The EFSA Guidance on Mixture Toxicity and recent developments

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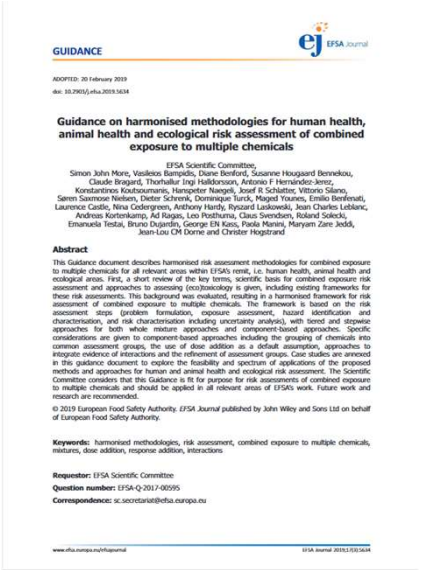
Content

1. Introduction to the EFSA guidance

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



GUIDANCE

EFSA Journal

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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,
Simon John More, Vasileios Bampidis, Diane Benford, Susanne Hougaard Bennekou, Claude Bragard, Thorhallur Ingi Halldorsson, Antonia F Hernández-Jerez, Konstantinos Koutsoumanis, Hanspeter Naegeli, Josef R Schlatter, Vittorio Silano, Søren Saxmose Nielsen, Dieter Schrenk, Dominique Turck, Maged Younes, Emilio Benfenati, Laurence Castle, Nina Cedergreen, Anthony Hardy, Ryszard Laskowski, Jean Charles Leblanc, Andreas Kortenkamp, Ad Ragas, Leo Posthuma, Claus Svendsen, Roland Solecki, Emanuela Testai, Bruno Dujardin, George EN Kass, Paola Manini, Maryam Zare Jeddi, Jean-Lou CM Dorne and Christer Hogstrand

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.

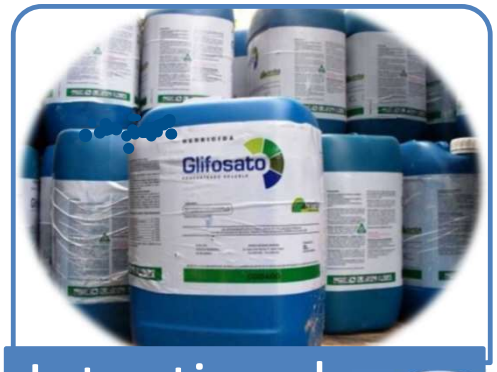
Keywords: harmonised methodologies, risk assessment, combined exposure to multiple chemicals, mixtures, dose addition, response addition, interactions

Requestor: EFSA Scientific Committee
Question number: EFSA-Q-2017-00595
Correspondence: sc.secretariat@efsa.europa.eu

2. Recent developments on assessment of combined exposure to human health
3. PARC developments for assessing combined effects in environmental risk assessments

- Overarching guidance with general recommendations
- Broad coverage: humans, animals and environment
- Combined (simultaneous) exposure
- Addresses all risk assessment steps
- Focused on EFSA needs: regulated products & contaminants
- Incudes some examples

