CUSP thematic workshop series: Human Risk Assessment of MNPs

Workshop 2: Human health risk assessment frameworks for micro- and nanoplastics

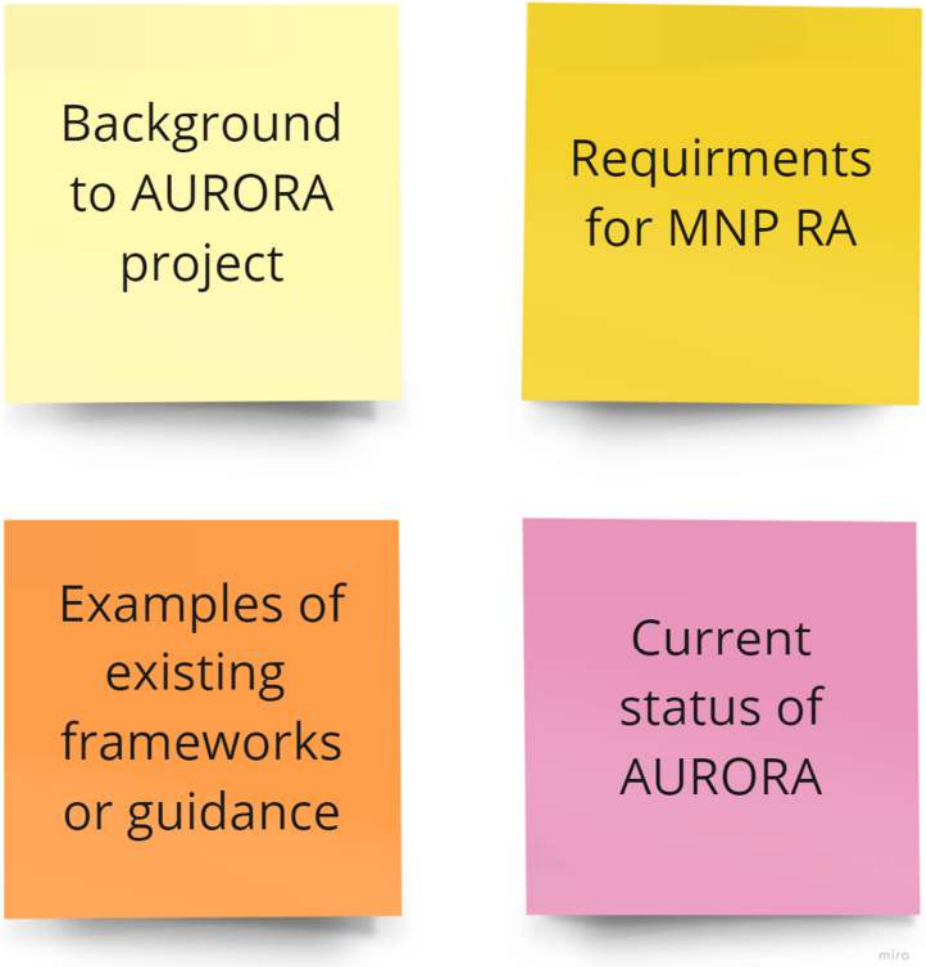
Why it is challenging for MNP risk assessment (RA) to conform to traditional RA approaches, and how can AURORA sufficiently assess risk to early-life health

Matthew Boyles, Institute of Occupational Medicine, UK

AURORA partner

This project has received funding from the European Union's Horizon 2020 research and innovation programme under AURORA grant agreement No 964827

Content of this session



Session description for: *Why it is challenging for MNP risk assessment (RA) to conform to traditional RA approaches, and how can AURORA sufficiently assess risk to early-life health*.

This session will look into why there are challenges faced when endeavouring to use accepted models of RA to sufficiently address the diverse risks posed by MNPs; the wide-ranging hazards of MNPs will be identified, as will their extensive routes of exposure, these will form the basis to advocate certain RA frameworks and concepts that may contribute to a holistic approach for MNP RA, and how further considerations are needed for the AURORA consortium to align with their requirement to address early-life health.

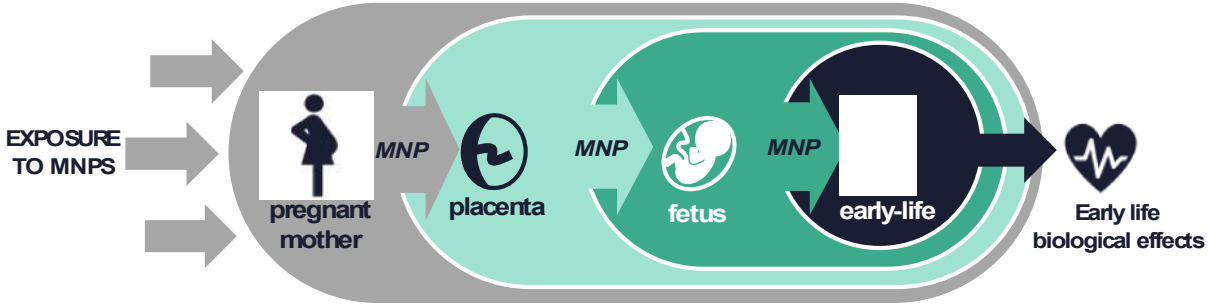
AURORA project

- **A**ctionable E**U**ropean **RO**admap for Early-life Health **R**isk **A**ssessment of Micro- and Nanoplastics

- Prof. **Roel Vermeulen**, UMC Utrecht / Utrecht University
- Coordinator AURORA

- Focusing on a **vulnerable period:**

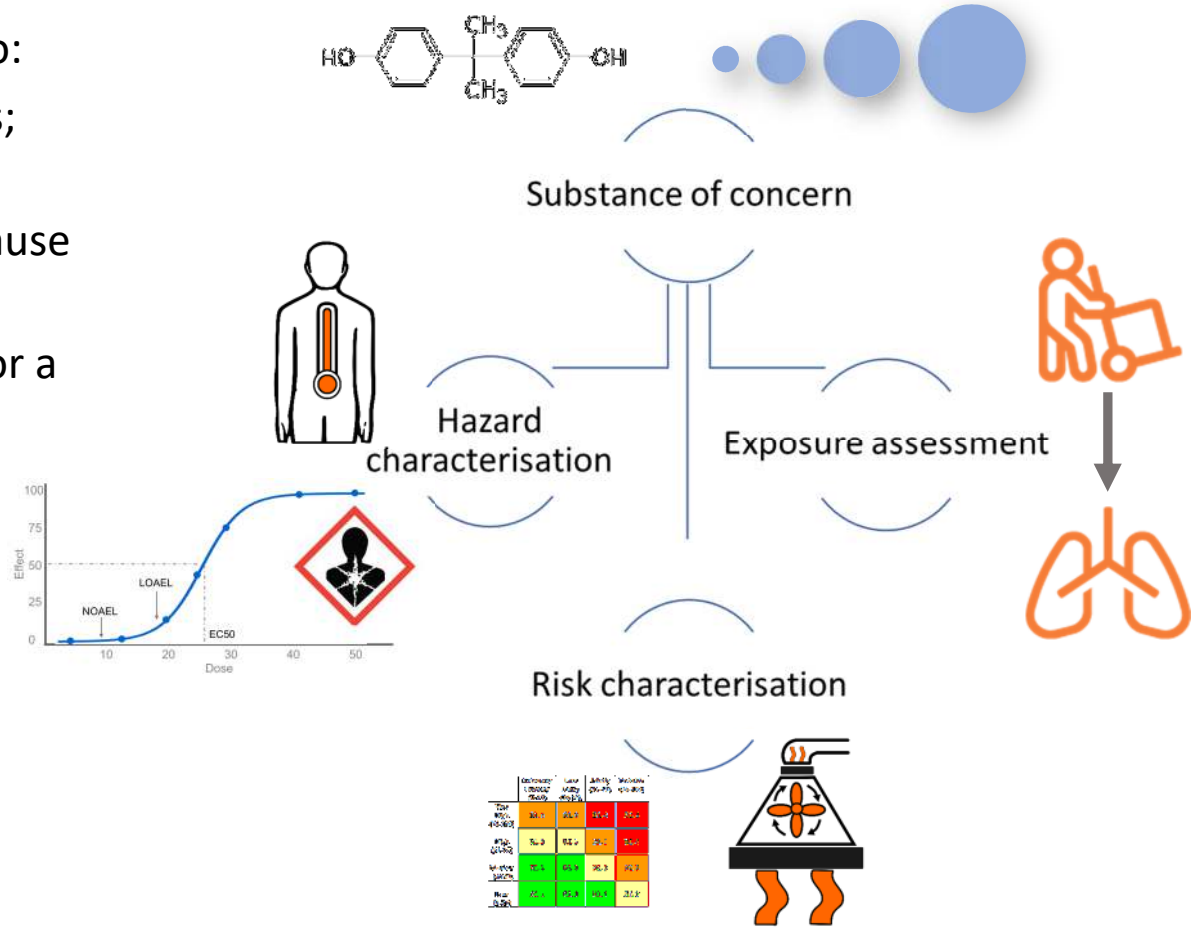
  pregnancy & early-life
  - exposure estimates
  - maternal reproductive health
  - placental transport and function
  - child development

