Combined exposure to multiple chemicals

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Content

Definitions

Combined Exposures and Mixture Toxicity

A mixture is…

- According to CLP & REACH Article 3 (2) "mixture" is a mixture or solution composed of two or more substances
  A mixture can be generated either intentionally by mixing two or more substances or unintentionally via the release of substances in the environment

- **UVCB and multi-constituent substances** from the toxicological point of view can be considered as mixtures and the methodology to follow for the hazard assessment for such substances follows the principles of mixture toxicity/assessment

Combined exposure is used to describe one of the following cases:

- Exposure to a single chemical by one source of release and/or use;
- Exposure to multiple substances by one source of release and/or use;
- Exposure to multiple substances by different sources of release and/or uses.

Defintions

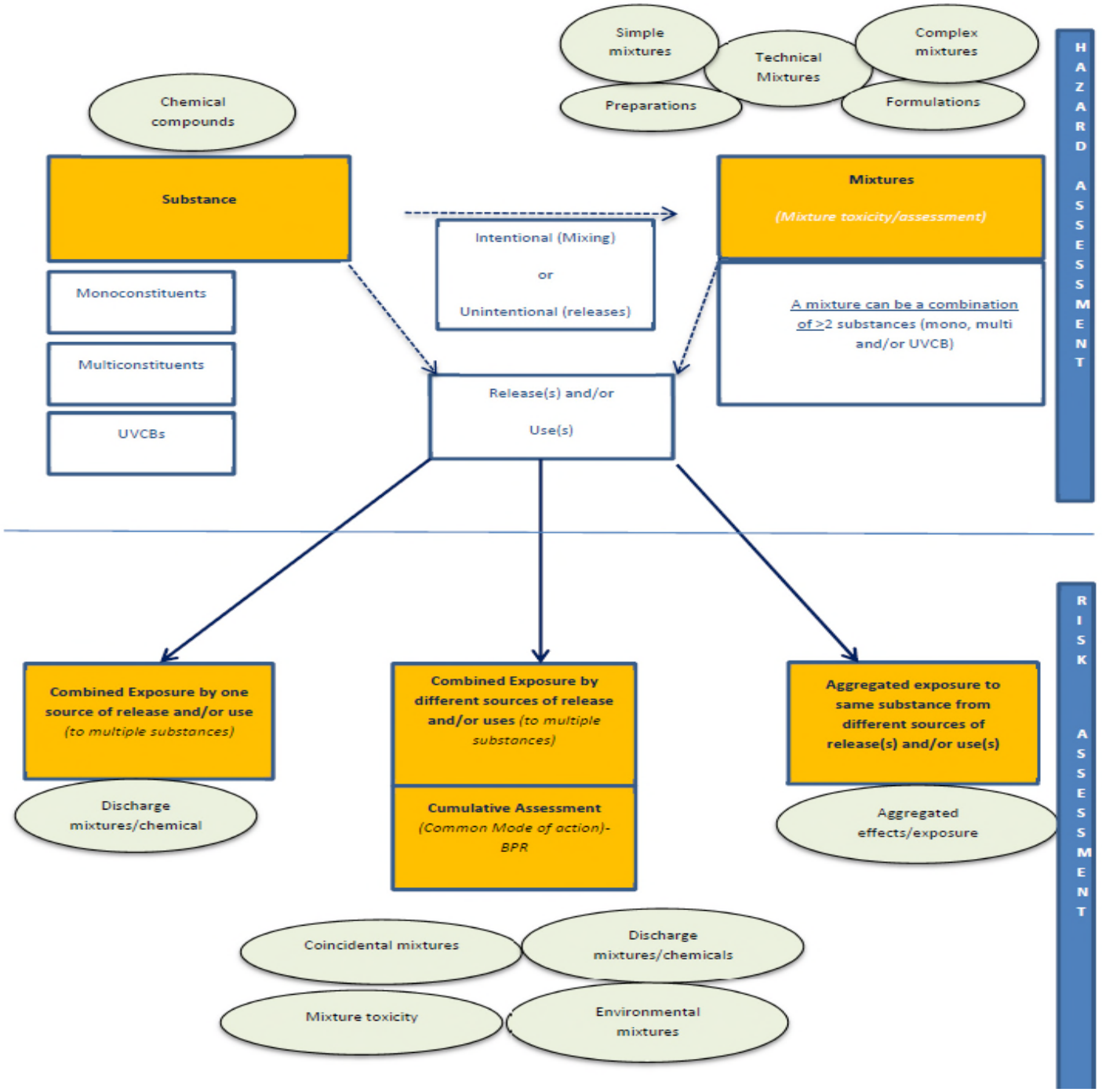
Combined Exposures and Mixture Toxicity

- **Mono-constituent substances: i.e.** serial exposure to the same chemical compound at different times from repeated release and release at different sites

- **Mono-constituent substances; i.e. combined exposure to multiple** different chemical compounds (either from concurrent release/exposure or from serial release/exposure)

- **UVCB substances and multi-component substances: i.e. combined exposure to multiple compounds from concurrent release**

- **Formulated Products: i.e. combined exposure to multiple compounds from concurrent release**


Simple mixtures
Technical Mixtures
Complex mixtures
Preparations
Formulations
Chemical compounds
Substance
Monoconstituents
Multiconstituents
UVCBs
Intentional (Mixing)
or
Unintentional (releases)
Mixtures
(Mixture toxicity/assessment)
A mixture can be a combination of >2 substances (mono, multi and/or UVCB)
Release(s) and/or Use(s)
HAZARD ASSESSMENT
Combined Exposure by one source of release and/or use (to multiple substances)
Discharge mixtures/chemical
Combined Exposure by different sources of release and/or uses (to multiple substances)
Cumulative Assessment (Common Mode of action)- BPR
Aggregated exposure to same substance from different sources of release(s) and/or use(s)
Aggregated effects/exposure
Coincidental mixtures