1. Characterising the kind of mixture



Intentional mixture

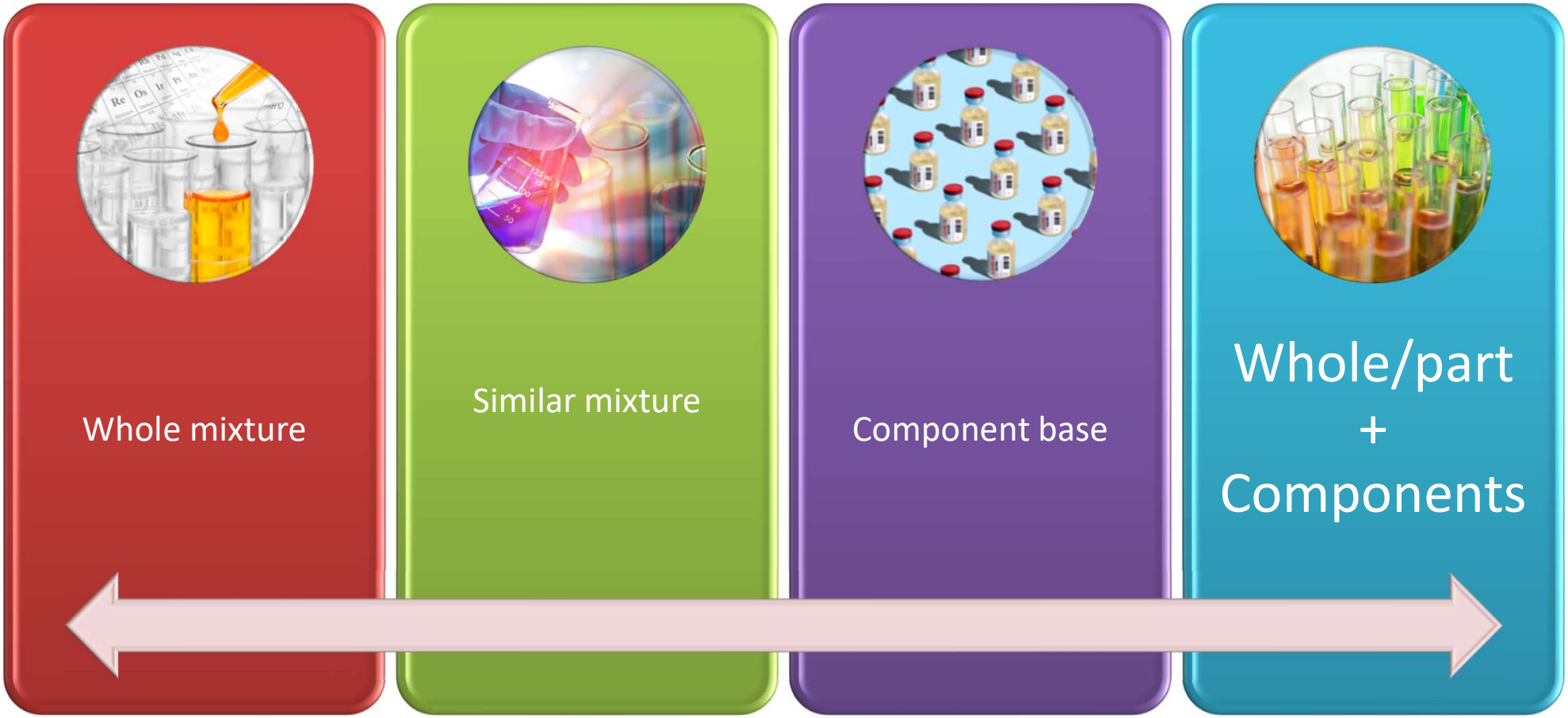
Emission

Transformation

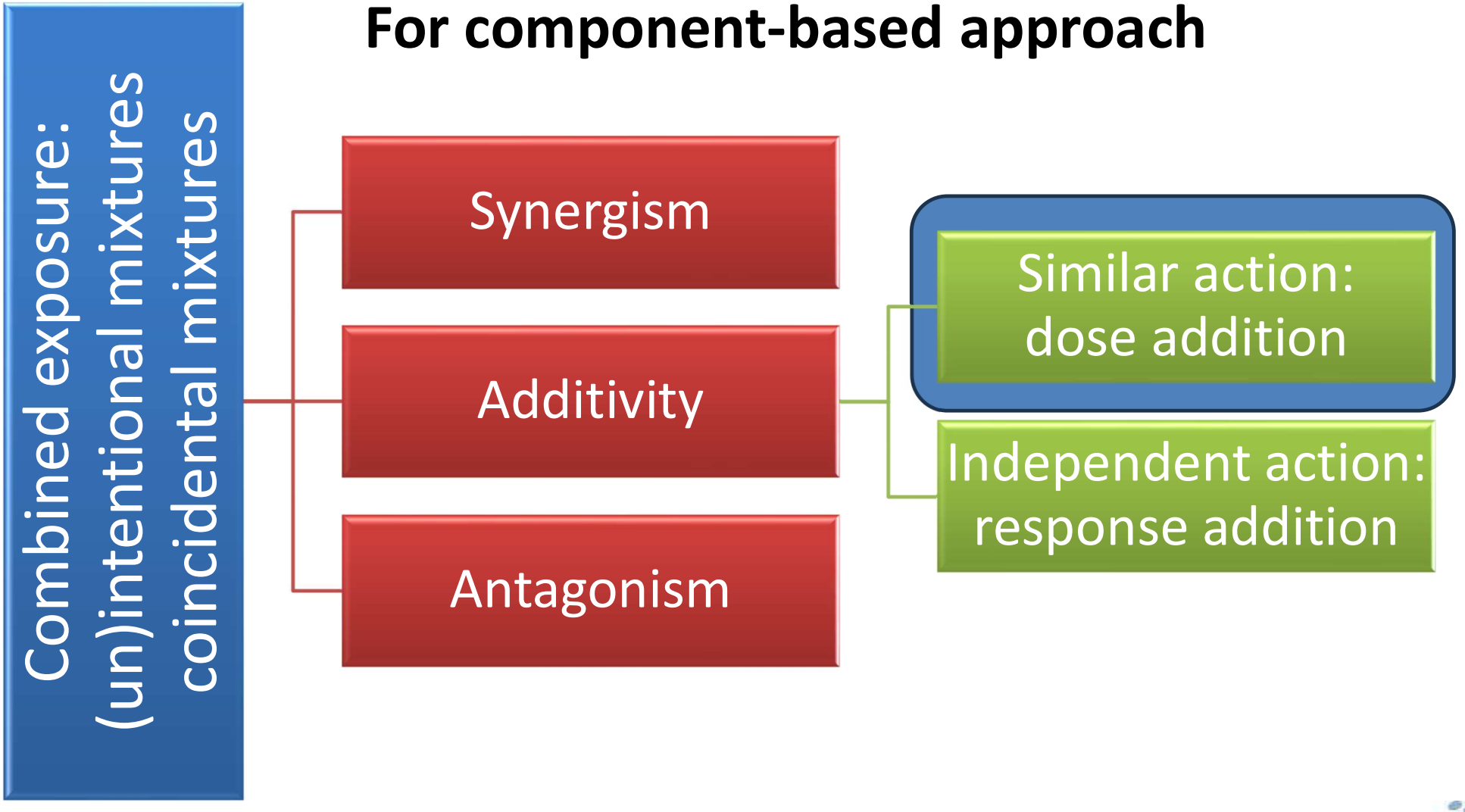
Unintentional mixture

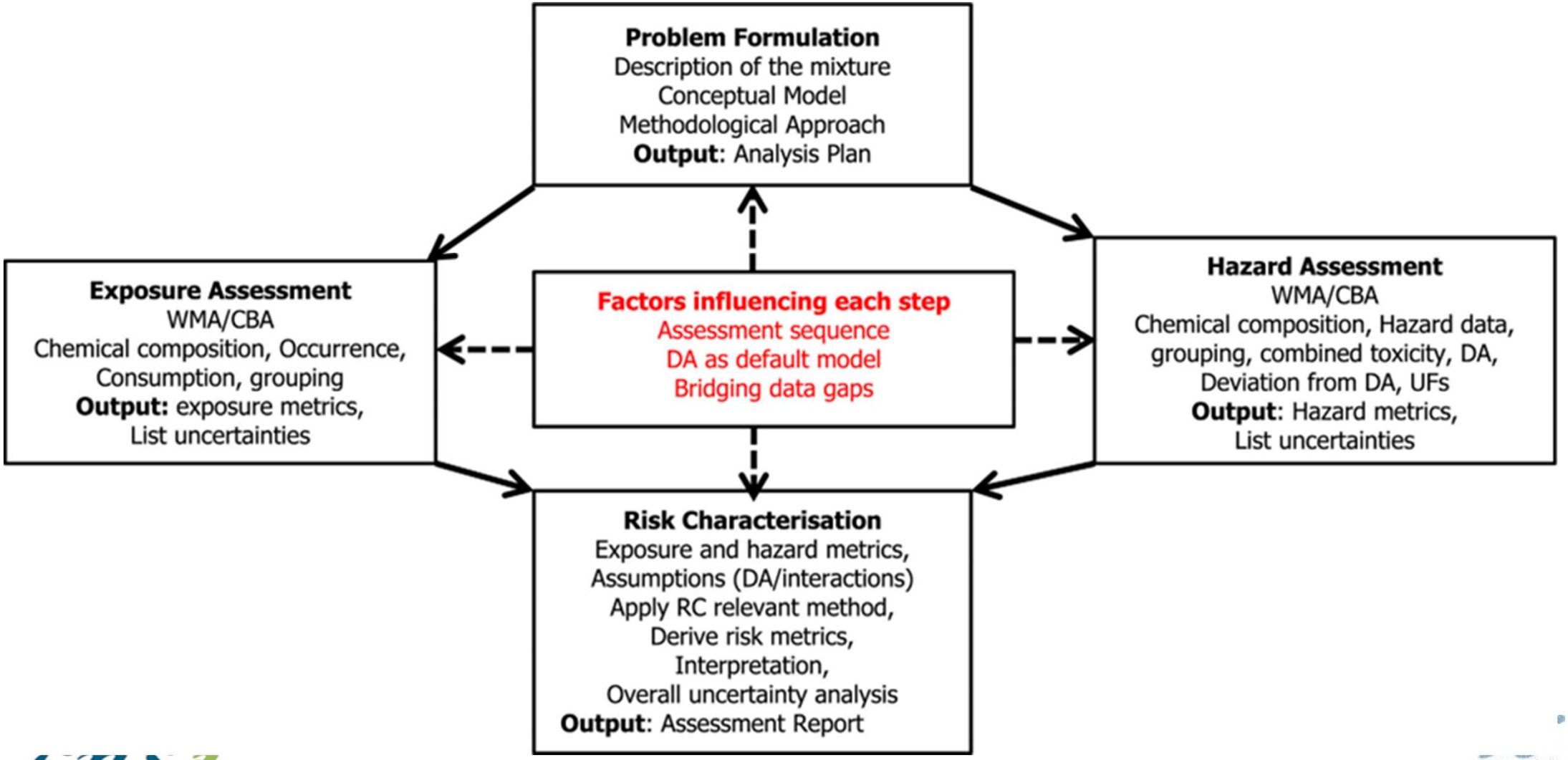
Coincidental mixture

2. Identifying the assessment approach

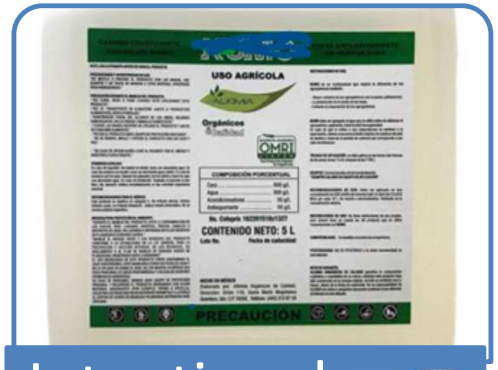


For component-based approach




Problem Formulation
Description of the mixture
Conceptual Model
Methodological Approach
Output: Analysis Plan
Exposure Assessment
WMA/CBA
Chemical composition, Occurrence,
Consumption, grouping
Output: exposure metrics,
List uncertainties
Factors influencing each step
Assessment sequence
DA as default model
Bridging data gaps
Hazard Assessment
WMA/CBA
Chemical composition, Hazard data,
grouping, combined toxicity, DA,
Deviation from DA, UFs
Output: Hazard metrics,
List uncertainties
Risk Characterisation
Exposure and hazard metrics,
Assumptions (DA/interactions)
Apply RC relevant method,
Derive risk metrics,
Interpretation,
Overall uncertainty analysis
Output: Assessment Report