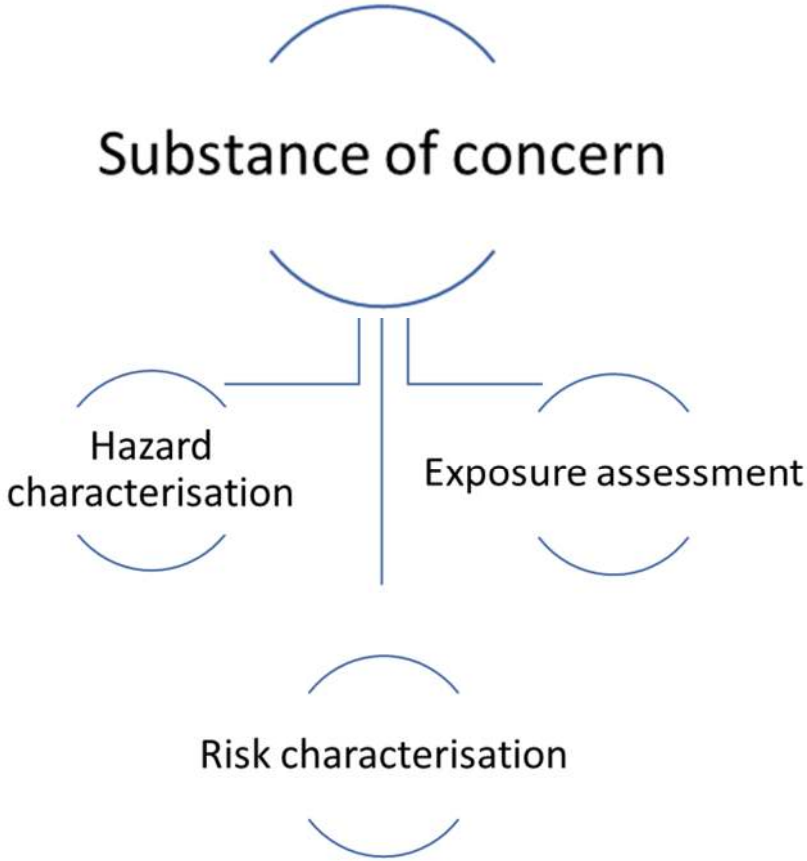


Risk assessment – general principles

To characterise risk, you need to:

- Know the material properties;
- Identify the hazard, i.e. the potential of a substance to cause harm;
- Understand the probability for a substance to cause harm;
- Contextualise the risk.




Substance of concern
Hazard characterisation
Exposure assessment
Risk characterisation

Substance of concern – RA in the context of MNP characteristics

Polymer chemistry

- Polymeric core – containing chemical contaminants e.g., bisphenol A
- Surface/unbound monomers

Leaching of contaminants

Morphology/ size

- Fibres
- Particles
- Nanoparticles
- Irregular shapes
- Films
- Foams
- Flakes

Surface properties

Contamination

- Absorbed environmental pollutants e.g. PCBs, PAHs

Contamination

- Vector: *colonised* surfaces e.g. with pathogens or mobile genetic materials (MGM)

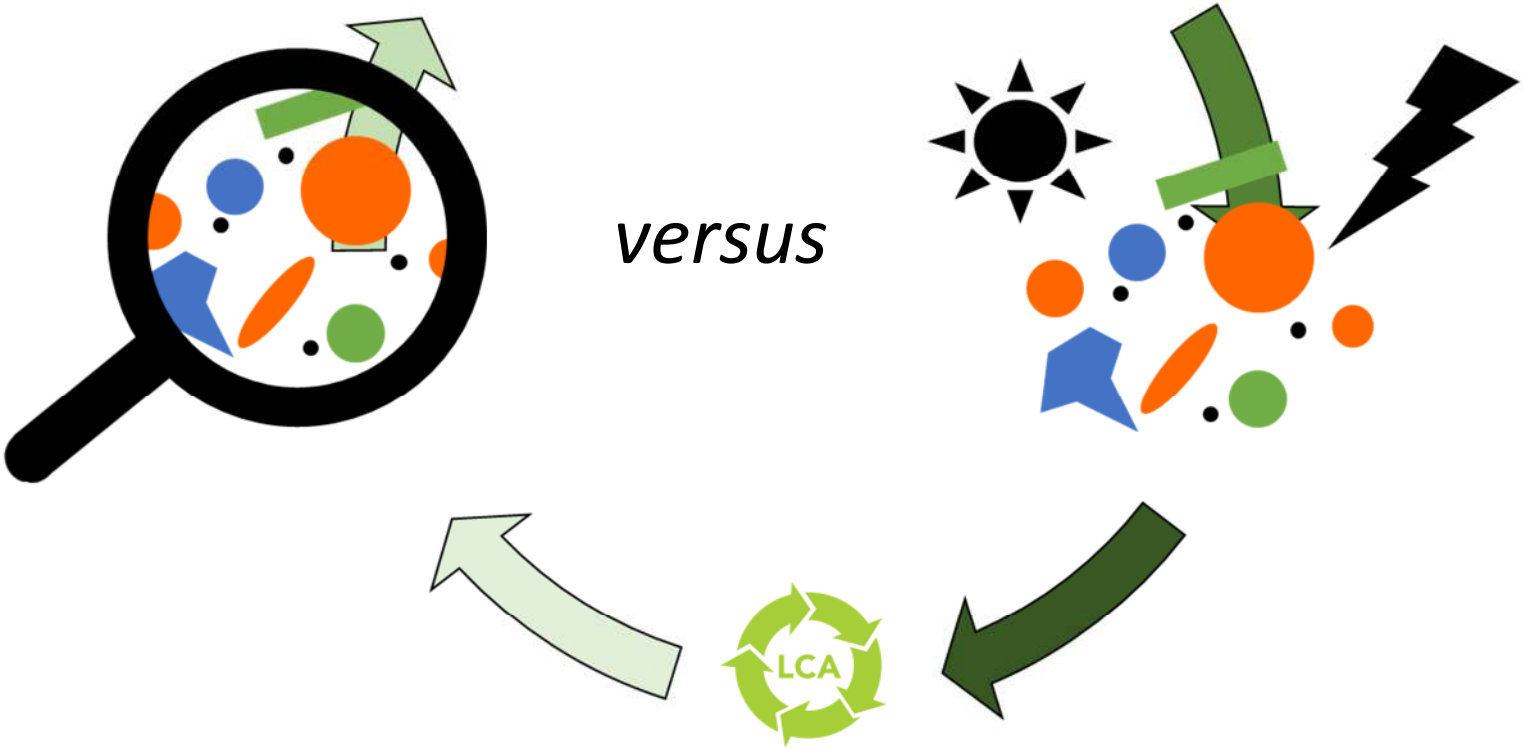
RA for chemicals | RA for particles | RA for plastics | RA for MNPs | RA for mixtures

