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International Workshop on Risk Assessment of Combined Exposure to Multiple Chemicals

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GUIDANCE



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Guidance on harmonised methodologies for human health, animal health and ecological risk assessment of combined exposure to multiple chemicals

EFSA Scientific Committee,

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Abstract

This Guidance document describes harmonised risk assessment methodologies for combined exposure to multiple chemicals for all relevant areas within EFSA's remit, i.e. human health, animal health and ecological areas. First, a short review of the key terms, scientific basis for combined exposure risk assessment and approaches to assessing (eco)toxicology is given, including existing frameworks for these risk assessments. This background was evaluated, resulting in a harmonised framework for risk assessment of combined exposure to multiple chemicals. The framework is based on the risk assessment steps (problem formulation, exposure assessment, hazard identification and characterisation, and risk characterisation including uncertainty analysis), with tiered and stepwise approaches for both whole mixture approaches and component-based approaches. Specific considerations are given to component-based approaches including the grouping of chemicals into common assessment groups, the use of dose addition as a default assumption, approaches to integrate evidence of interactions and the refinement of assessment groups. Case studies are annexed in this guidance document to explore the feasibility and spectrum of applications of the proposed methods and approaches for human and animal health and ecological risk assessment. The Scientific Committee considers that this Guidance is fit for purpose for risk assessments of combined exposure to multiple chemicals and should be applied in all relevant areas of EFSA's work. Future work and research are recommended.

- **Harmonised Guidance**
 - Whole Mixture approach
 - Component-based approach
 - Include interactions
- **Problem Formulation**
- **Exposure and Hazard Assessment**
- **Risk Characterisation**
- **Reporting Table**
 - Human Health, Animal Health
 - Environment

Areas of relevance for EFSA



Human Risk Assessment

Regulated products: Food additives,
Feed additives, Food contact materials,
Pesticides