3. Linking mixture type with assessment approach



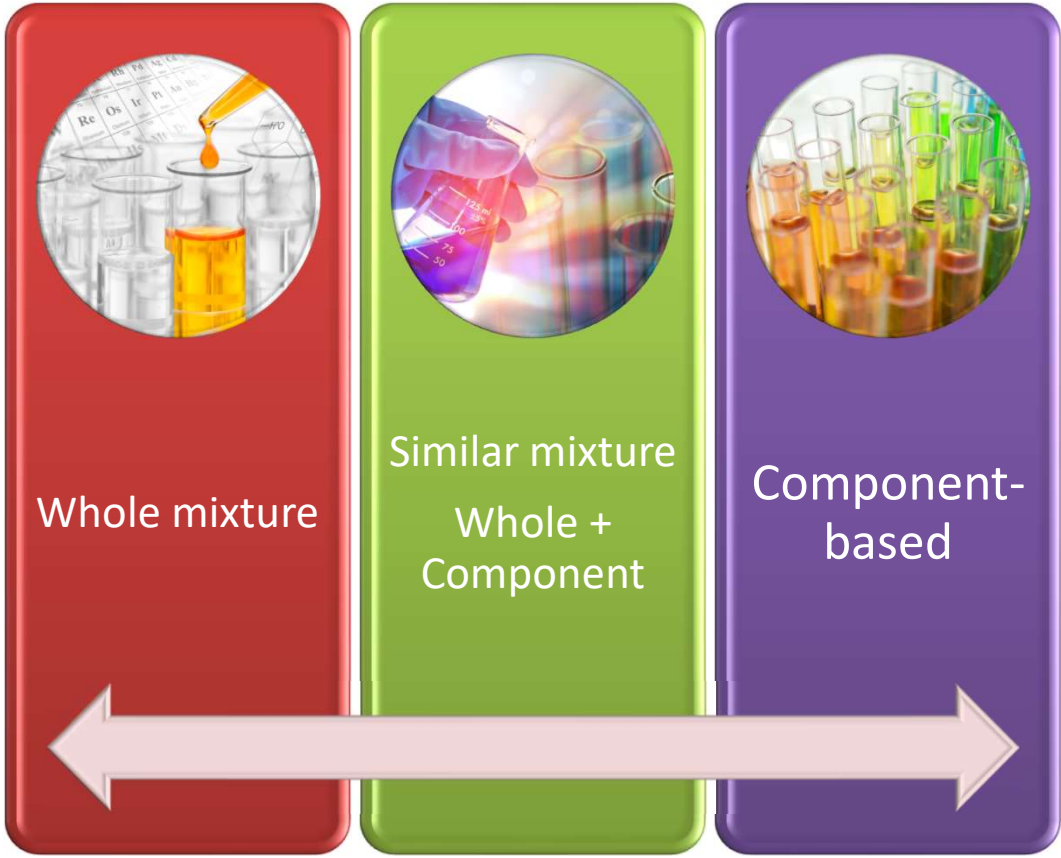
Intentional mixture

Emission

Transformation

Unintentional mixture

Coincidental mixture



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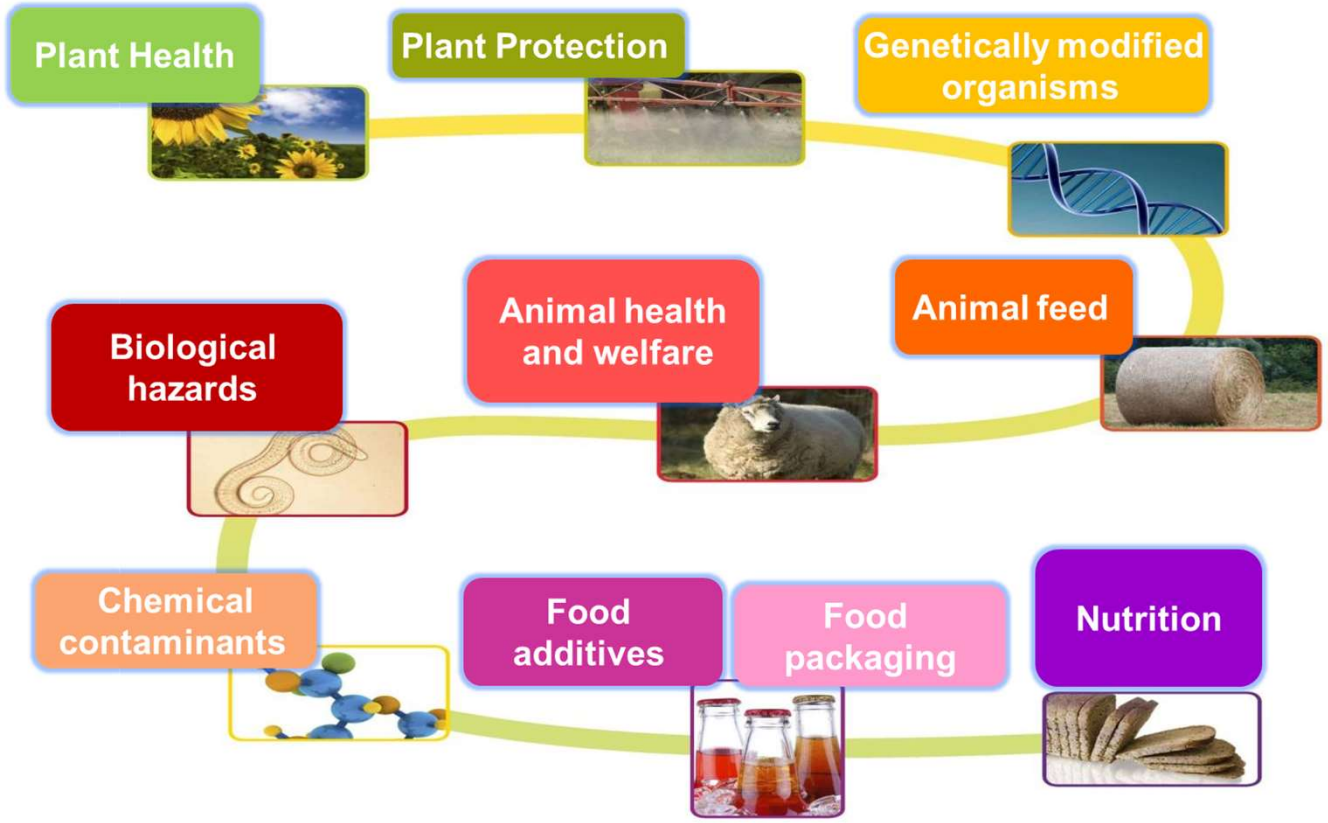
Is combined exposure assessment warranted?	Combined effects are likely Regulatory framework
Characterisation of the mixture	Origen, composition, temporal variability, …
Whole mixture and/or component-based approach?	Information on the composition
Approach to exposure assessment	Availability of data on the components and/or a marker for the full mixture
Criteria for inclusion in the assessment group?	Origin, Mode of action, Target organ, …
What to do with chemicals belonging to different groups?	Consider applying response addition
What risk metrics to use?	Margin of Exposure, hazard or risk quotient

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

CROSS-CUTTING GUIDANCE

SECTOR-SPECIFIC GUIDANCE

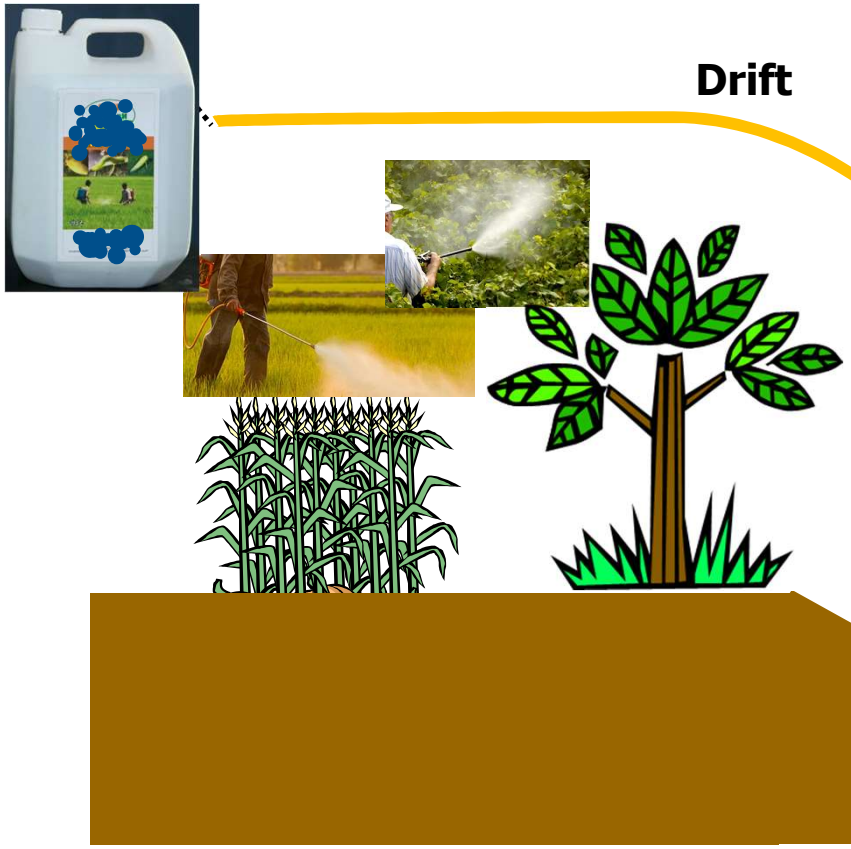


Scenarios for pesticide risk assessment

- Occupational risks:
  - Applicant
  - Other agricultural workers
- Risk for humans exposed from the environment
  - Bystanders
  - Residents
- Risks to consumers from residues in food

- Risk for non-target organisms
  - Mammals and birds
  - Aquatic organisms (fish, invertebrates, algae, plants)
  - Bees
  - Other terrestrial arthropods
  - Non-target terrestrial plants
  - Soil organisms (macro and microorganisms)
- Risk for WWTP biological treatments