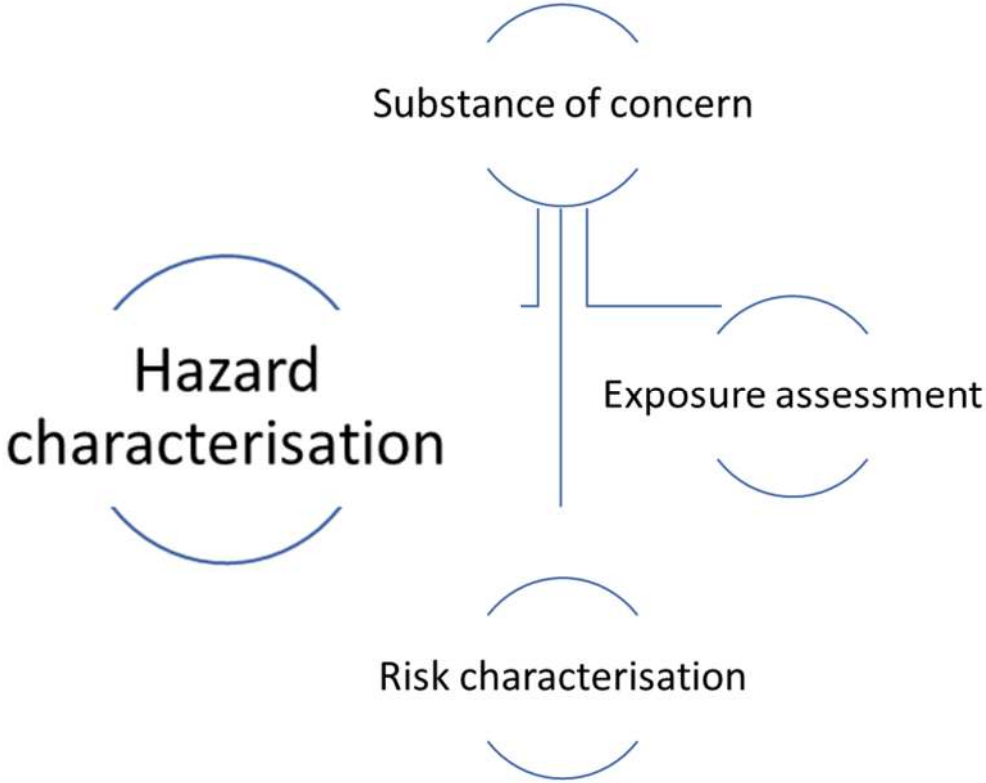
Substance of concern

– RA in the context of MNP characteristics

Intrinsic properties

Properties influenced/altered by exogenous factors




Substance of concern
Hazard characterisation
Exposure assessment
Risk characterisation