Contaminants in food and feed chain



Animal Risk Assessment

Pesticides

Feed additives

Contaminants in feed



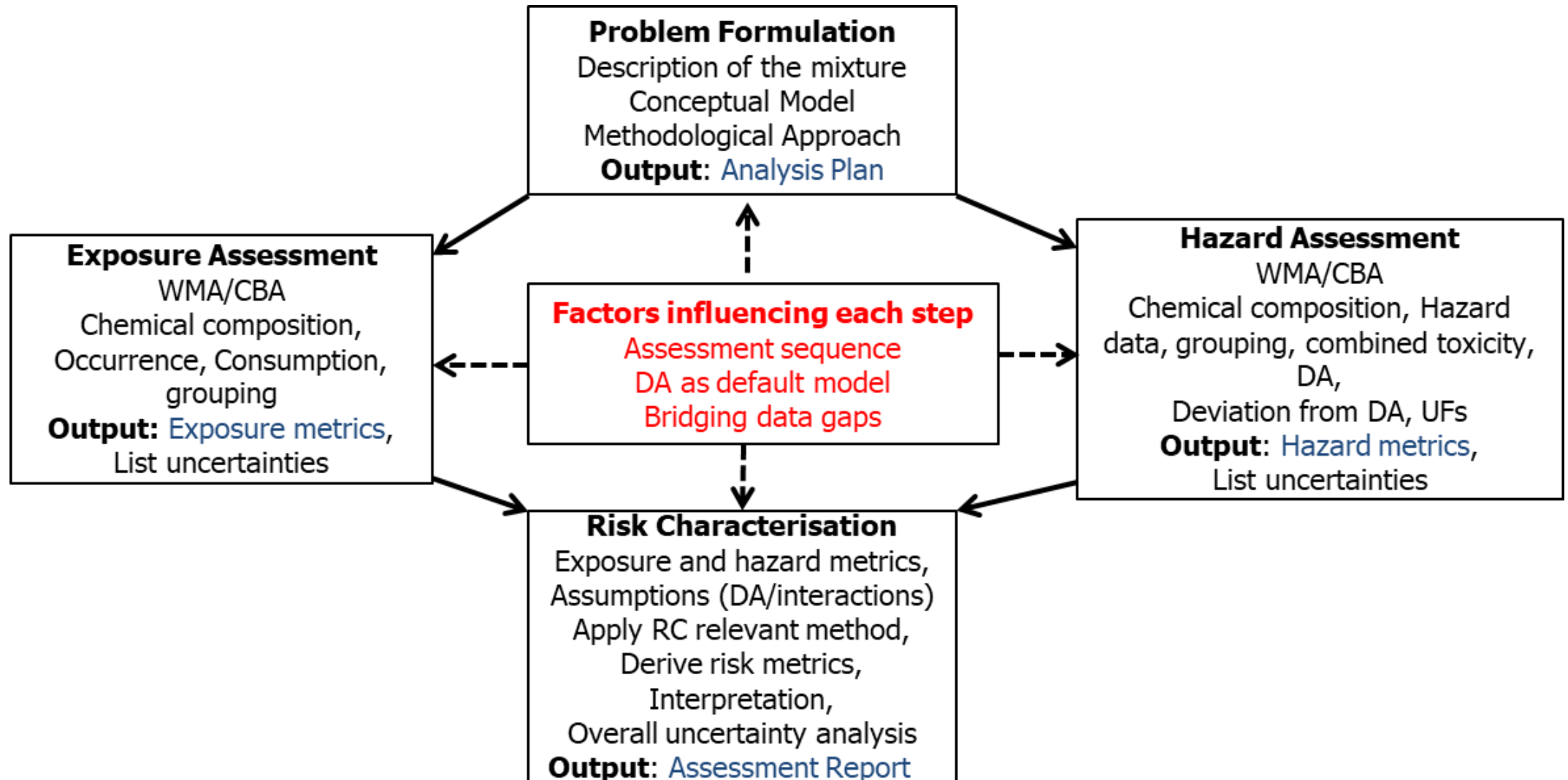
Ecological Risk Assessment

Pesticides

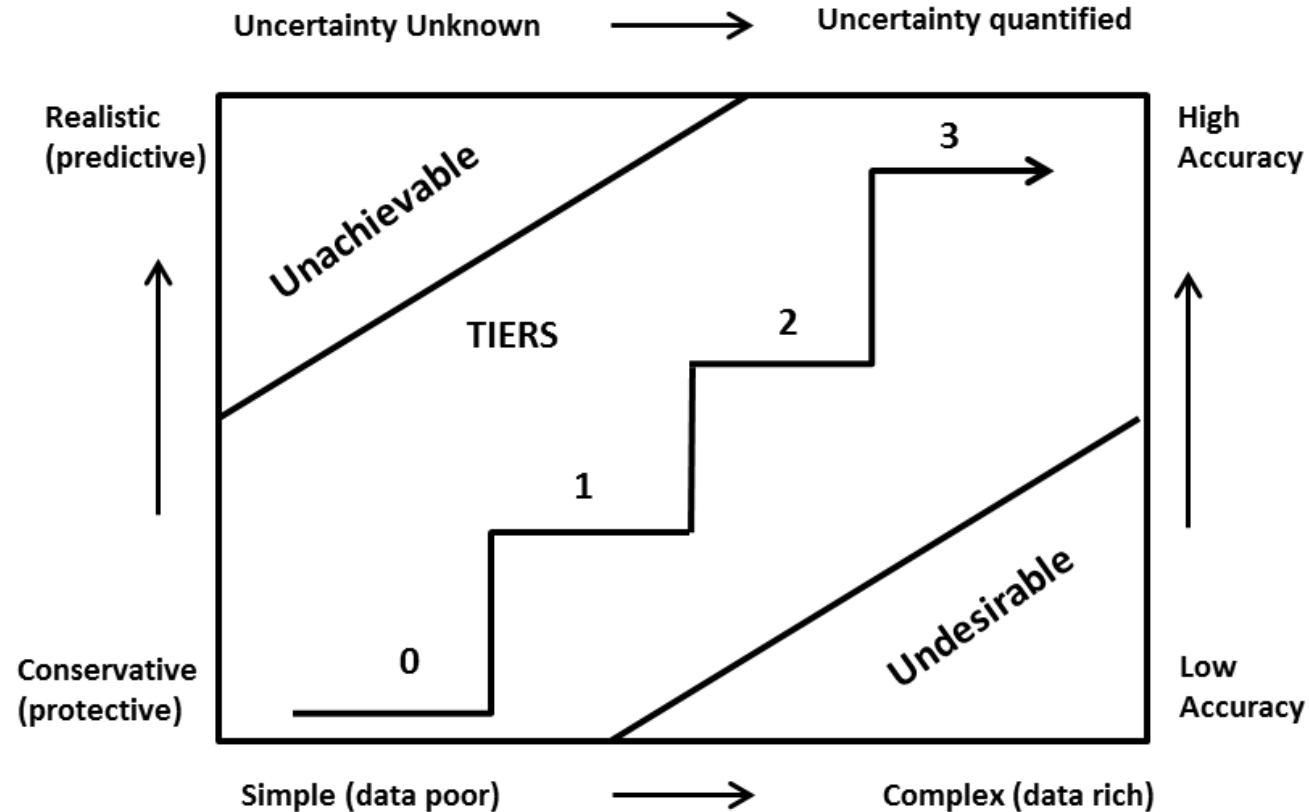
Feed additives

Contaminants in food and feed chain

Harmonised Framework

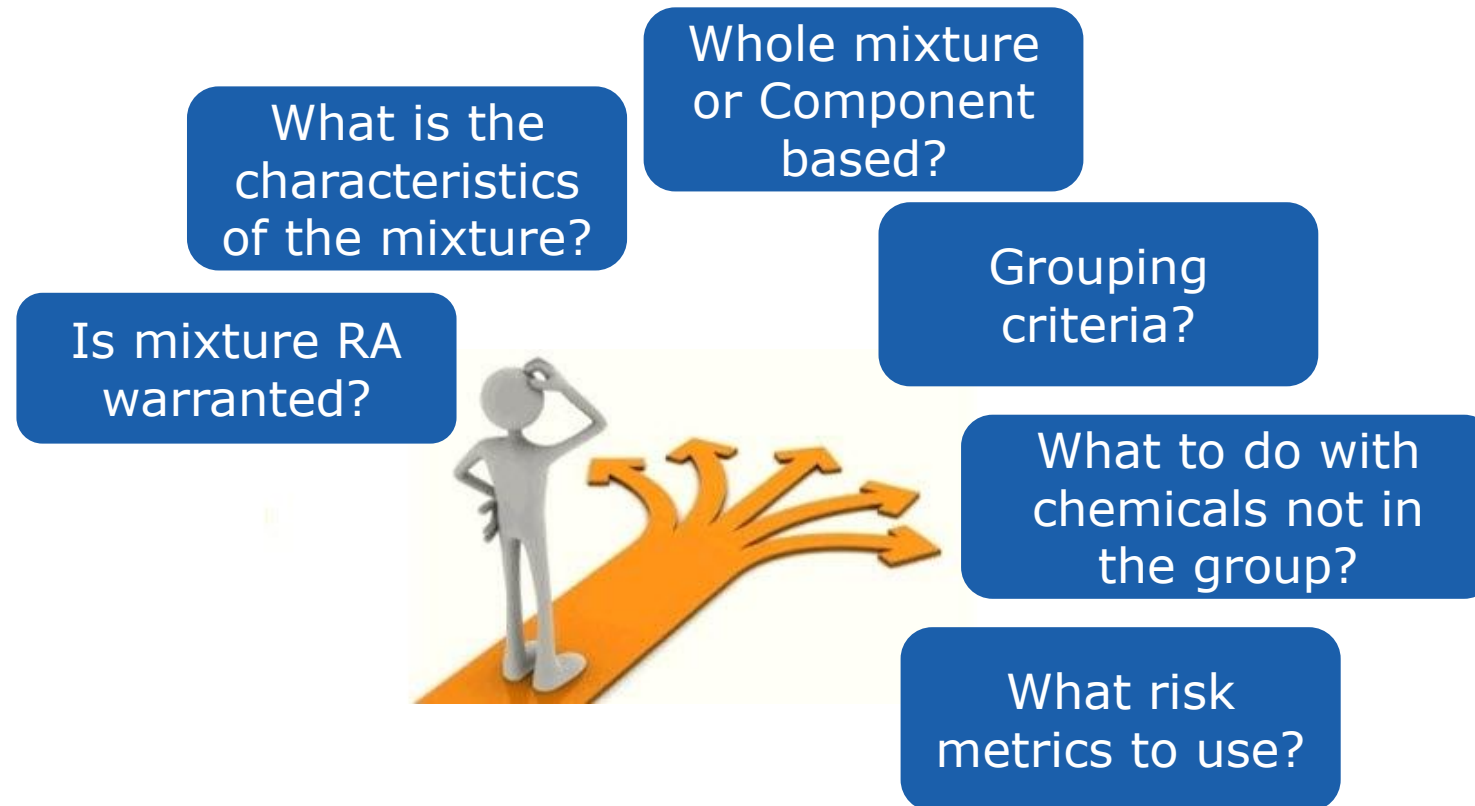


Tiering Principles



Relationships between tiers, data availability, uncertainty, accuracy and outcome of a risk assessment. Solomon et al. (2006) and MIXTOX GD.

Problem Formulation



Exposure Assessment

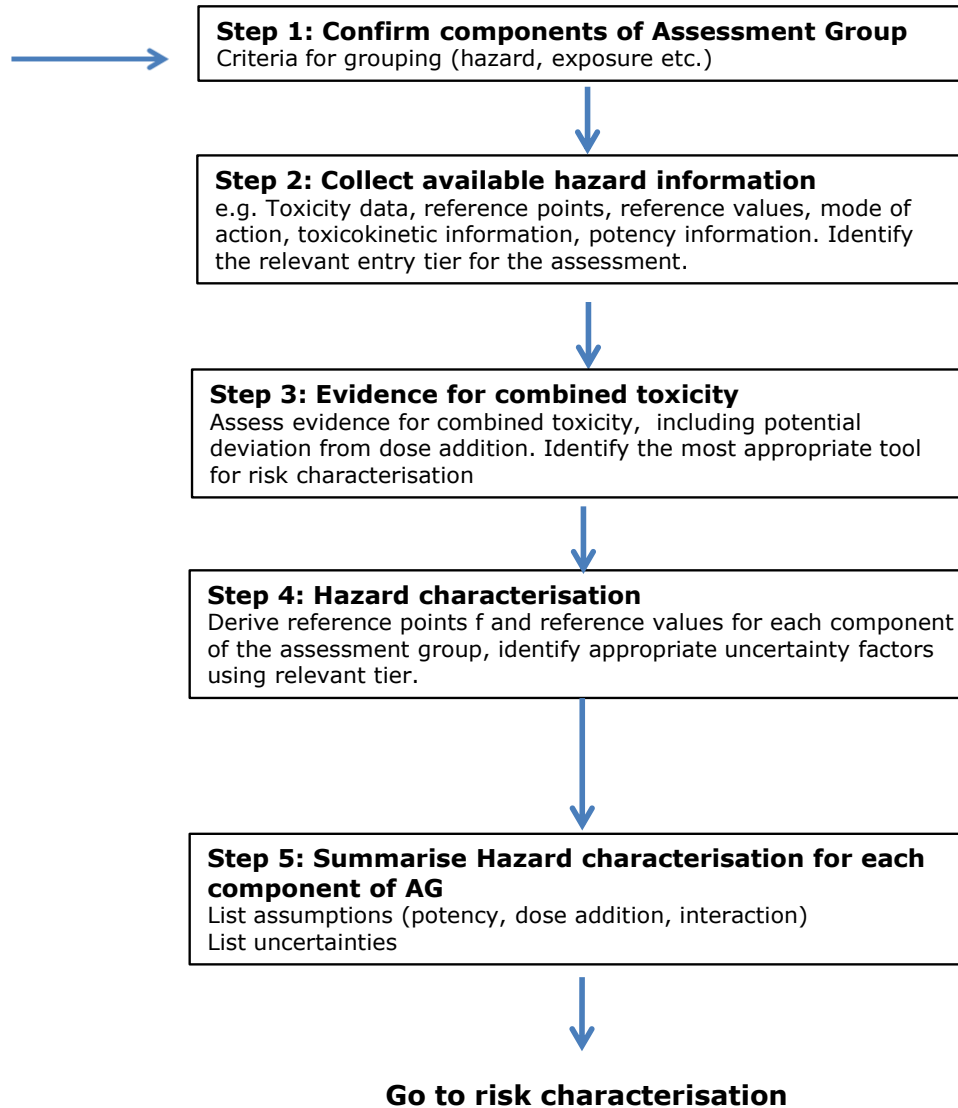
	Occurrence data	Exposure estimate	Consumption data
Tier 0	Default values, permitted levels	Semi-quantitative point estimates	Default values, portion sizes
Tier 1	Modelled and experimental data	Deterministic	Food balance sheet food basket
Tier 2	Monitoring Surveys	Semi-probabilistic	Summary statistics
Tier 3	Individual co-occurrence data	Probabilistic	Individual data

- Amount of each chemical in food
- How much food is consumed ?
- Combine the two together for each chemical

Note: Occurrence and consumption tiers often do not match. The resulting exposure tier will be determined by the available data including for the occurrence of different components of a mixture