Discharge mixtures/chemicals
Mixture toxicity
Environmental mixtures
RISK ASSESSMENT

Content

1. Definitions
2. **Legal background (REACH, CLP, BPR)**
3. Current Guidance (BPR)
4. Outlook

REACH
Combined Exposure

- REACH covers combined exposure from single chemicals since it is requirement to perform risk characterisation for combined routes of exposure; oral, dermal and inhalation (Annex I, section 6)

REACH Combined Exposure

- REACH focus on assessment of single chemicals and therefore does not cover explicitly assessment from combined exposure to multiple chemicals.

  - Combined effects are not covered in the chemical safety assessment
    (by registrants – they are not aware and cannot be held responsible for the use for other substances by other actors)
  - In specific cases of regulatory risk management combined exposure to single or multiple chemicals has been considered, for instance to form the basis of the rationale for proposing a restriction
    (by authorities, e.g. Restriction processes and during Substance Evaluation)

REACH Combined Exposure (examples)

- **Restriction**

  Combined risk assessment for a group of 4 Phthalates (DEHP, BBP, DBP, DIBP)
  - Structural similarity
  - Same ED mode of action (anti androgenic) and apical effects
  - Similar exposure and use pattern

  ⇨Dose addition assumed (Hazard Index = $\Sigma C_i/DNEL_i$)

- **Authorisation**

  Prioritisation of groups of SVHCs for inclusion in the List of Substances subject to Authorisation (Annex XIV)
  - e.g. certain chromium VI, lead & arsenic compounds, phthalates

  SVHC identification of a group of substances because of a common degradation product with SVHC properties
  - e.g. 4-nonylphenol ethoxylates and 4-tert-octylphenol ethoxylates

REACH Combined Exposure (examples)

➢ Substance Evaluation

DE, **N-1-naphthylaniline**

Prove that the corresponding N-nitrosamine to N-1-naphthylaniline is not formed during use of N-1-naphthylaniline above a concentration of 0.001 % (w/w) in mixtures or 0.075 µg/m^3 in the air.

Principally non-threshold carcinogenic N-nitrosamines are known to be formed under real work place conditions by reaction with nitrogen oxides.[1] Nitrogen oxides are ubiquitous in the environment and their occurrence at the workplace in particular is frequently unavoidable (exhaust fumes from internal combustion engines, etc.).