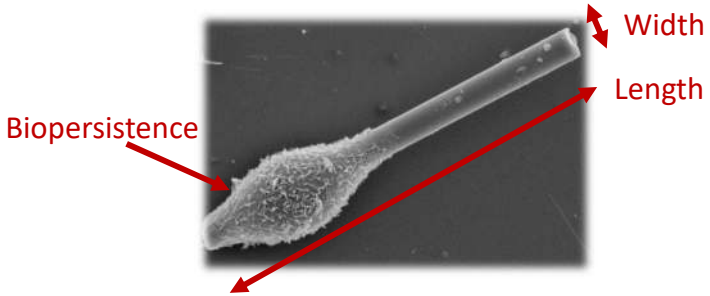
Hazard characterisation

– in the context of MNP characteristics

In the context of the characteristics of the substance of concern

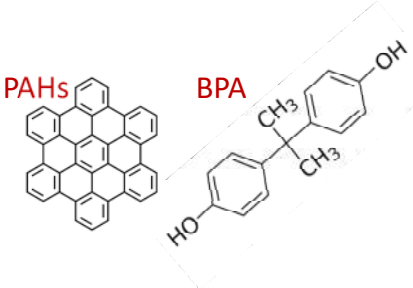
In the context of early-life health

Fibres

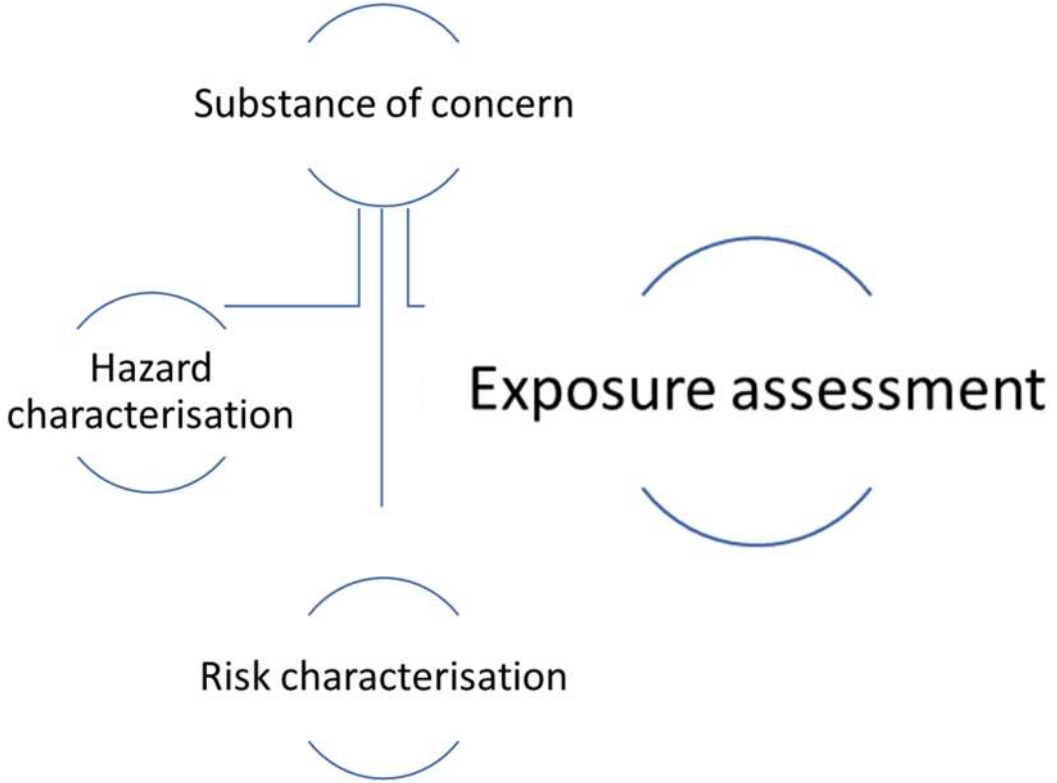


Size dependent reactivity & translocation

Chemical leaching or adsorption

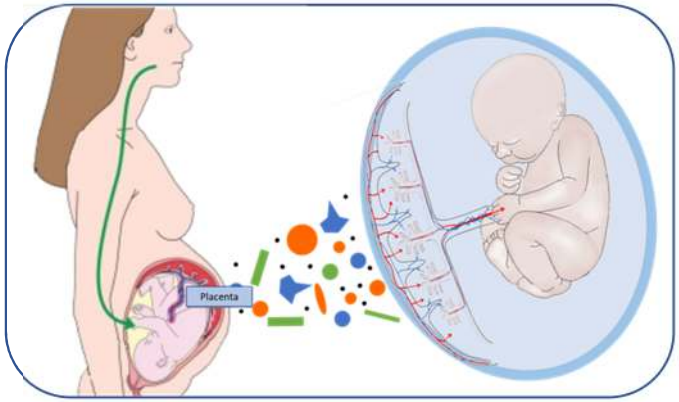


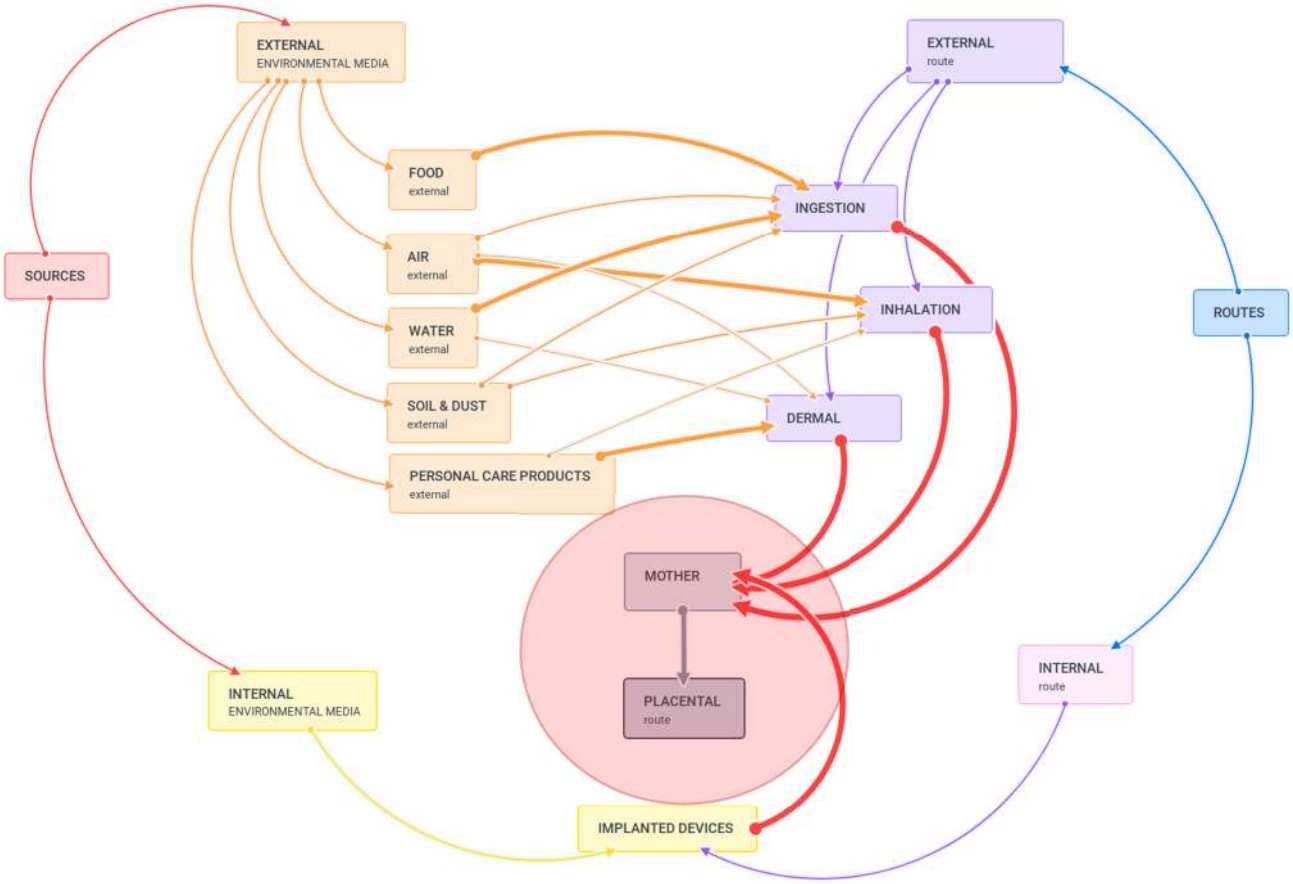
Carc. 1B	H350
STOT RE 1	H372
Muta. 2	H341
Repr. 2	H361
Acute Tox. 2	H330

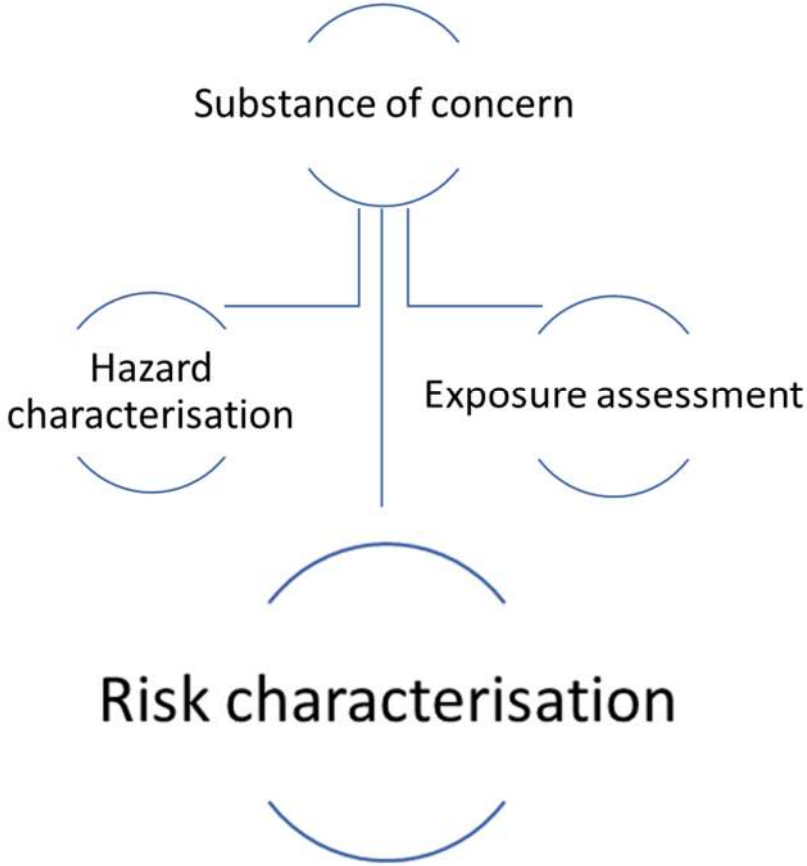

Substance of concern
Hazard characterisation
Exposure assessment
Risk characterisation

Exposure assessment – in the context of MNP characteristics

A key question for AURORA: to define a risk to the foetus, would it be acceptable to know only maternal transfer?
Note that to enable a risk mitigation strategy it will also be important to know source exposure.