Hazard Assessment

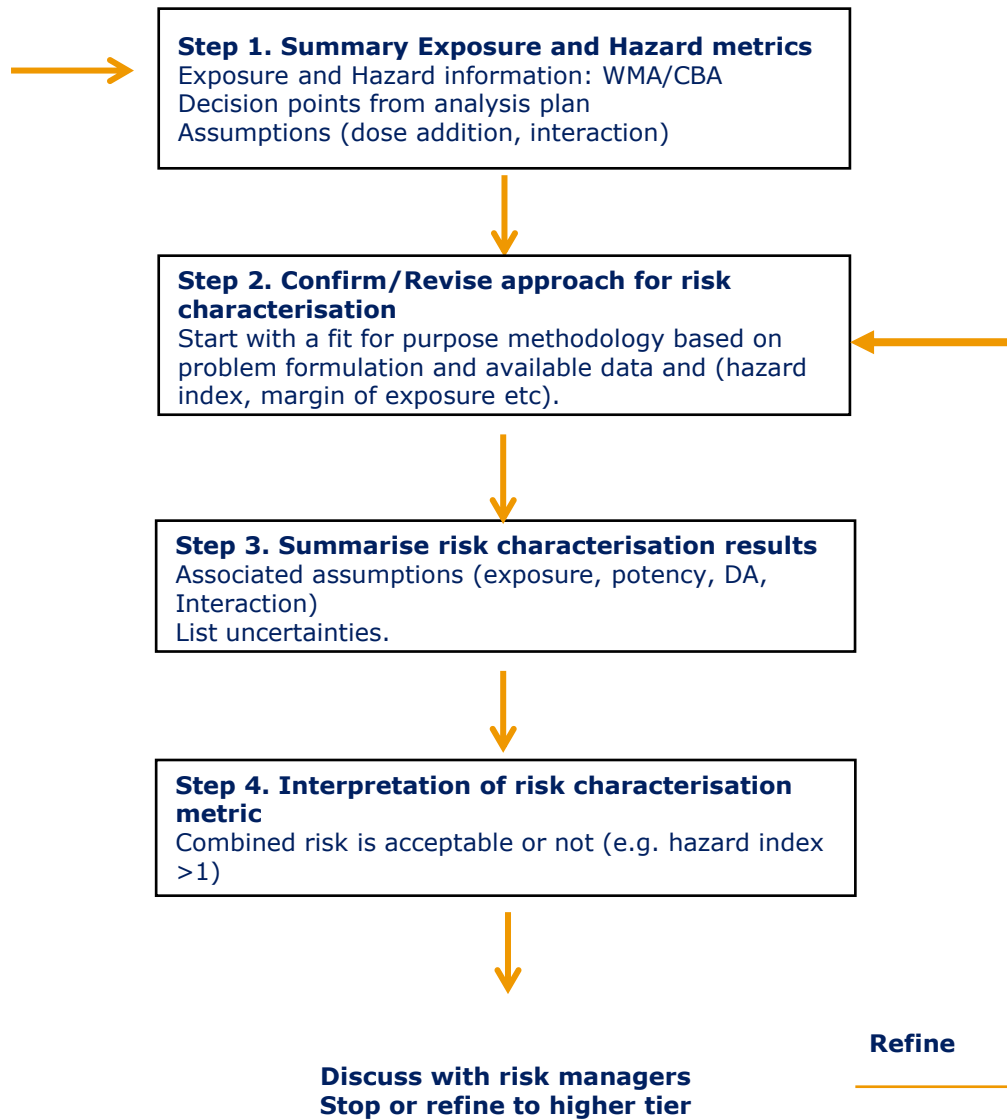
Hazard Identification
Hazard characterisation
Human/Sub-population(s)
Farm/Companion Animals
Environmental Specie(s)
Ecosystem(s)



- How toxic is each chemical ?
- Get the toxicity values for each chemical
- Do they interact and become more toxic together?

Risk Characterisation

Risk characterisation
Human/Sub-population(s)
Farm/Companion Animals
Environmental Specie(s)
Ecosystem(s)



- Combine exposure and toxicity data for all chemicals to get risk values
- Is there a concern for human health or for the environment ?
- If No, Stop!
- If Yes, Refine or discuss with risk managers to reduce exposure ?

TECHNICAL REPORT



APPROVED: 10 December 2019

doi:10.2903/sp.efsa.2020.EN-1759

Human risk assessment of multiple chemicals using component-based approaches: A horizontal perspective

European Food Safety Authority (EFSA),

Jean Lou CM Dorne, Amélie Crépet, Jan Dirk te Biesebeek, Kyriaki Machera, and Christer Hogstrand

TECHNICAL REPORT



APPROVED: 10 December 2019

doi:10.2903/sp.efsa.2020.EN-1760

Animal Health Risk assessment of multiple chemicals in essential oils for farm animals

European Food Safety Authority (EFSA),
Jean Lou CM Dorne, Paola Manini and Christer Hogstrand

Interactions: The "Cocktail Effect"