CLP Mixture Rules

- *Annex I to CLP specifies "bridging principles" which enables suppliers to derive health or environmental classifications of their mixtures based on available data on similar tested mixtures and on the ingredient substances. It also provides specific rules for the classification of mixtures based on the classification of the individual substances in the mixture.*

BPR Combined Exposure

Article 19(2) of the Biocidal Products Regulation (BPR, 528/2012 EU) states that *"the evaluation […] shall take into account the following factors: […] (d)* ***cumulative effects****, (e)* ***synergistic effects****."*

This is further elaborated in Annex VI (common principles for the evaluation of biocidal products) which states that the "**risks associated with the relevant individual components of the biocidal product shall be assessed, taking into account any cumulative and synergistic effects."**

BPR Combined Exposure

Point 9.1 of Annex III to the BPR states that "***Where valid data on the components are not available or where synergistic effects may be expected then testing of components and/or the biocidal product itself may be necessary.***"

…"***further studies chosen from among the endpoints referred to in section 9 of Annex II for relevant components of the biocidal product or the biocidal product itself may be required if the data on the active substance cannot give sufficient information and if there are indications of risk due to specific properties of the biocidal product***."

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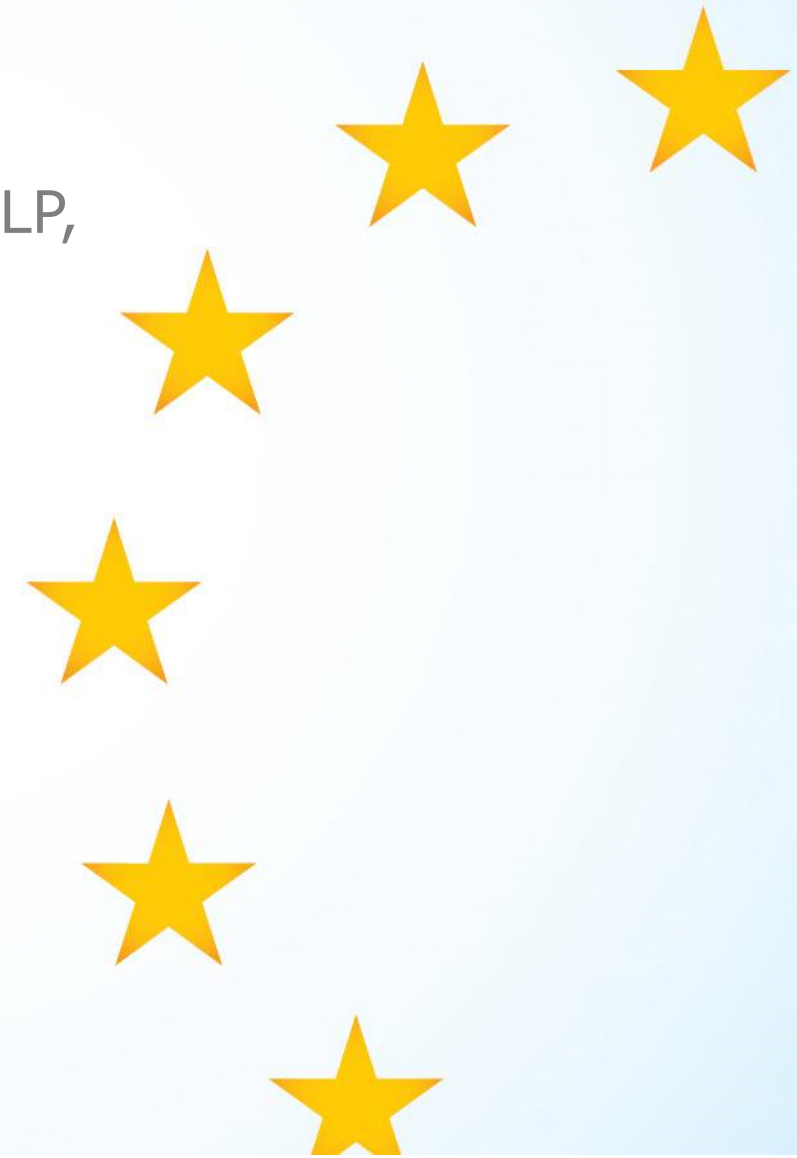