APPLICATION



APPLICATION → ENVIRONMENTAL PROCESSES

Drift

Volatilization

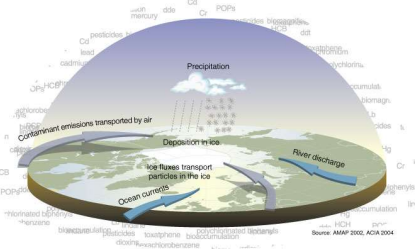
Runoff

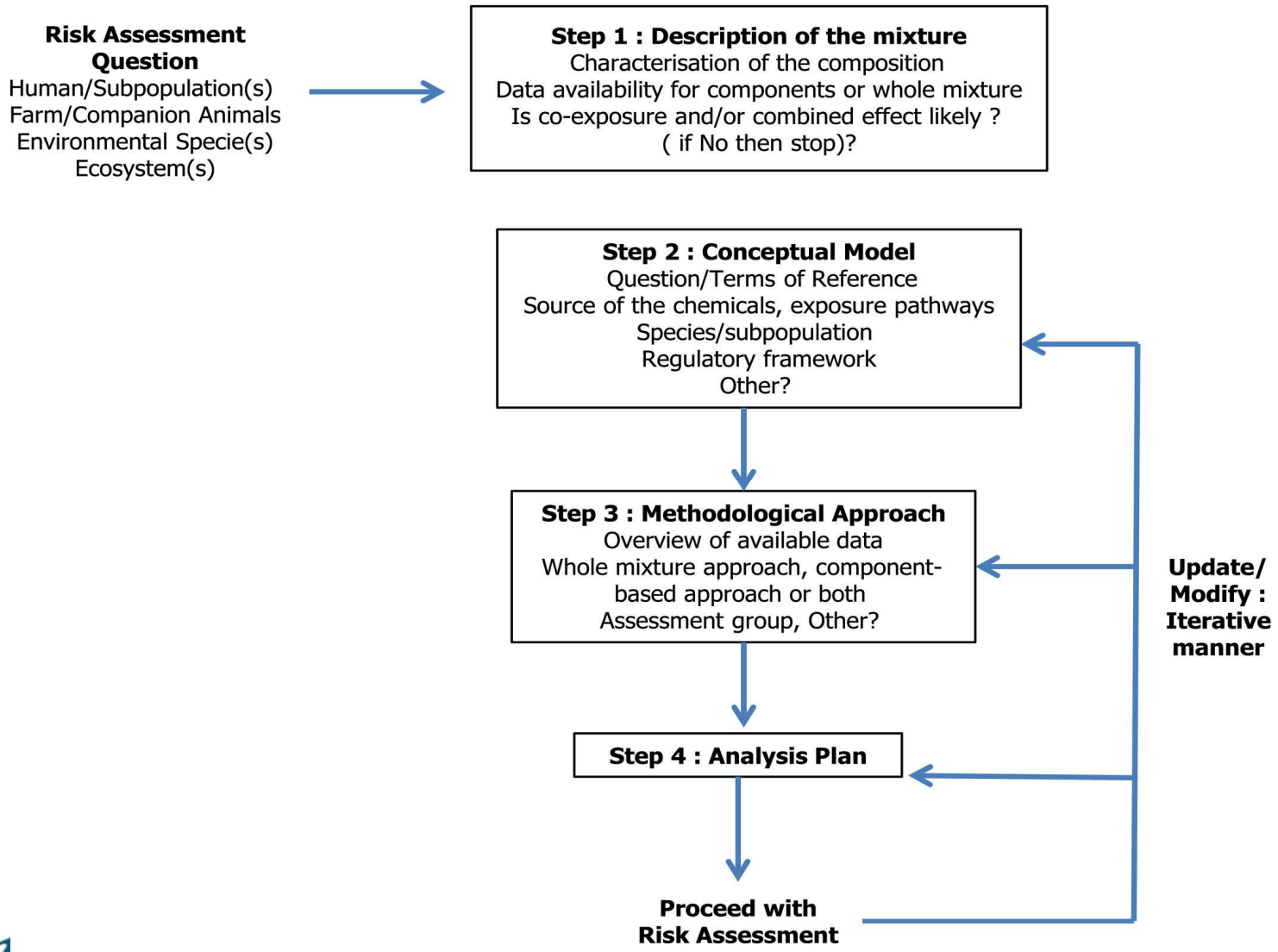
Lixiviation

Drainage

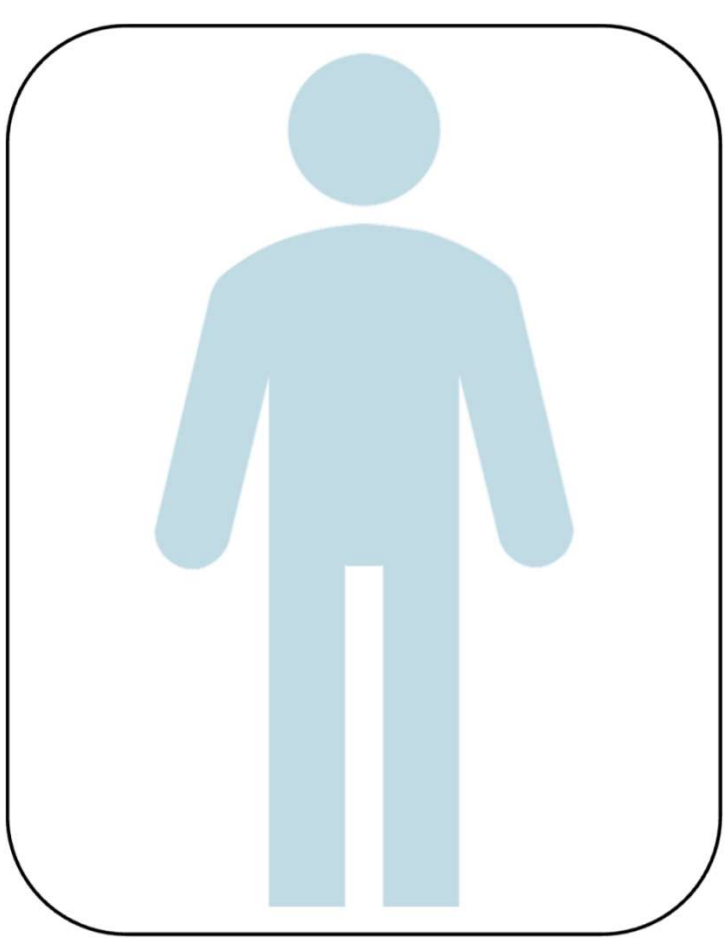
WATER/SEDIMENT

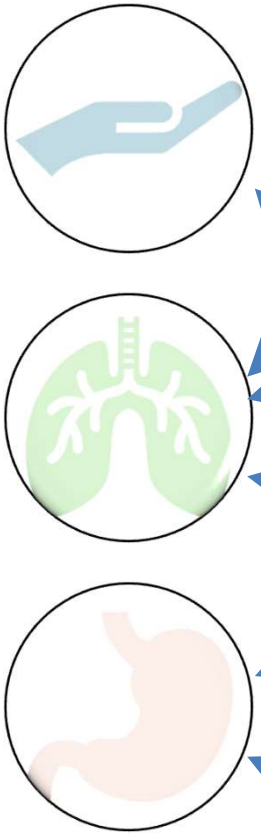
Deposition following medium and long-term transport




Risk Assessment Question
Human/Subpopulation(s)
Farm/Companion Animals
Environmental Specie(s)
Ecosystem(s)
Step 1 : Description of the mixture
Characterisation of the composition
Data availability for components or whole mixture
Is co-exposure and/or combined effect likely ?
(if No then stop)?
Step 2 : Conceptual Model
Question/Terms of Reference
Source of the chemicals, exposure pathways
Species/subpopulation
Regulatory framework
Other?
Step 3 : Methodological Approach
Overview of available data
Whole mixture approach, component-based approach or both
Assessment group, Other?
Step 4 : Analysis Plan
Proceed with Risk Assessment
Update/ Modify : Iterative manner

Exposure characterisation





PRODUCT

FOLIAR RESIDUES

DRIFT AND DEPOSITION RESIDUES

RESIDUES IN FOOD

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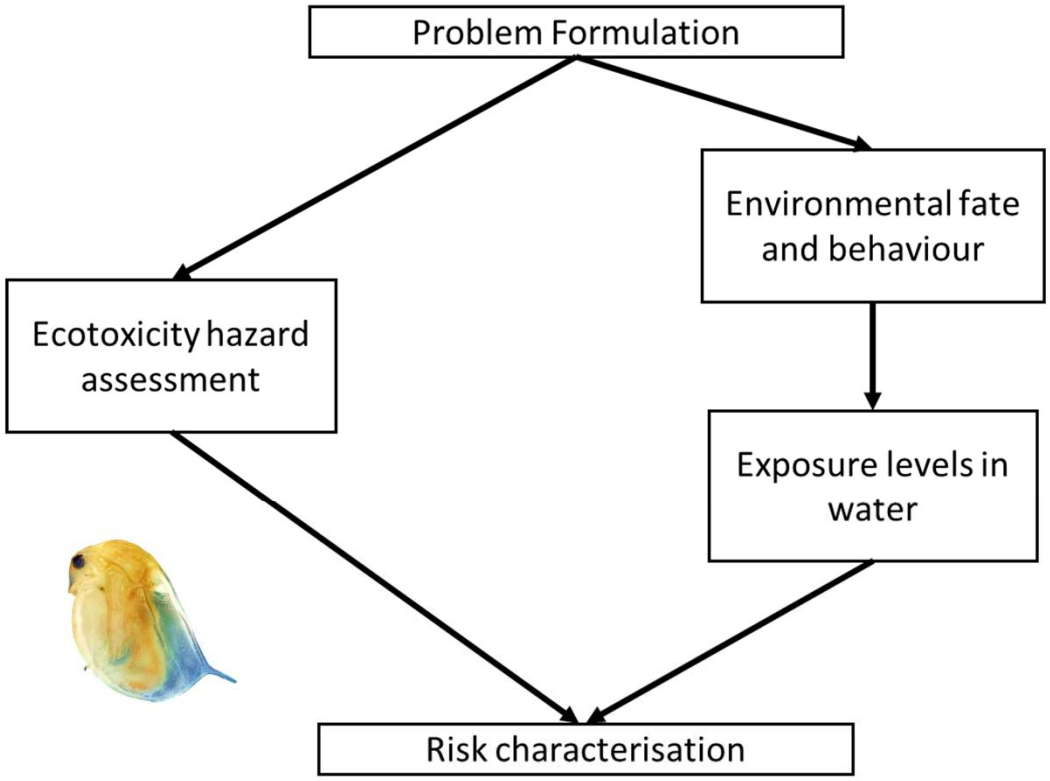