Limoncello

+

Bagnolino

+

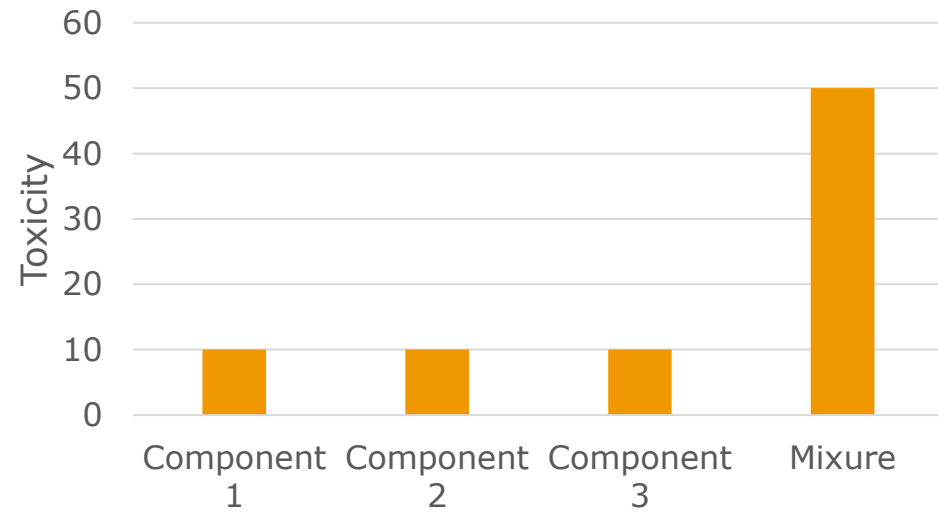
Nocino

**Hazardous
mixture
Be Careful
With This One !**

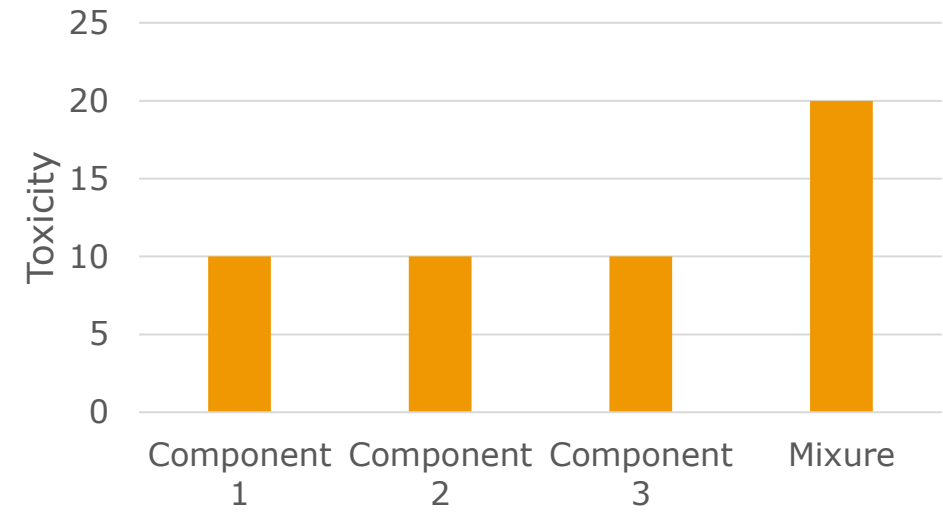
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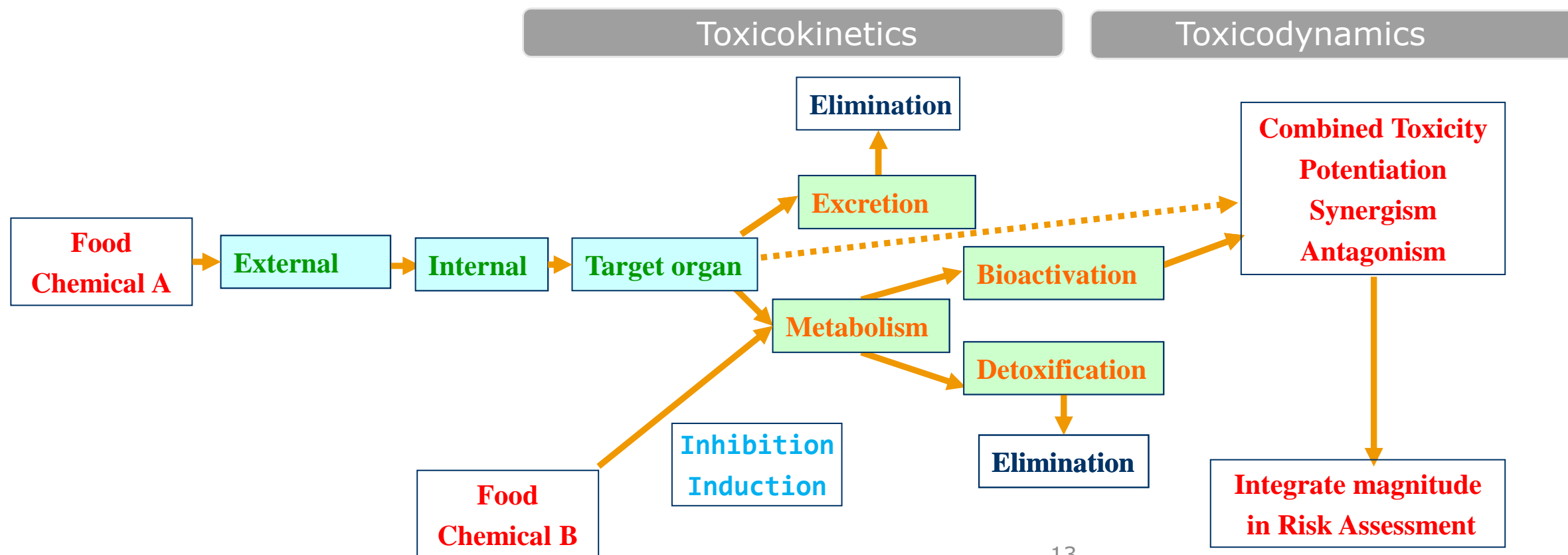
Synergism



