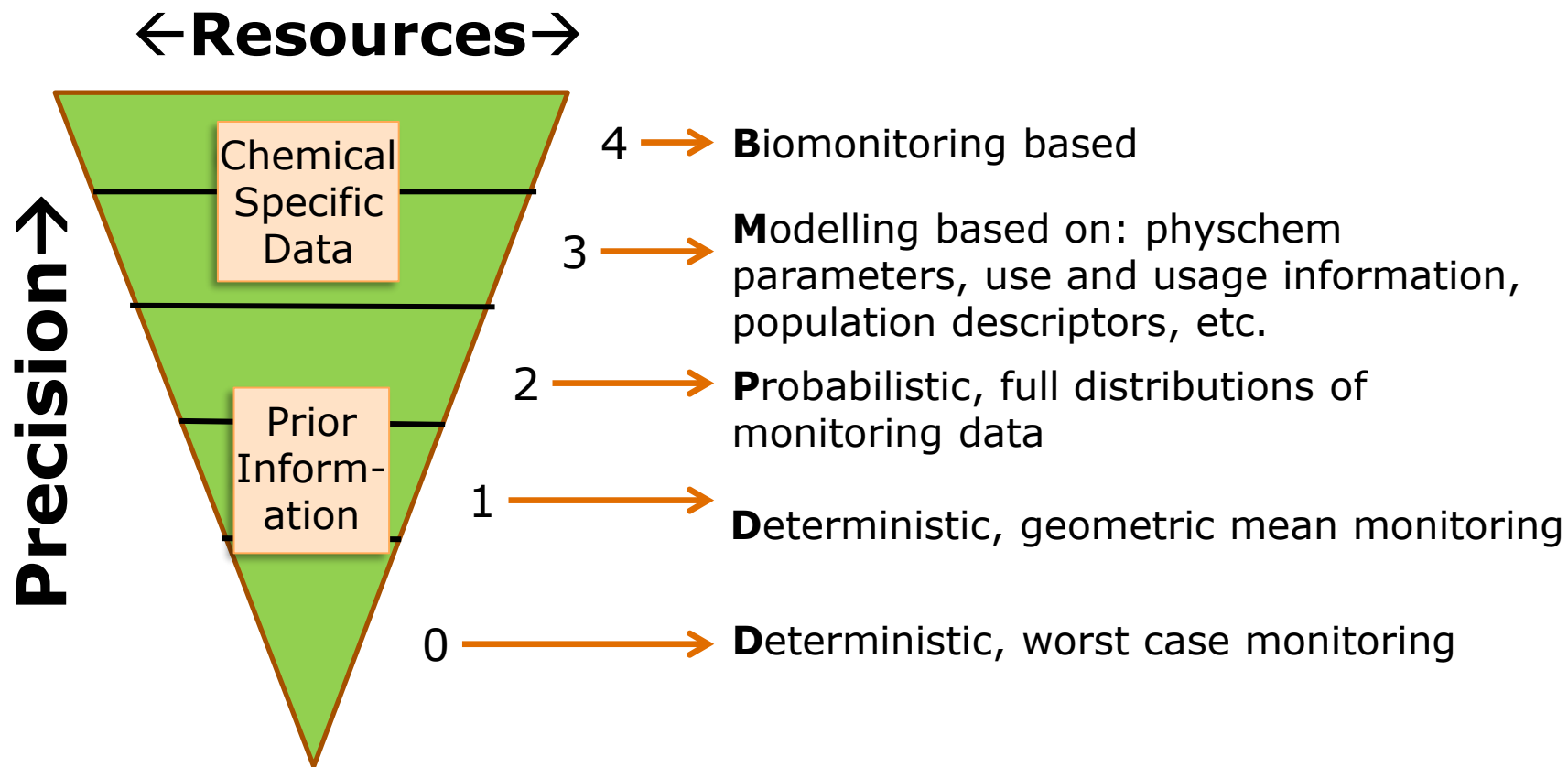


## Problem formulation: exposure

- What is the nature of **combined exposure**?
  - If not known: may need risk management or data on key components/mixture
- Is **exposure likely** taking into account the context?
  - consideration of use profile, environmental dilution/degradation, substance not absorbed
- Is there a **likelihood of co-exposure** within a relevant time frame ?
  - Consider time related aspects, both external exposure and mode of action (toxicokinetics and -dynamics)
  - Co-exposure possible from different sources/routes of exposure?
  - If likelihood of co-exposure low, don't assess as group