Methodology (HH) (BPR)

Risk Characterisation from combined exposure to several active substances or substances of concern within a biocidal product

- **Tiering** for both Hazard and Exposure Refinements (in parallel) (based on WHO/IPCS Combined Exposures Framework)
- Exposure Refinement mentioned under the Exposure Chapter of the Guidance (following tiering methodologies, from simple to more advanced tools and measured data)
- Exposure critical factor for combined exposures
- Consideration of MoA/Human Relevance and application of methodologies to identify uncertainties both in Hazard and Exposure components needed at higher tiers
- Available guidance on Uncertainty for hazard and exposure by WHO/IPCS

Methodology ENV

A number of ways to include mixture toxicity in risk assessment have been proposed in literature:

A. Mixture assessment factor (MAF): safeguarding against mixture effects by means of a special factor, similar to other uncertainty factors in single substance assessment.

B. Bridging or read-across:

drawing conclusions from available data from similar mixtures.

C. Component-based approaches (CBA):

calculating the expected joint toxicity from the toxicity data for the individual mixture components by applying corresponding prediction models (**CA and IA**)

D. Direct experimental testing of the mixture of concern:

i.e. the whole product or the environmentally relevant mixture resulting from the use of the product.

Methodology ENV (BPR)

Mixture toxicity: refers to the combined toxicity and risk to human and animal health, and the environment, from all relevant substances in a biocidal product, including their degradation products and regardless of the underlying mechanism(s) of mixture toxicity (non-interactive or interactive joint action) and taking into account the different environmental, occupational and residential mixture(s) which are formed during all life cycle steps relevant under the BPR.

Methodology ENV (BPR)

Substances as relevant for mixture assessment:

1) Active substances.

2) Substances of concern.

3) Active substances from other Product Types

4) Other ingredients which do not fall under one of the aforementioned categories but might be relevant for mixture assessment like e.g. known synergists should be considered as well on a by-case basis.

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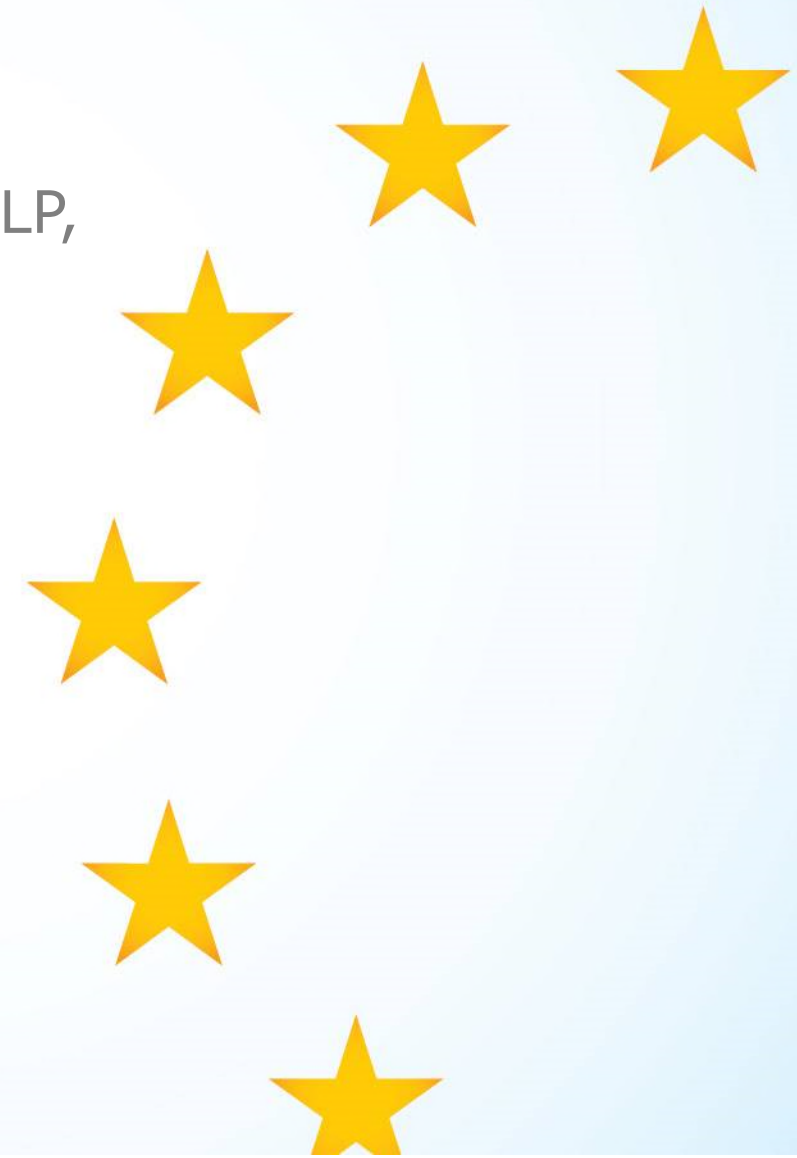