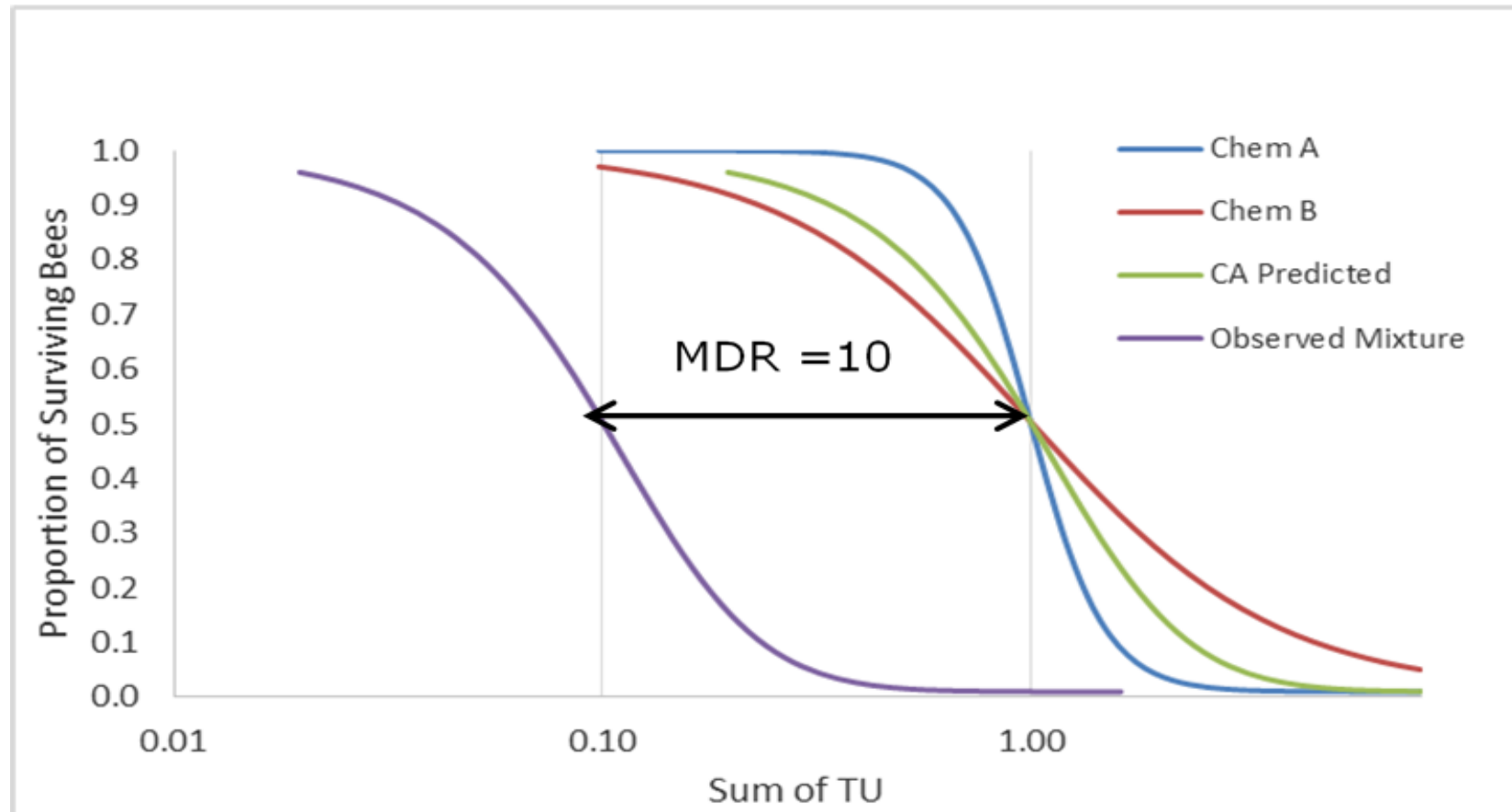
Antagonism



- Mixture Toxicity can involve interactions
 - Check interactions for the RA if occurs at current levels of exposure
 - Integrate in risk characterisation (extra uncertainty factor, biological-based model etc)



Hazard characterisation of interactions between two chemicals in worker honey bees: Comparison of effect prediction using concentration addition and experimental data (observed mixture) for the characterisation of **Model Deviation Ratio (MDR)**



MIXTOX2: Scientific criteria for grouping chemicals into assessment groups for Human Risk Assessment

- **May 2019-EFSA request for a scientific opinion on criteria for grouping chemicals for human RA of mixtures**
 - Key element for setting cumulative assessment groups for human RA of pesticides as requested by DG-SANTE
 - Relevance to CONTAM for grouping contaminants (PFAs, brominated FR etc)
 - Relevance to FEEDAP in mixture RA of essential oils/botanicals
 - Relevance to GD from FAF Panel for smoke flavourings and grouping. Includes chemical properties (e.g. structure, class, functional group etc). Use ECHA read across GD and OECD QSAR toolbox.
 - Overall support all panels dealing with chemical RA

1 Draft Guidance Document on
2 Scientific criteria for grouping
3 chemicals into assessment groups for
4 human risk assessment of combined
5 exposure to multiple chemicals