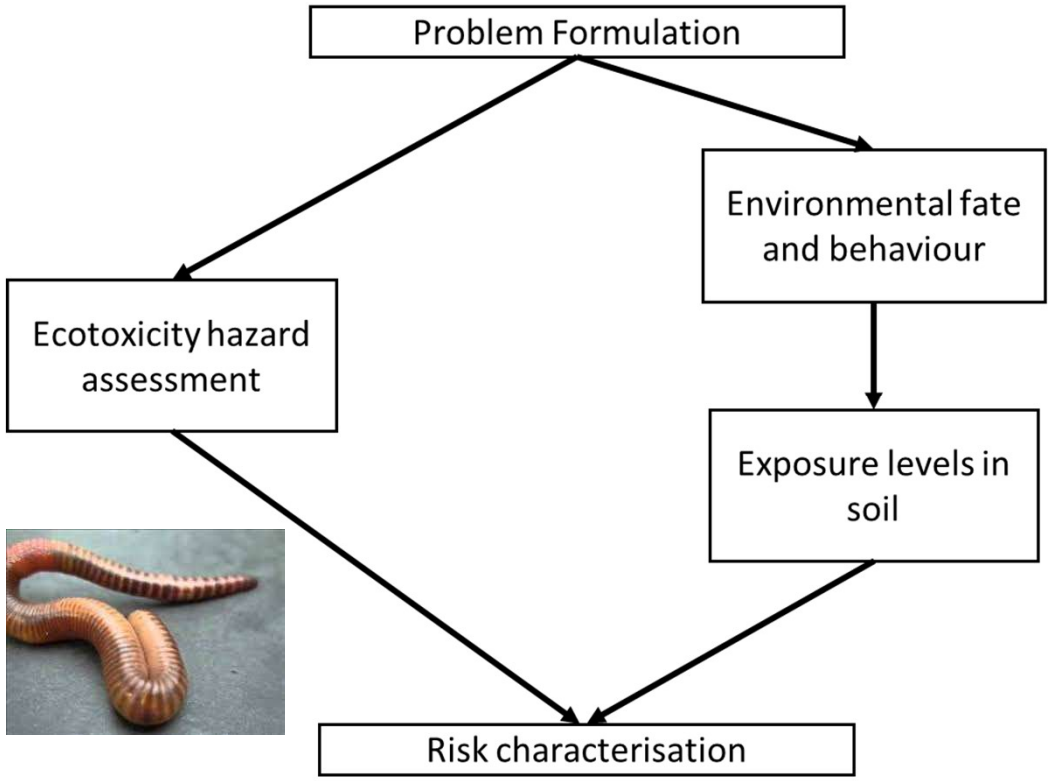

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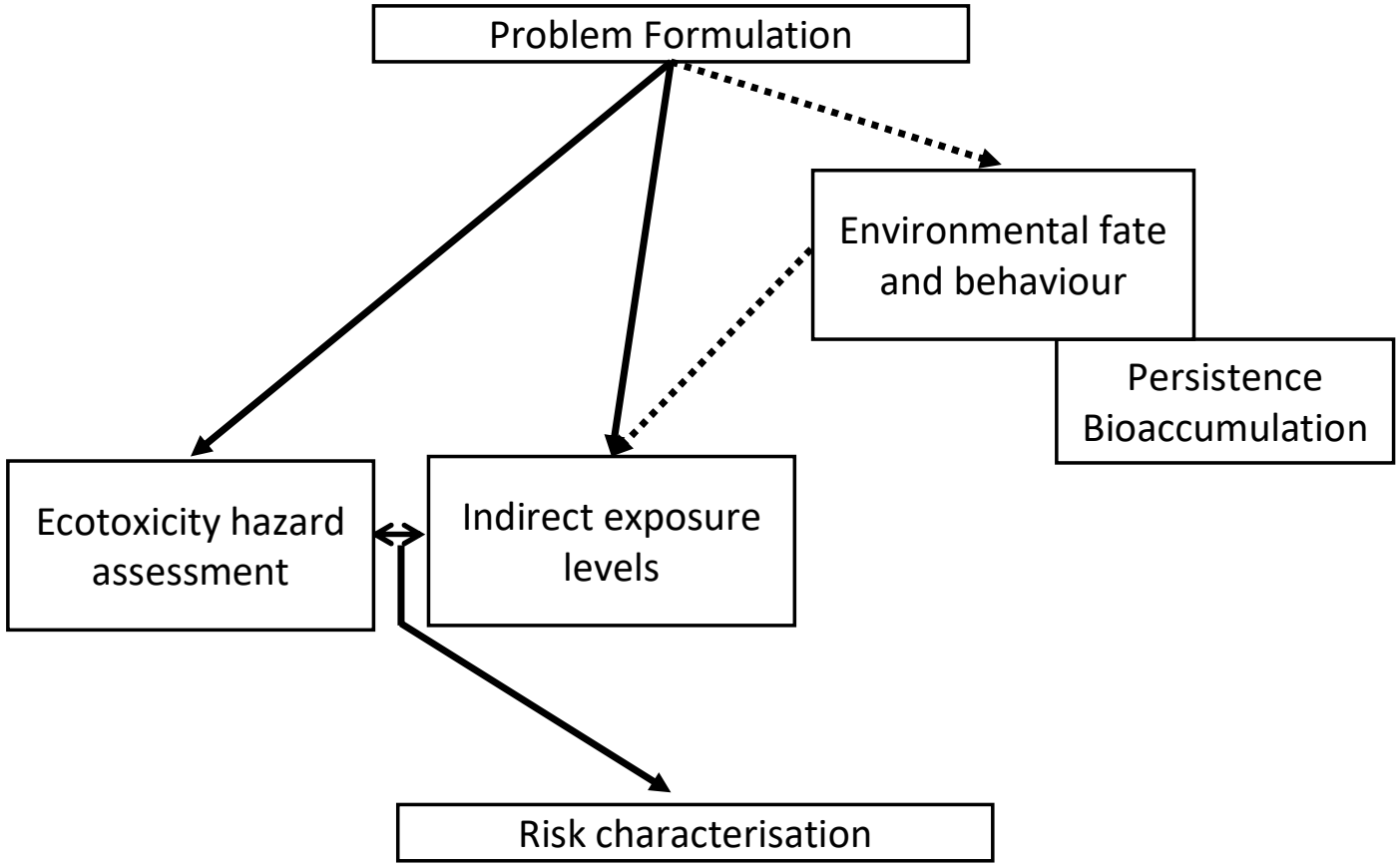
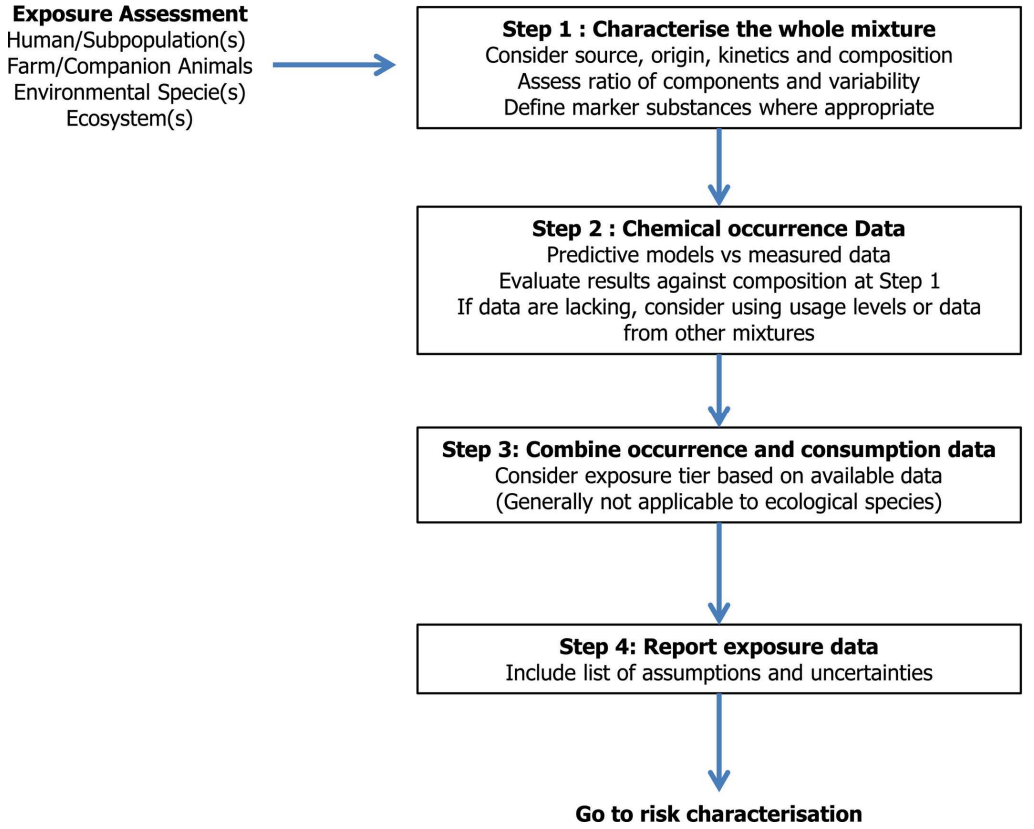
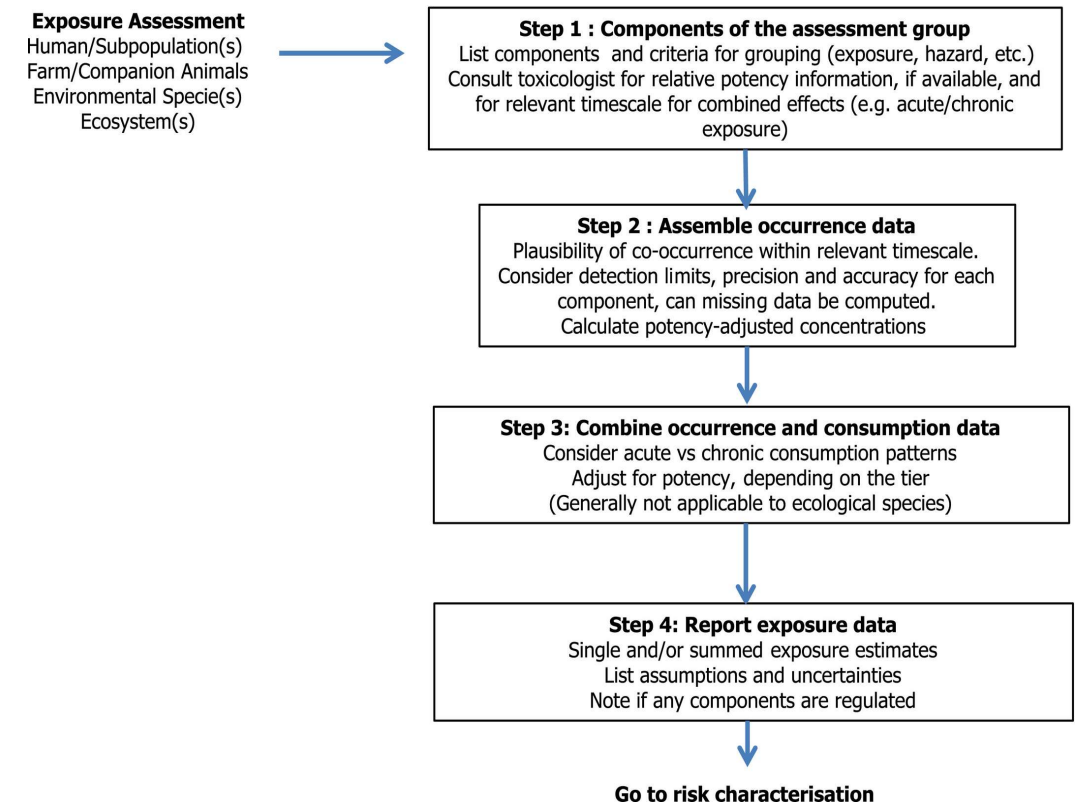