# Exposure Profiling (RISK21)



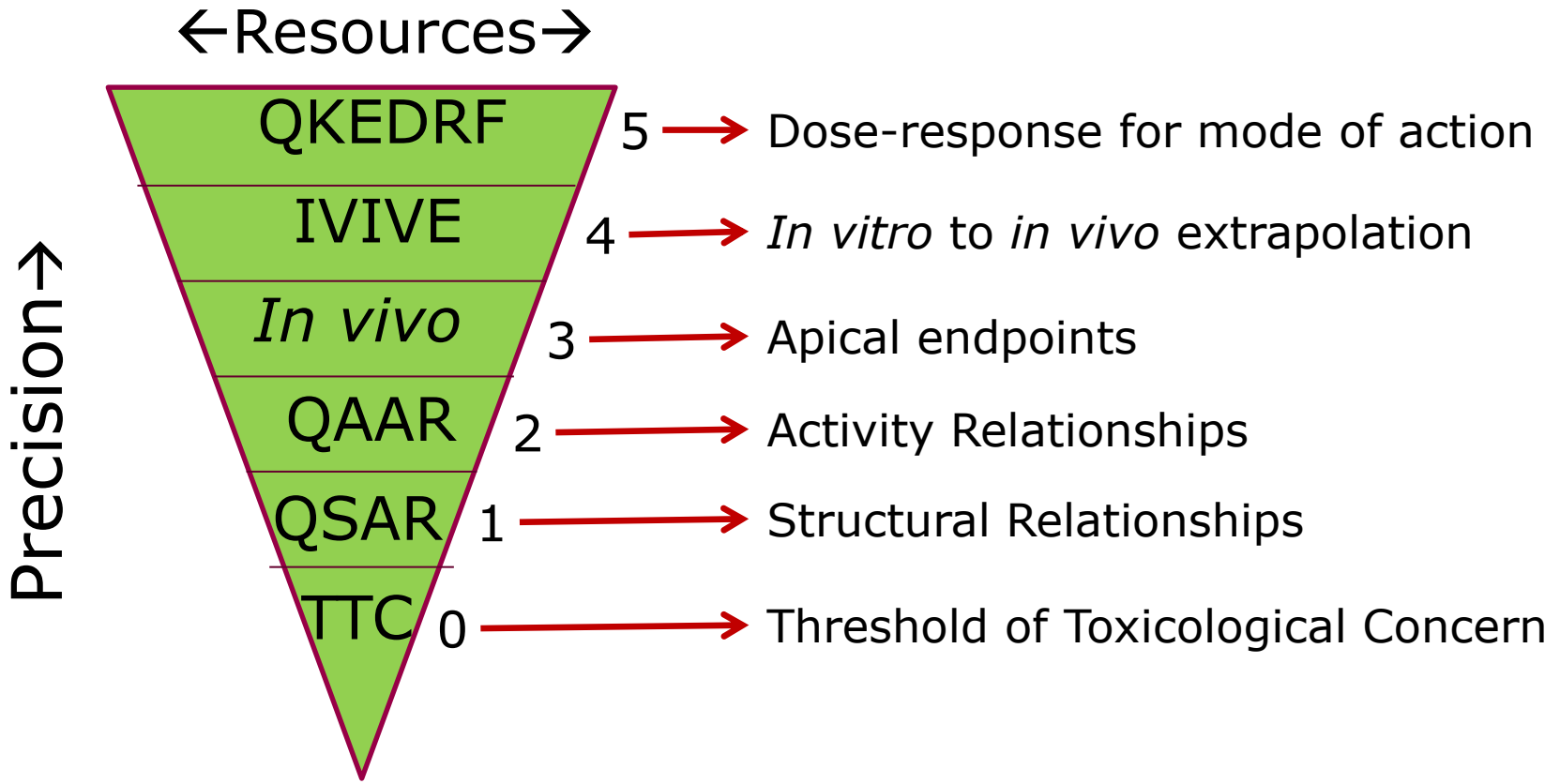


## Problem formulation: hazard

- What is the rationale for considering compounds in an **assessment group**?
  - Information on chemical structure (SAR, QSAR, structural alerts)
  - Hazard or other biological data
  - Same target organs
    - > Same biological outcome
    - > Same intended use target of the chemical (e.g. anti-oxidant use in fat, moulting inhibitors)



# Tiered approach to hazard assessment (RISK21)



# Which mixtures?



*Hertzler et al.,  
(2021)  
The "EU chemicals  
strategy for  
sustainability"  
questions regulatory  
toxicology as we  
know it: is it all  
rooted in sound  
scientific evidence?  
Archives of  
Toxicology 95:2589–  
2601.  
<https://doi.org/10.1007/s00204-021-03091-3>*

For discussion:

“Toxicologically speaking, for an adverse mixture effect currently not covered by the existing regulatory system to become relevant in terms of regulatory risk assessment, the following aspects need to come together:

1. To act together via dose addition/concentration addition, chemicals need to have common/interlinked MoAs.
2. The hazard posed by the individual components must be of high concern. This primarily involves substances with CMR properties or Specific Target Organ Toxicity after Repeated Exposure (STOT RE) properties, including those acting via ED-related MoAs.
3. Humans must be exposed to each individual mixture component below their individual regulatory thresholds (otherwise the scenario is already covered by the existing system), and in combination a toxic level must be reached.
4. These levels have to remain more or less constant (not above the individual thresholds, not below an overall toxic level of the mixture) over the whole time-window relevant for the effect (shorter for reproductive effects, longer for STOT RE and cancer)”



## Statements

It is reasonable to assume that, in the absence of synergy, combinations of substances with independent joint action will produce no effect when exposure is below their respective reference values

For chemicals with different modes of action (independently acting), no robust evidence is available that exposure to a mixture of such substances is of health or environmental concern if the individual chemicals are present at or below their zero effect levels.

A hazard based approach such as the MAF-factor of 100 is not (yet) sufficiently data driven. Careful consideration of likelihood that EU consumers are currently confronted with significant health risks from the exposure to mixtures is needed.