Substance of concern
Hazard characterisation
Exposure assessment
Risk characterisation

– using existing frameworks

RA for chemicals	RA for plastics	RA for particles	RA for MNPs	RA for mixtures
WHO human health risk assessment toolkit.	**USEPA guidelines applied to PET-containing water bottles.**	**EFSA Guidance on RA of NMs in food chain.**	**Noventa *et al*. 2021; https://doi.org/10.1186/s43591-021-00011-1**	**ECHA defined MAF.**
ICCA Guidance on Chemical Risk Assessment.	**EFSA protocol for hazard identification and characterisation of BPA.**	**Many NM-focussed frameworks.**	**Koelmans 2022; doi.org/10.1038/ s41578-021-00411- y.**	**Harmonised risk assessment methodologies**

RA for chemicals

ICCA Guidance on Chemical Risk Assessment (2011)

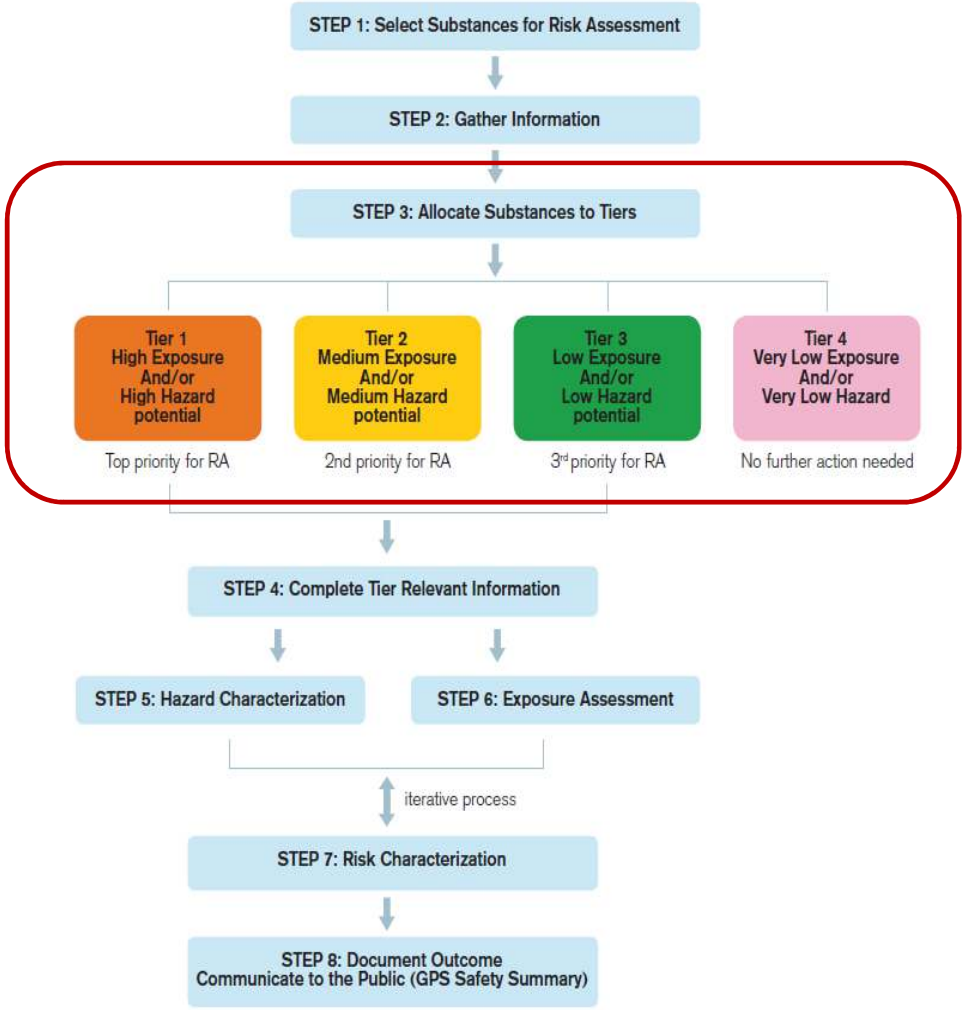
- Provides technical advice that is pragmatic and simplified;
- Guidance allows for two stages:

Preparation:

- Selection of substances;
- Gathering information;
- Allocating priority tiers;
- Reassessment of relevant info according to priority level assigned.

Implementation:

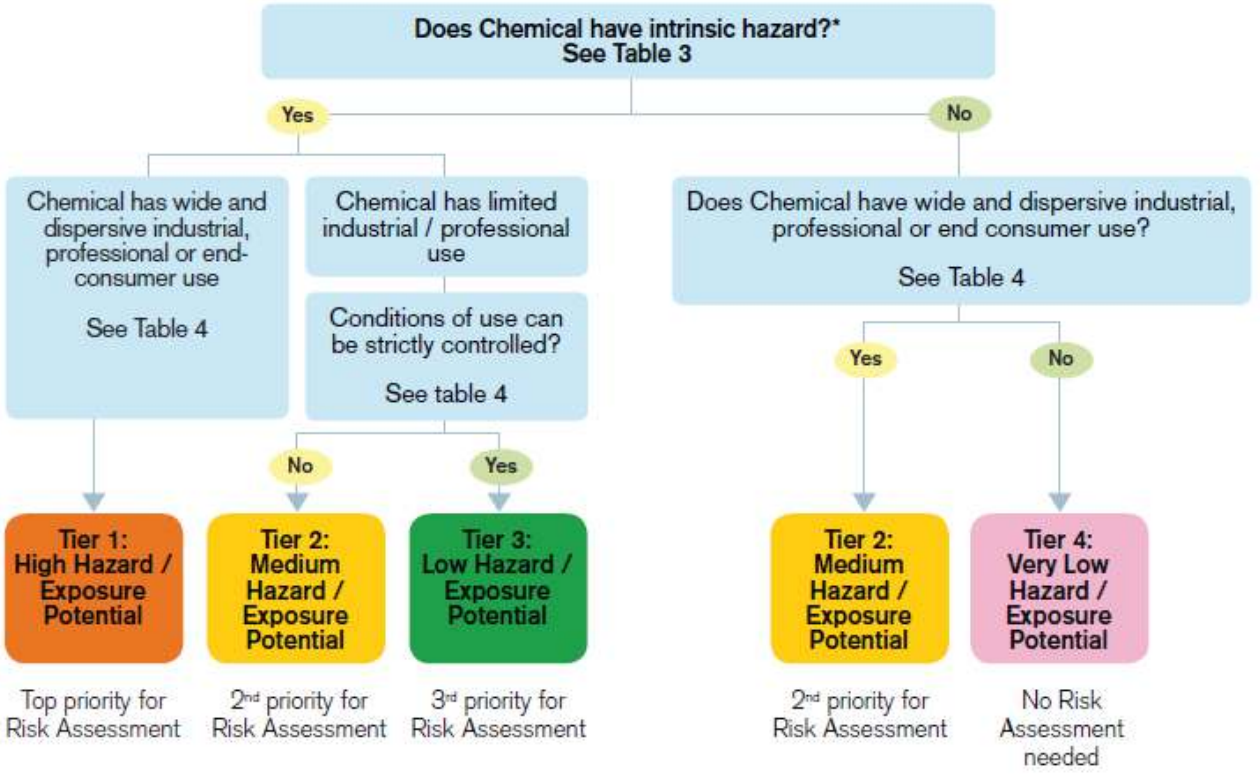
- Characterisation of the hazard;
- Assessing exposure;
- Risk characterisation based on hazard and exposure;
- Document outcomes.