Problem Formulation
Environmental fate and behaviour
Persistence
Bioaccumulation
Ecotoxicity hazard assessment
Indirect exposure levels
Risk characterisation

Dietary exposure assessment

Tier	Occurrence data	Consumption data	Exposure estimate
0	Default Values, Permitted Levels	Default Values, Portion Sizes	Semi-Quantitative Point estimates
1	Modelled and Experimental Data	Food Balance Sheet Food Basket	Deterministic
2	Monitoring Surveys	Summary Statistics	Semi-Probabilistic
3	Individual Co-Occurrence data	Individual data	Probabilistic

Exposure assessment frameworks





Hazard assessment frameworks

Hazard Identification
Hazard characterisation
Human/Subpopulation(s)
Farm/Companion Animals
Environmental Specie(s)
Ecosystem(s)

Step 1: Data collection
Collect toxicity data on the mixture of concern,
or if not sufficiently available then on a similar mixture

↓

Step 2: Reference points
Identify or derive a reference point for the mixture
or for the similar mixture

↓

Step 3: Reference values
If limited data or read-across is required from a sufficiently similar mixture then consider whether additional uncertainty factors are required in establishing reference values
or applying a margin of exposure approach to the reference point

↓

Step 4: Report
Summarise hazard, associated assumptions and uncertainties

↓

Go to risk characterisation

Hazard Identification
Hazard characterisation
Human/Subpopulation(s)
Farm/Companion Animals
Environmental Specie(s)
Ecosystem(s)

→

Step 1: Confirm components of Assessment Group
Criteria for grouping (hazard, exposure, etc.)

↓

Step 2: Collect available hazard information
e.g. Toxicity data, reference points, reference values, mode of action, toxicokinetic information, potency information.
Identify the relevant entry tier for the assessment

↓

Step 3: Evidence for combined toxicity
Assess evidence for combined toxicity,
including potential deviation from dose addition.
Identify the most appropriate tool for risk characterisation

↓

Step 4: Tools for hazard characterisation
Assess evidence available for combined toxicity of the assessment group, including deviation from dose addition.
This can include quantification of the magnitude of interactions.
Identify the most appropriate tool for risk characterisation

↓

Step 5: Summarise Hazard characterisation for each component of Assessment Group
List assumptions (potency, dose addition, interaction)
List uncertainties

↓

Go to risk characterisation

Selection of Point of Departure (PoD)
Guidance Value = PoD/(10x10xadditional UF)

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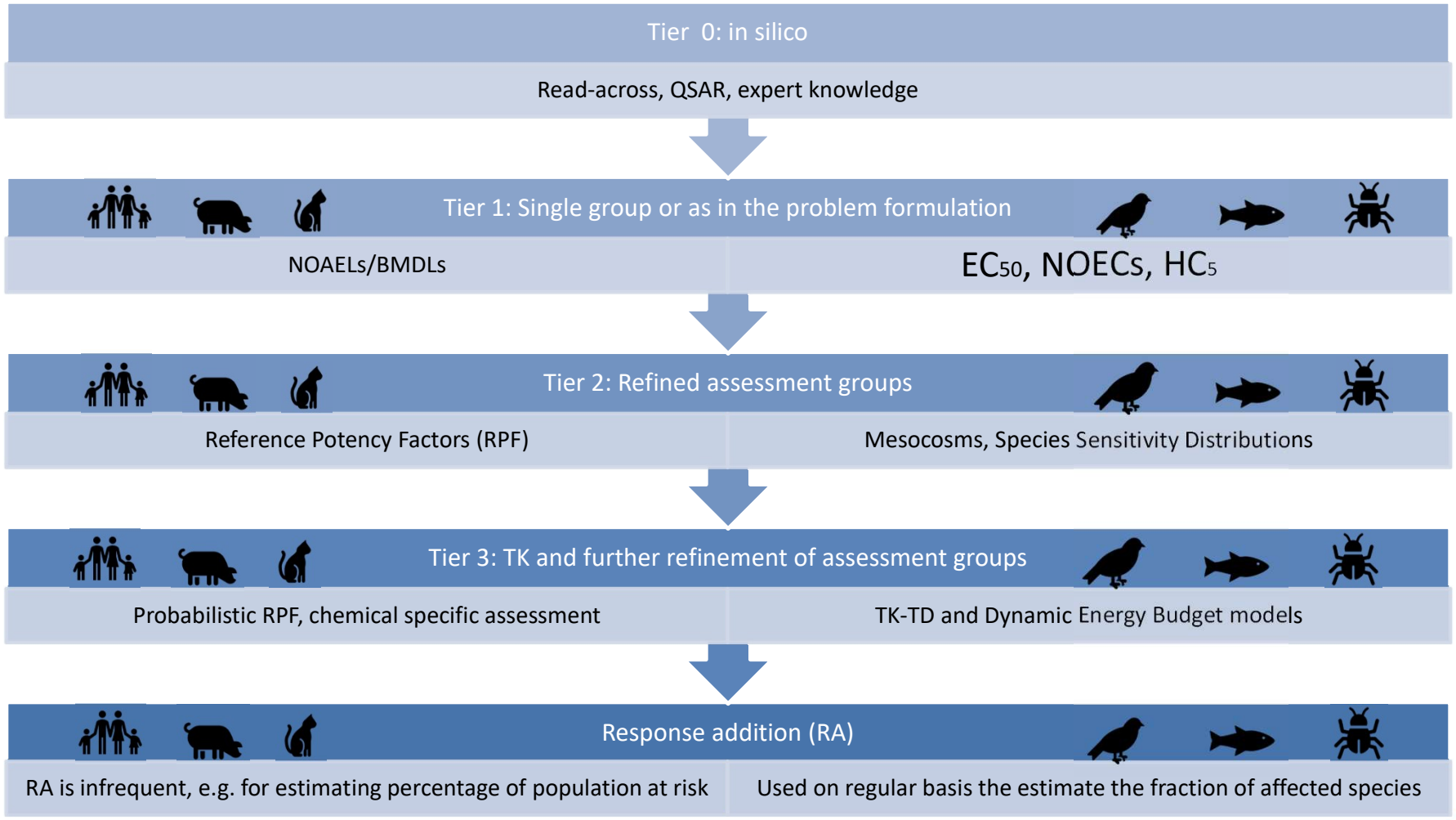
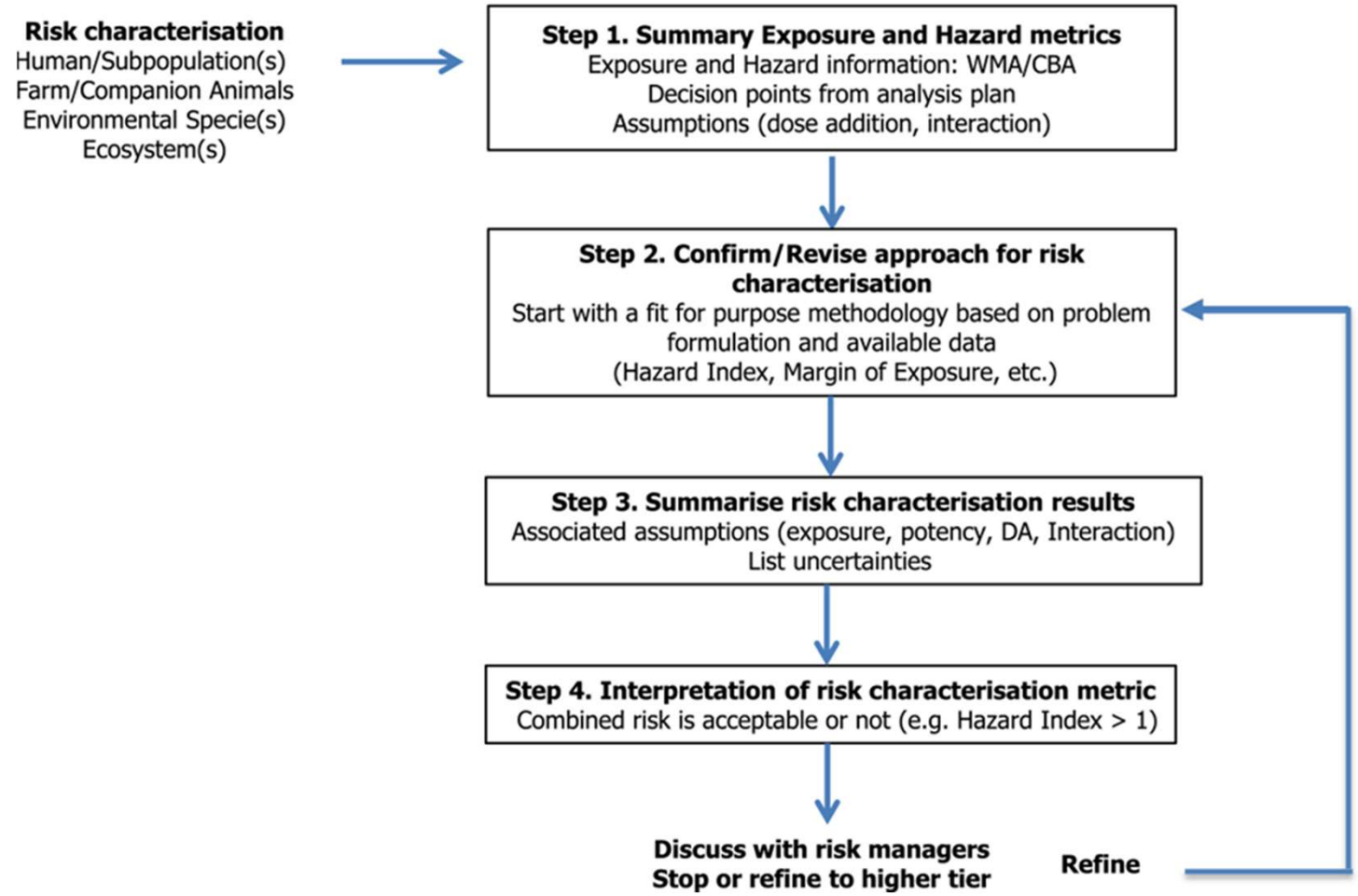
Hazard assessment tiers for component-based approach