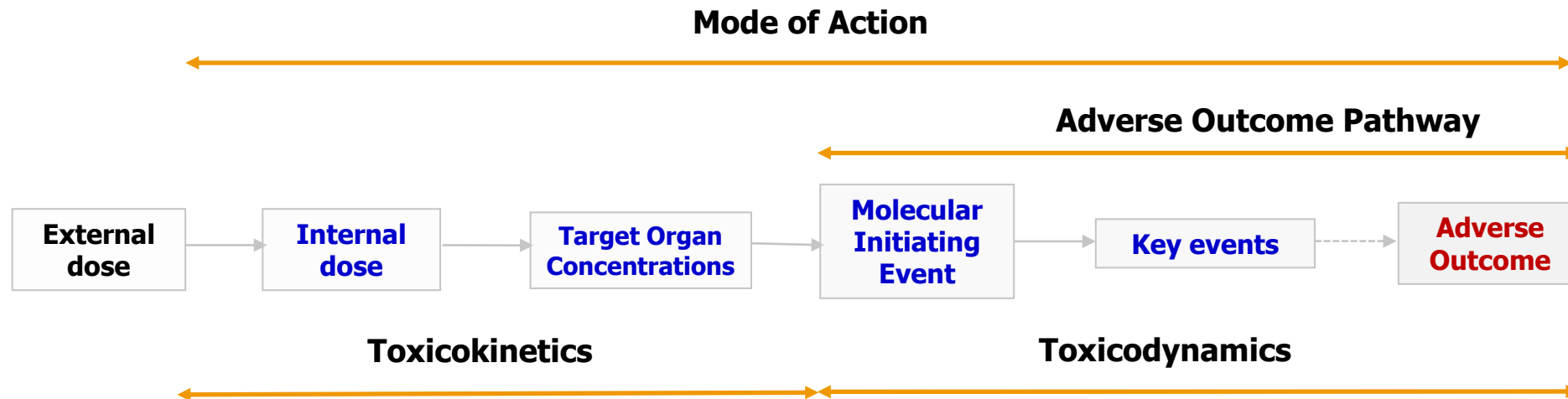
6 EFSA Scientific Committee, Simon John More, Vasileios Bampidis, Diane Benford,
7 Claude Braquard, Antonio Hernandez-Jerez, Susanne Hougaard Bennekou, Thorhallur
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11 Biesebeek, Emanuela Testai, Bruno Dujardin, Jean Lou C M Dorne, Christer Hogstrand

12 Abstract

13 This guidance document provides harmonised and flexible methodologies to apply scientific
14 criteria for grouping chemicals into assessment groups and prioritisation methods for human
15 risk assessment of combined exposure to multiple chemicals. In the context of EFSA's risk
16 assessments, the problem formulation step defines the chemicals to be assessed in the Terms
17 of Reference usually through regulatory criteria often set by risk managers based on legislative
18 requirements. Scientific criteria such as hazard-driven criteria can be used to group these
19 chemicals into assessment groups. In this guidance document, a framework is proposed to
20 apply hazard-driven criteria for grouping of chemicals into assessment groups using
21 mechanistic information on toxicity as the gold standard where available (i.e. common mode
22 of action or adverse outcome pathway) through a structured weight of evidence approach.
23 However, when such mechanistic data are not available, grouping may be performed using a
24 specific effect on target organs or a common adverse outcome. Toxicokinetic data can be
25 useful for grouping particularly when common toxicologically relevant metabolites are shared
26 among chemicals. In addition, prioritisation methods provide means to identify low priority
27 chemicals and reduce the number of chemicals in an assessment group. Prioritisation methods
28 include combined risk-based approaches, and risk-based approaches for single chemicals and
29 exposure-driven approaches. Case studies have been provided to illustrate the practical
30 application of hazard-driven criteria and the use of prioritisation methods for grouping of
31 chemicals in assessment groups. Recommendations for future work are discussed.

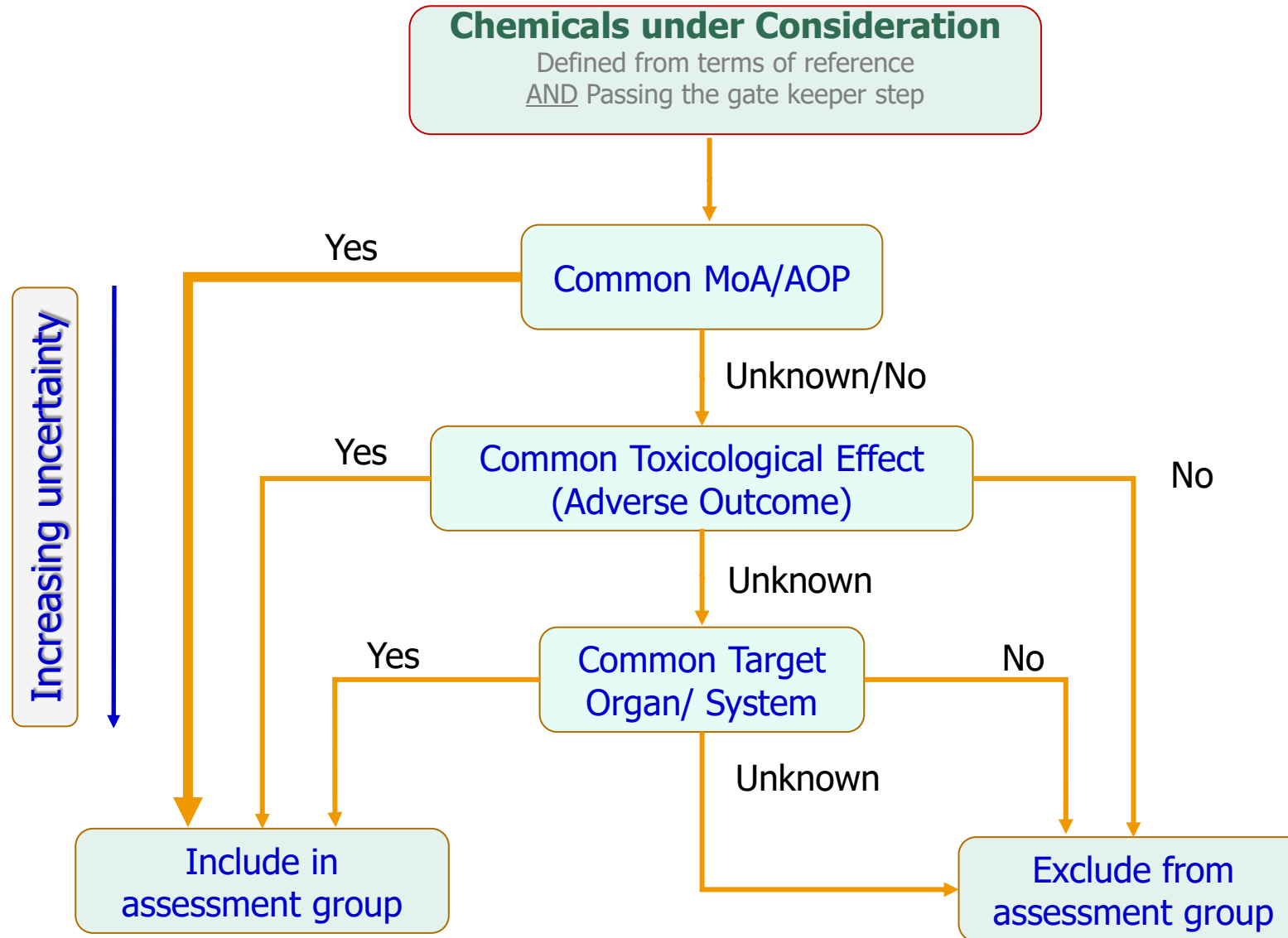
- Scientific principles and relevant cross-cutting guidance
- Context of risk assessment (priorities, urgent, pre- and post-market)
- Tiering and fit for purpose scenarios consider available data
- Prioritisation approaches: Risk-based and exposure-driven
- Relevant EFSA areas and international activities
- Harmonisation, avoid duplication
- Publication for public consultation