RA for chemicals

ICCA Guidance on Chemical Risk Assessment (2011)

- As a concept, priority tiers would be beneficial in MNP RA;
- To define which e.g. phys-chem properties are highest priority, or which MNP sources are highest priority;
- Although these questions may not be suitable, the concept is useful.



RA for chemicals

WHO human health risk assessment toolkit/roadmap (2021)

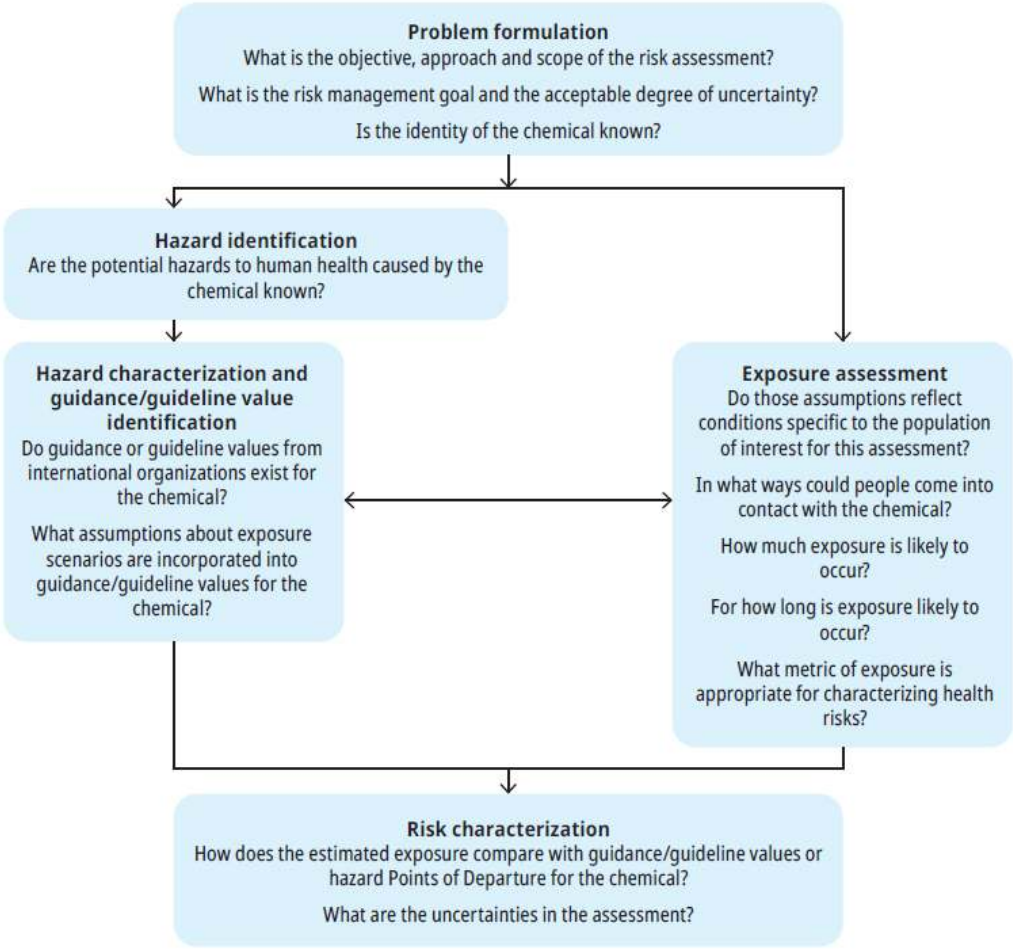
Provides guidance on chemical risk assessment, includes

- Advice of sourcing and using relevant information;
- Stepwise approaches describing HHRA requirements;
- Does not provide guidance on risk management nor risk communication.

The generic road map follows conventional RA:

- Problem formulation;
- Hazard identification;
- Exposure assessment;
- Risk characterisation.

But then offer detailed and step-wise procedures:



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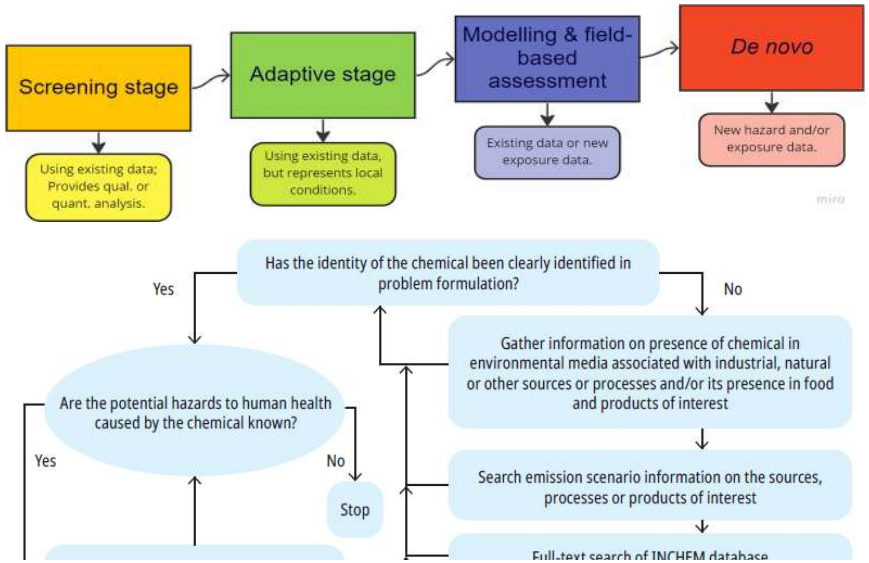
The generic road map follows conventional RA:

- Problem formulation;
- Hazard identification;
- Exposure assessment;
- Risk characterisation.

But then offer detailed and step-wise procedures:

- **Through Q&A for each step;**
- **By providing a tiered strategy;**
- **By offering a decision tree function;**

Problem formulation	
What is the objective, approach and scope of the risk assessment?	Clear idea of the objective and scope of the assessment, the resources available and the approach to be followed
What is the risk management goal and the acceptable degree of uncertainty?	Clear vision of what is needed to achieve the risk management goal
Is the identity of the chemical known?	Clear identification of chemical in question through Chemical Abstracts Service (CAS) registry number
Hazard identification	
Are the potential hazards to human health caused by the chemical known?	Description of health hazards obtained from internationally available information