Risk characterisation options



WHOLE MIXTURE

- Margin of Exposure
- Hazard Quoting
- PEC/PNEC

COMPONENT BASED

A. DOSE ADDITION

- Combined Margin of Exposure
- Sum of hazard quotients
- Sum of Toxicity Units
- Sum of Toxic Equivalent Factors

B. RESPOSE ADDITION

- Combination of independent random events

$$R_{mix} = 1 - \prod_{i}^{n} (1 - R_i)$$

Content

1. Introduction to the EFSA guidance

2. Recent developments on assessment of combined exposure to human health: **NAM-based assessments**
3. PARC developments for assessing combined effects in environmental risk assessments: **Landscape-based risk assessments**

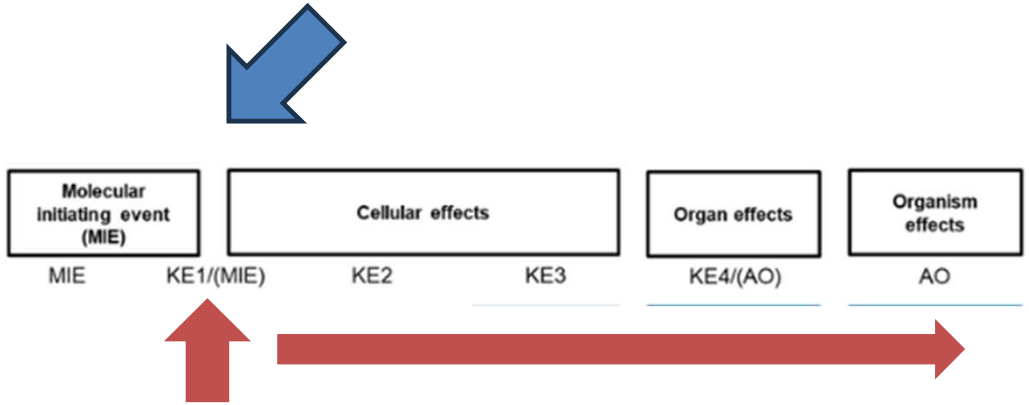
NAM-based hazard assessment approaches

21st Century Toxicology

Pathways for adversity

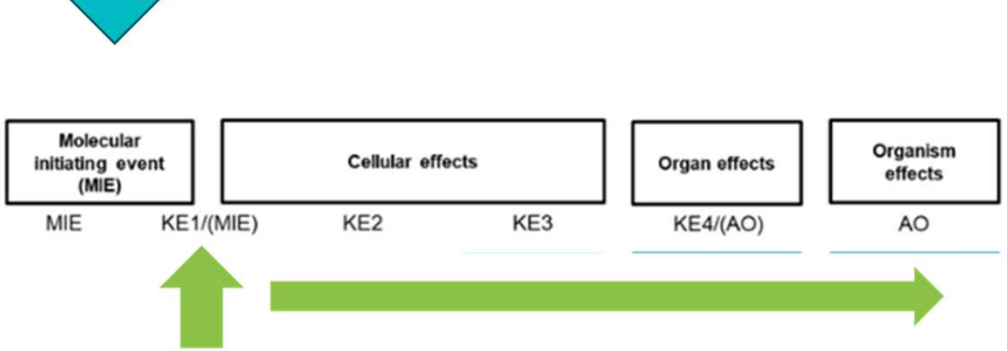
Intermediate endpoints
Mechanistic connectors

- Substances of assumed no concerns
  - No MIE or low KE induction



- Substances with expected (or observed) concerns
  - Bioactivity mechanism(s)
  - Progression of adversity

Safe use: No MIE (or KE) induction



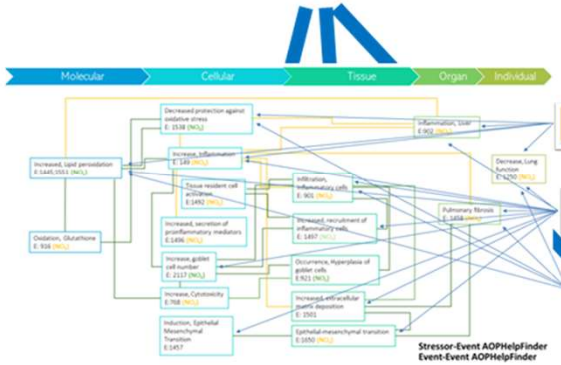
Bioactivity mechanism(s) and progression towards adversity

Identify vulnerable groups: those with reduced capacity for recovery and/or compensation

4

Mechanistic information

- Similar pathways
- Related pathways



Combined adversity

Adversity estimations

Adversity relationships

Criteria

Toxicity & Biology

Lines of evidence

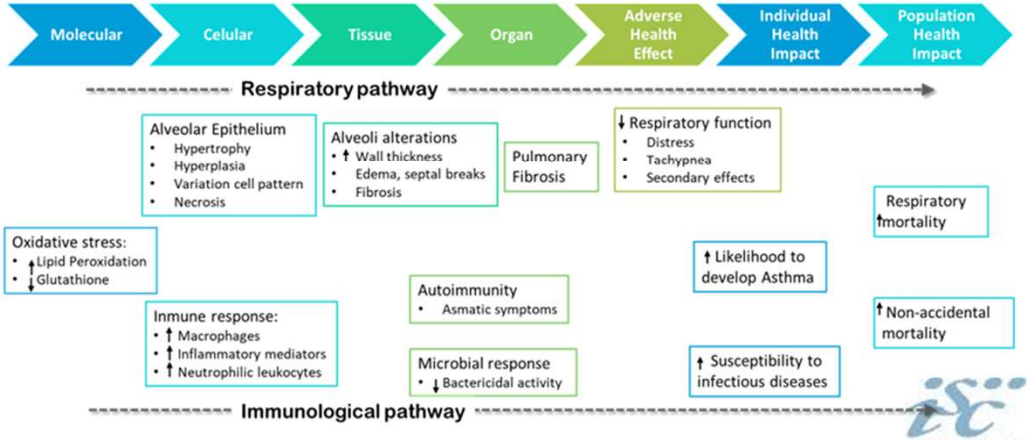
Probabilistic link with Health Impact Indicators


Chemosphere

Combination of toxicological and epidemiological approaches for estimating the health impact of atmospheric pollutants. A proof of concept for NO_2