Outlook

- Science is sufficiently clear
- Adequate Guidance internationally and at EU Level exists for the hazard assessment of combined exposure to multiple or single chemicals for human health, with dose addition representing the most conservative approach.
- No specific guidance for combined exposure from multiple chemicals available under REACH
- Actors cannot be held responsible for the use of other substances by other actors
- Assessing all possible exposure combinations is a dead end route for REACH

Outlook

- Difficulties in carrying out an environmental risk assessment for mixtures arises
  - the individual components have different physico-chemical properties and different distribution and fate in the environment.
  - Concepts for calculating/estimating effects of mixtures under laboratory conditions are fairly well developed for wildlife, but extrapolation to real-world or their use in risk assessment is more complicated.
- Possibility
  - Use of MAF to reduce the probability that effects through combined exposure occur by reducing the toxic pressure. Which MAF?
- Difficulties in carrying out an human health assessment for combined exposures in BPR:
  - Limited EU based models for exposure assessment from combined exposures
  - Limitations from lack of hazard data for all components

Outlook Biocides

- Promote that MS and companies start applying the principles of the updated guidance under biocides
- Prepare an Authority database on endpoints for SoC for consistency
- Organize a workshop among MS and Industry in order to share experiences when applying the guidance on mixture toxicity
- Future update of the guidance