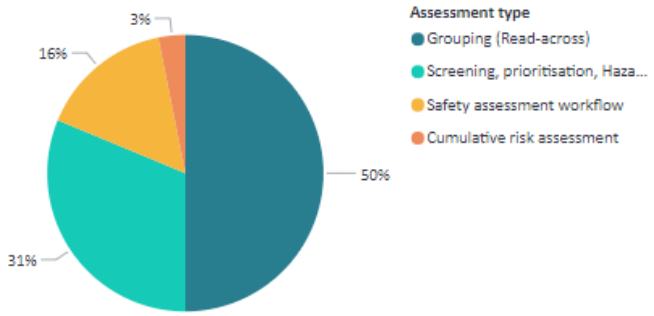


RA for chemicals

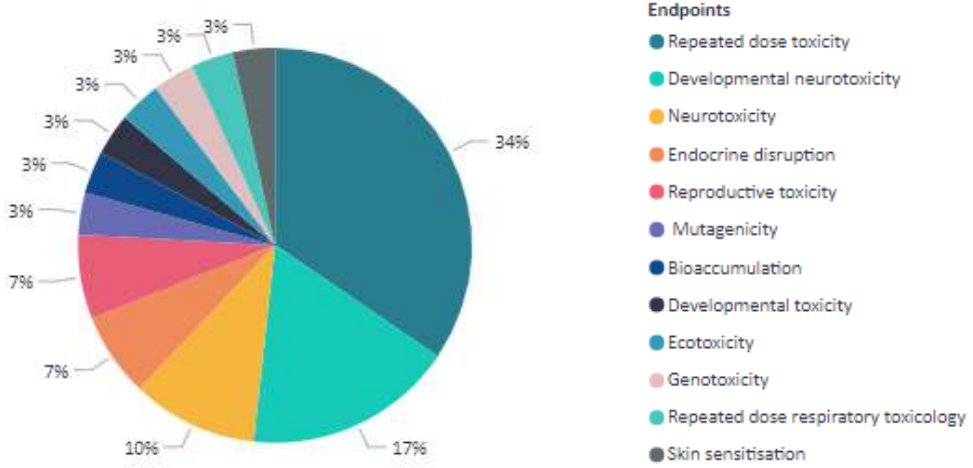
RA for particles

IATA and tiered testing

Case studies for assessment purpose



Case studies for specific endpoints



Human Health

17 IATAs (including sub- IATAs)

- 6 for inhalation route
- 7 for oral route
- 4 for dermal route

RA for chemicals

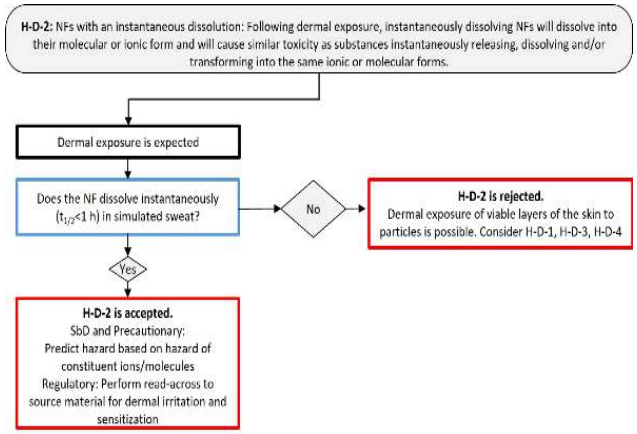
RA for particles

IATA and tiered testing

Dermal exposure to nanoforms

Integrated Approaches to Testing and Assessment for Grouping Nanomaterials following Dermal Exposure. Luisana di Cristo, Gemma Janer, Susan Dekkers, Matthew Boyles, Anna Giusti, Johannes G. Keller, Wendel Wohlleben, Hedwig Braakhuis, Lan Ma-Hock, Agnes G. Oomen, Andrea Haase, Vicki Stone, Fiona Murphy, Helinor J Johnston and Stefania Sabella. Nanotoxicology, 2022

Human dermal hypotheses	
H-D-1	NFs with constituent substance(s) or degradation products classified for dermal irritation or sensitization: Dermal exposure to the NFs will result in comparable dermal irritation or sensitization depending on NF dissolution rate.
H-D-2	NFs with an instantaneous dissolution: Following dermal exposure, instantaneously dissolving NFs will dissolve into their molecular or ionic form and will cause similar toxicity as substances instantaneously releasing, dissolving and/or transforming into the same ionic or molecular forms.
H-D-3	NFs that are not biopersistent: Dermal exposure to NFs will not lead to accumulation of NFs or subsequent systemic toxicity.
H-D-4	NFs that are larger than 5nm and which are not flexible: Following dermal exposure, NFs will result in limited or no dermal absorption and no dermal or systemic toxicity.



IATA for H-D-2. Blue bordered boxes are decision nodes, red bordered boxes are hypothesis conclusions, black bordered boxes describe options to consider.

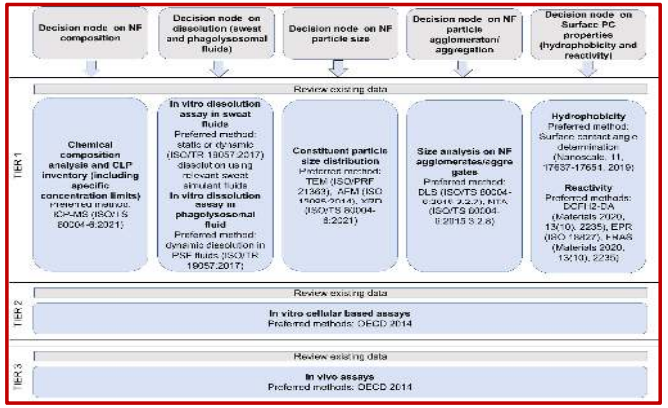


Figure 5: TTS developed for each DN of the IATAs for hypotheses H-D-1, H-D-2, H-D-3 and H-D-4. The TTS provides specific acellular in vitro methods to use to satisfy each DN of the dermal IATAs in Tier 1 and more general cellular in vitro and in vivo methods to evaluate the specific hazard endpoints (i.e., dermal irritation, sensitization and toxicity) at Tier 2 and Tier 3, respectively.

RA for particles

Covered previously

NanoRiskCat

A decision-making framework for the grouping and testing of nanomaterials (DF4nanoGrouping)

Josje H.E. Arts [a], Mackenzie Hadi [b], Muhammad-Adeel Irfan [c], Athena M. Keene [d], Reinhard Kreiling [e], Delina Lyon [f], Monika Maier [g], Karin Michel [h], Thomas Petry [i], Ursula G. Sauer [j], David Warheit [k], Karin Wiench [c], Wendel Wohlleben [c], Robert Landsiedel [c,*]

gracious

LiCARA

NANOREG

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Sustainable Nanotechnologies Project

RA for mixtures

Assessing combined risk from exposure to multiple chemicals or multifaceted MNPs

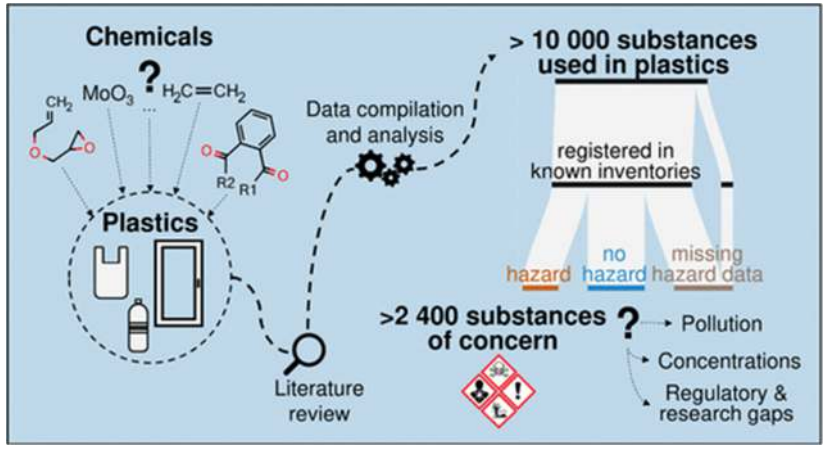
Individual components combined to a potential mixtures exposure?