Lines of Evidence for AOP → HIP implementation

Nitrogen dioxide & Related atmospheric pollutants



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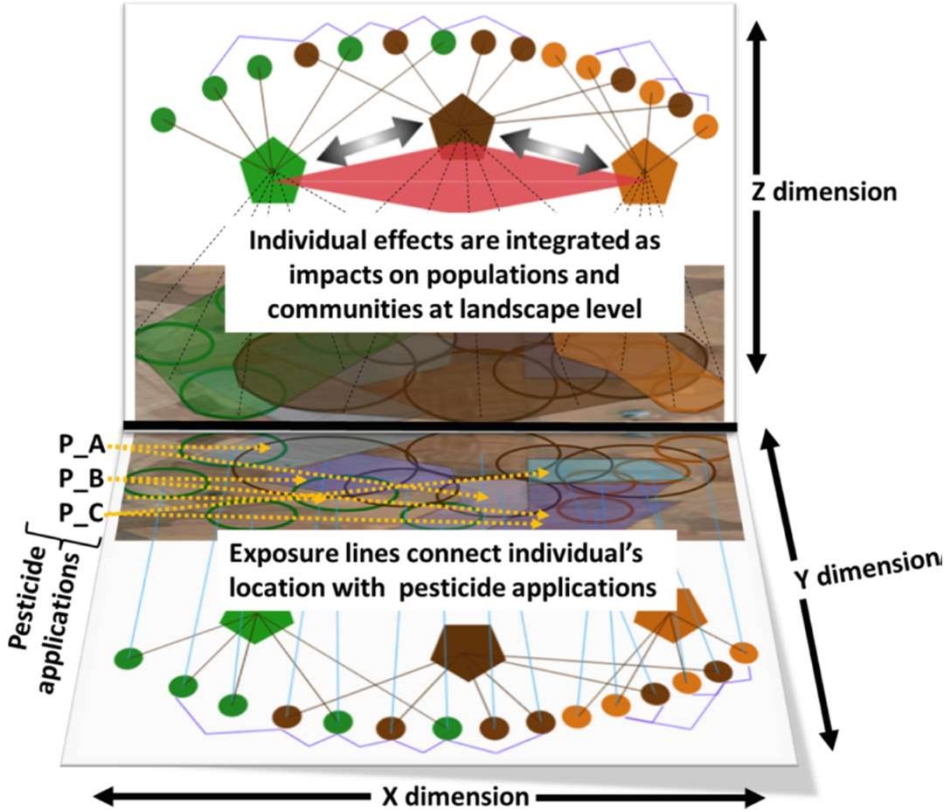
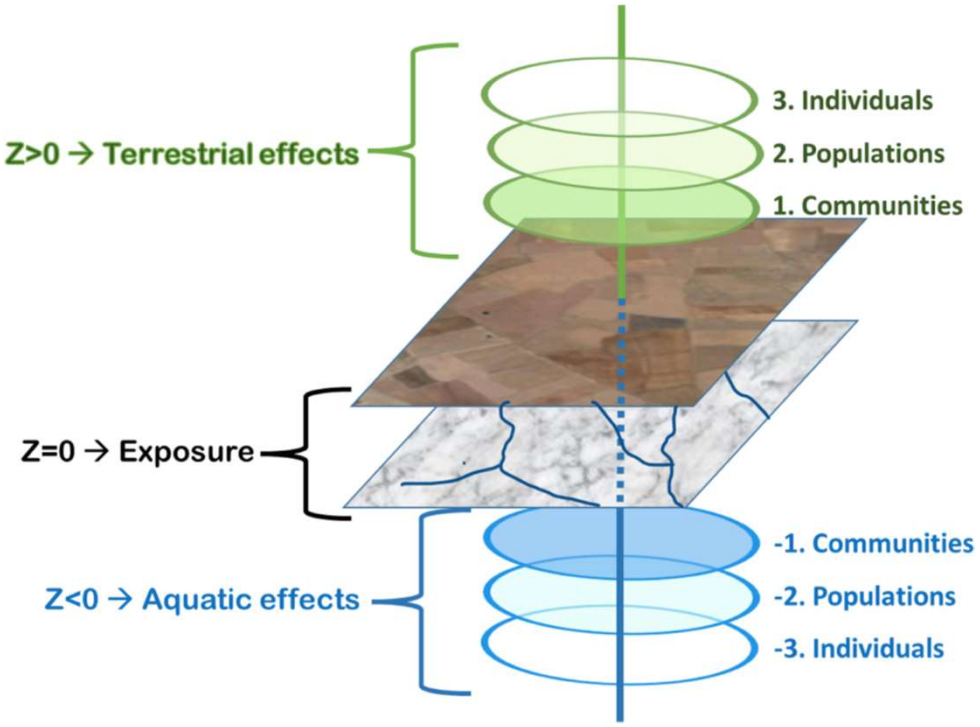
Spatial explicit combination: landscape ERA models






Environment International

A conceptual framework for landscape-based environmental risk assessment (ERA) of pesticides

The 3D structure of the landscape ERA model

Landscape filtering (|Z| = 0):

- combine substance concern × landscape exposure
- identify taxa of highest concern

Regulatory data (|Z| = 1-3):

- standard endpoints
- Integration (e.g. population dynamics models)

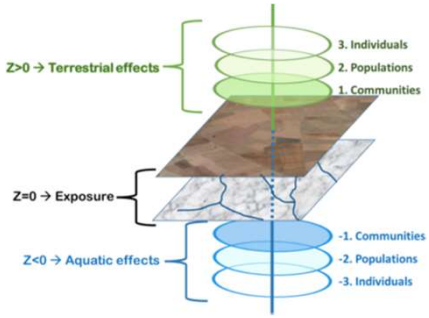
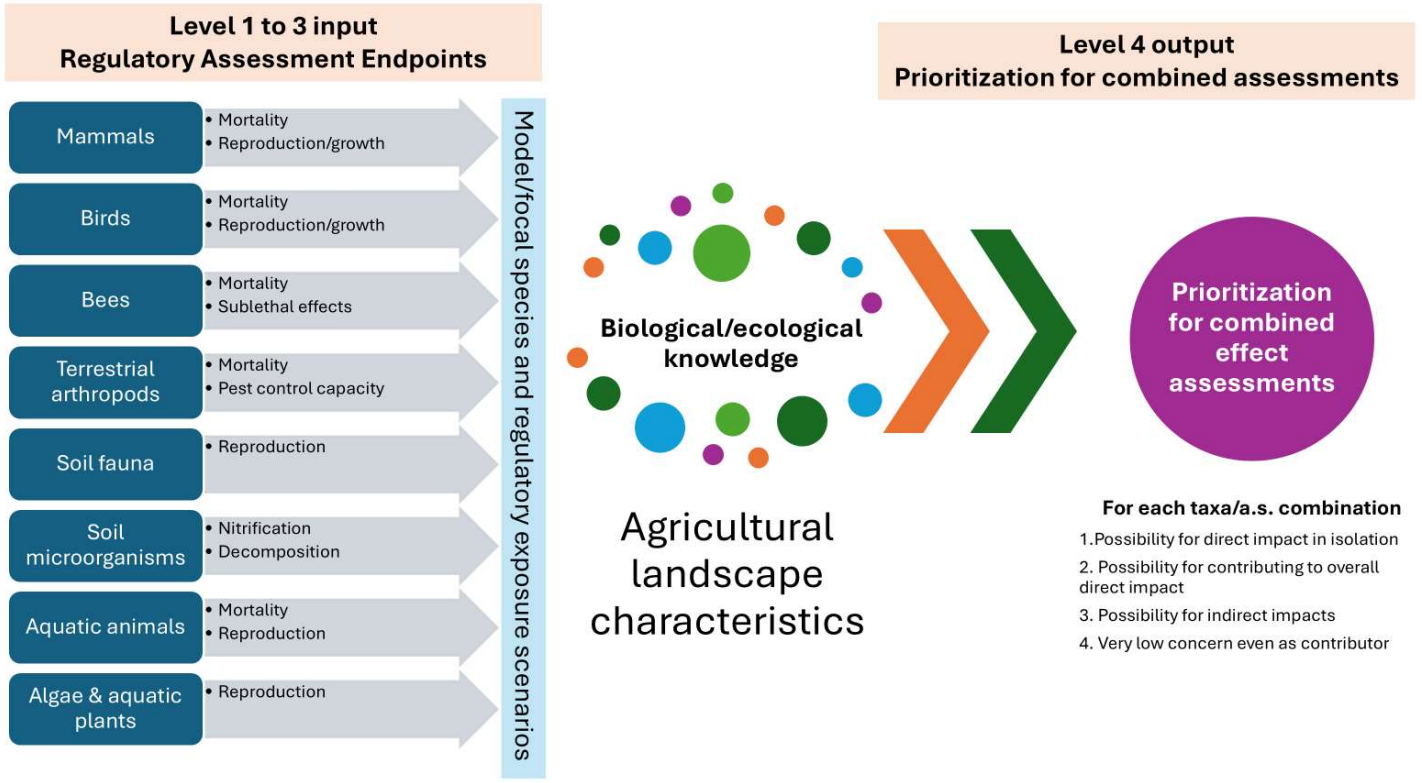


Table 5
Final equation for the effects on morbidity, mortality and reproduction for mammals and birds obtained for exposure to folpet and pirimicarb.

Pesticide	Class	Effect	Equation	Factors
Folpet	**Mammals**	**Morbidity**	MB = 1.2D	Yes (factor of 100)
		Mortality due to morbidity	M(M) = 0.12D	Yes (factor of 10)
		Reproduction	RE = 1.667D	Yes (factor of 10)
	Birds	**Morbidity**	MB = 1.2D	–
		Mortality	MT = 0.12D	–
		Reproduction	RE = 12D	Yes (factor of 10)
Pirimicarb	**Mammals**	**Morbidity**	MB = 1.5385 (D) + 3.5385	No
		Mortality due to morbidity	M(M) = 0.15385(D)+ 3.5385	Yes (factor of 10)
		Mortality	MT = 6.25(D) - 24.375	Yes (factor of 10)
		Reproduction	RE = 4.286(D) - 0.7143	Yes (factor of 10)
	Birds	**Morbidity**	N/A	–
		Mortality	MT = 27.008 (D)- 21.487	Yes (factor of 10)
		Reproduction	RE = 0.954(D)- 3.7547	Yes (factor of 10)

Legend: *MT (Mortality), MB (Morbidity), M(M) (Mortality due to morbidity), RE (Reproduction effect), D (Dose (mg/kg bw)), N/A (Not applicable).*

Mechanistic expansion: Level 4



Problem formulation to be published soon!!!

Thank you

Any question?