Mode of Action and Adverse Outcome Pathways

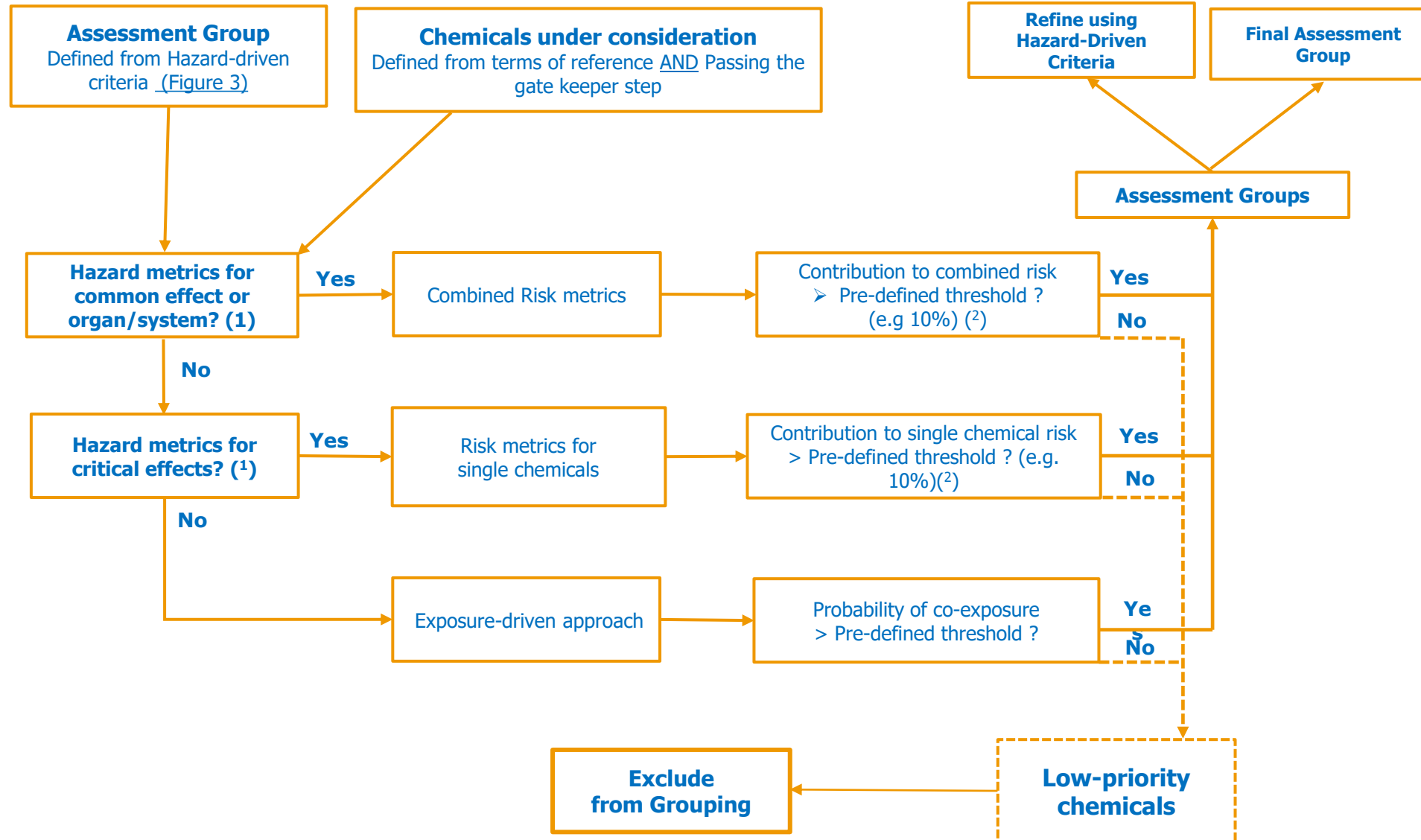


Hazard-Driven Criteria for grouping chemicals into assessment groups

Top-down hierarchical process for grouping chemicals into Assessment Groups using hazard-driven criteria



Prioritisation Methods: Risk-based and Exposure driven



- **MIXTOX** provides **Harmonised GD for RA of multiple chemicals**
Incl. Frameworks for each RA step and reporting Table to summarise results of RA
- **Scientific criteria for grouping** Public consultation Draft Guidance (May 2021)
- **Experience with Pesticide Residues:** towards faster implementation and cooperation with Member States Organisations
- **Future work in this area includes**
 - *New Approach Methodologies (NAMs)* for RA of multiple chemicals
 - Dealing with interactions
 - Physiologically-based models and other biologically-based models
- Environmental RA: Multiple stressors for bees (MUST-B opinion-May 2021)

Thank you for listening!