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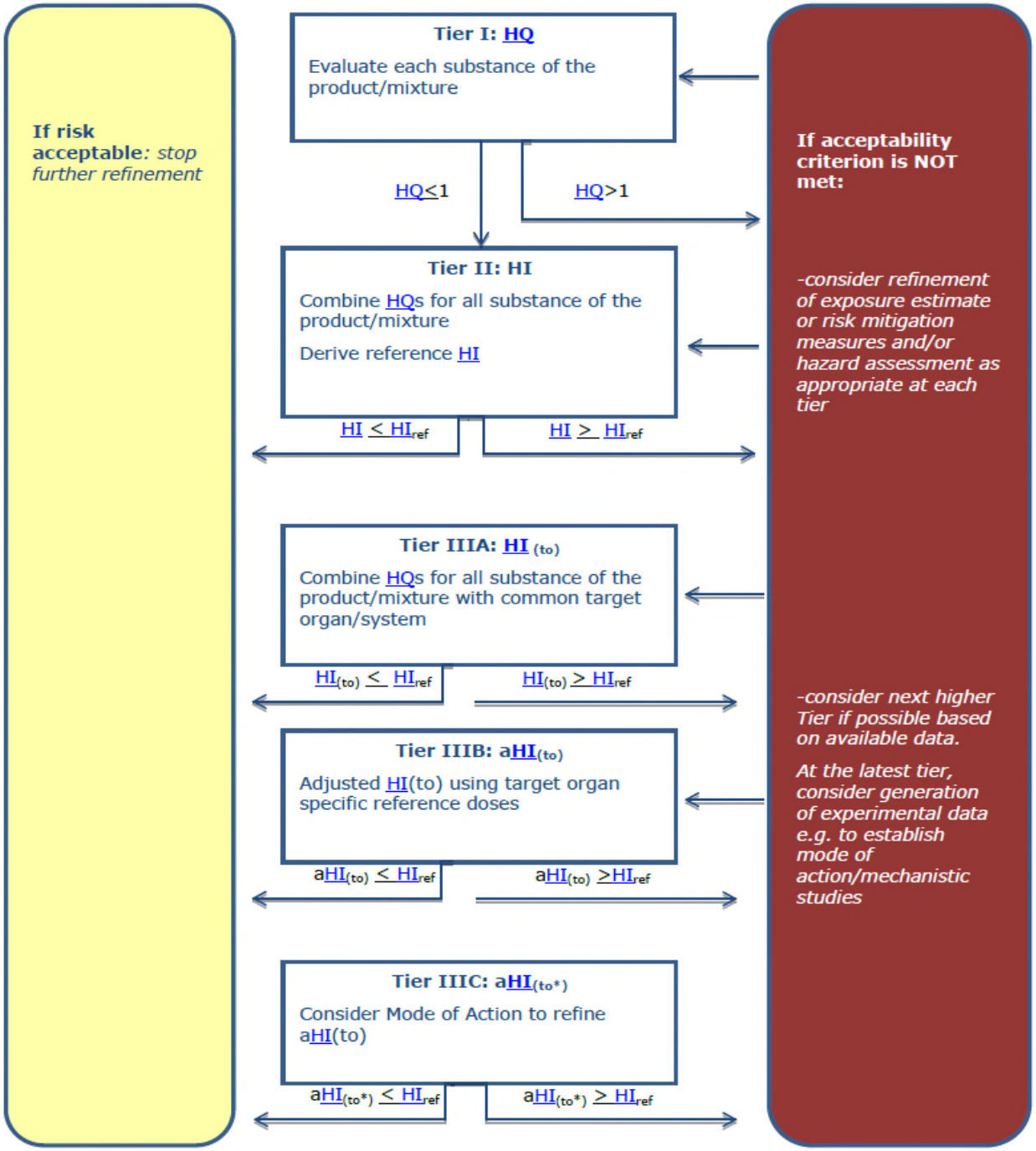
If risk acceptable: stop further refinement
Tier I: HQ
Evaluate each substance of the product/mixture
HQ≤1
HQ>1
If acceptability criterion is NOT met:
Tier II: HI
Combine HQs for all substance of the product/mixture
Derive reference HI
HI ≤ HIref
HI > HIref
-consider refinement of exposure estimate or risk mitigation measures and/or hazard assessment as appropriate at each tier
Tier IIIA: HI (to)
Combine HQs for all substance of the product/mixture with common target organ/system
HI(to) ≤ HIref
HI(to) > HIref
Tier IIIB: aHI(to)
Adjusted HI(to) using target organ specific reference doses
aHI(to) ≤ HIref
aHI(to) >HIref
-consider next higher Tier if possible based on available data.
At the latest tier, consider generation of experimental data e.g. to establish mode of action/mechanistic studies
Tier IIIC: aHI(to*)
Consider Mode of Action to refine aHI(to)
aHI(to*) ≤ HIref
aHI(to*) > HIref

Methodology ENV (BPR)

Tier I

$$RQ_{\text{Product}} = \sum_{i=1}^{n} \left(\frac{PEC}{PNEC} \right)_i$$

Tier II

$$RQ_{\text{Product}} = \max \sum_{i=1}^{n} \left(\frac{PEC}{ECx / AF} \right)_i$$

Tier III

$$RQ_{\text{Product}} = \max \left(\sum_{i=1}^{n} \frac{PEC_i}{ECx_{i,j}}, \sum_{i=1}^{n} \frac{PEC_i}{ECx_{i,j}}, \ldots, \sum_{i=1}^{n} \frac{PEC_i}{ECx_{i,m}} \right) \times AF$$

Tier IV

Direct testing of the whole product