MNP chemical composition:

- 5300 polymer formulations; 2400 plastic-related substances of potential concern
- Monomers and oligomers
- Chemical additives (up to 50% weight) (e.g., plasticizers, flame retardants, stabilizers, pigments, biocides)
- Non-intentionally added substances (i.e., impurities, reaction by-products, degradation products)

Adsorbed/absorbed:

Microbes/bioflims, chemicals, metals



Weithmann et al Science Advances 2018; Wiesinger et al. Environ Sci Technol 2021

A Mixture Assessment Factor (MAF).

Harmonised risk assessment methodologies – when sufficient data and resources are available.

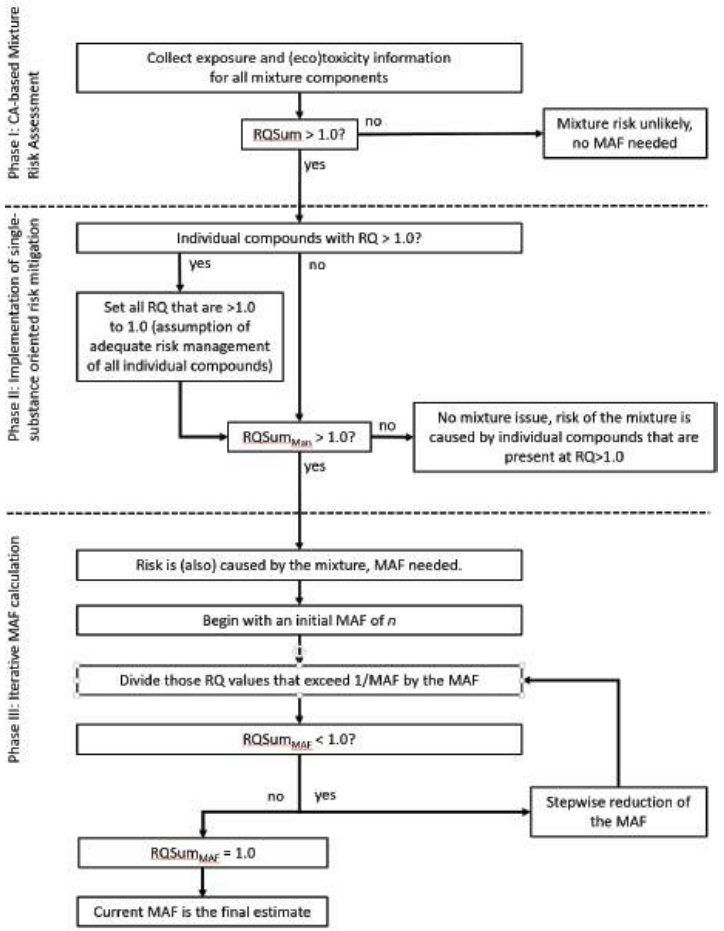
RA for mixtures

Assessing combined risk from exposure to multiple chemicals or multifaceted MNPs

A Mixture Assessment Factor (MAF).

- Reported recently by the Swedish Chemicals Agency (KEMI)[1] and undergoing consideration for use within REACH;
- Used in data-poor scenarios;
- Not to be used to replace full mixture risk assessment when sufficient data are available;
- Predicts a risk based on the sum of calculated Risk Quotient (RQ);
- E.g. PEC/PNEC ratio or Exposure/DNEL ratio
- If <1 considered safe, if >1 considered unsafe.

Harmonised risk assessment methodologies – when sufficient data and resources are available.



[1]KEMI. 2021, Improving the regulatory assessment of combination effects: steps towards implementing the mixture assessment factor (MAF) in chemical regulation. pp 1-61. : s.n., 2021. Article number: 511 421.

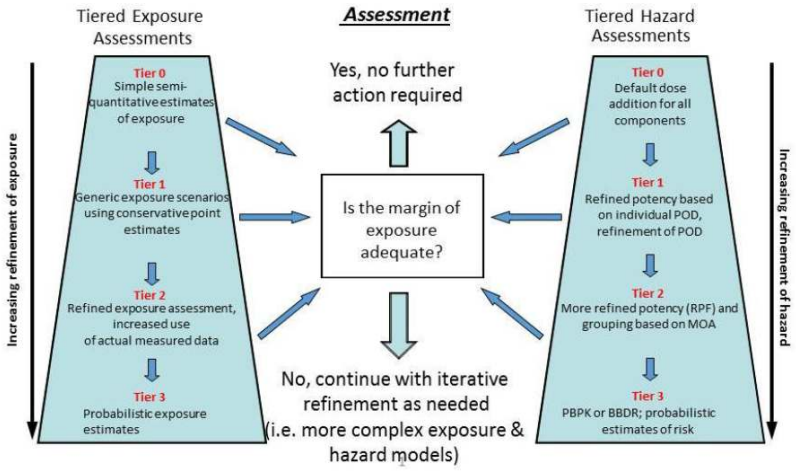
RA for mixtures

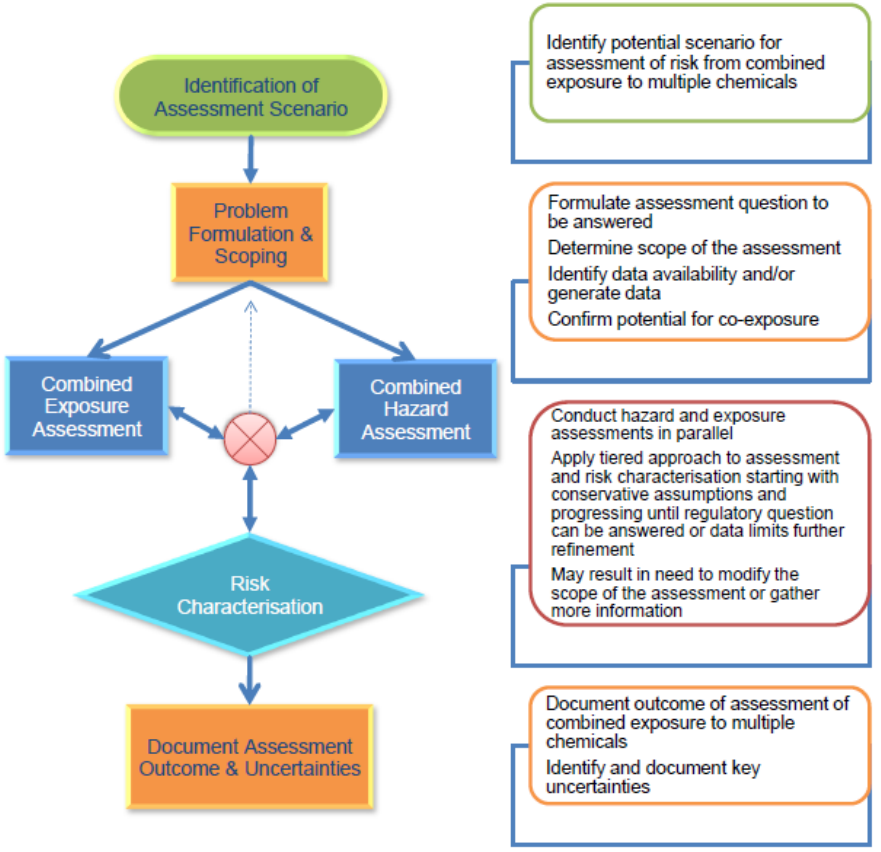
Assessing combined risk from exposure to multiple chemicals or multifaceted MNPs

A Mixture Assessment Factor (MAF).

Harmonised risk assessment methodologies – when sufficient data and resources are available.

- Various framework suggestions e.g. from OECD (2018), EFSA (2019), WHO (2009), and others;
- Follows general/ more traditional RA format;
- Provide risk characterisation for the whole mixture and component-based approaches.





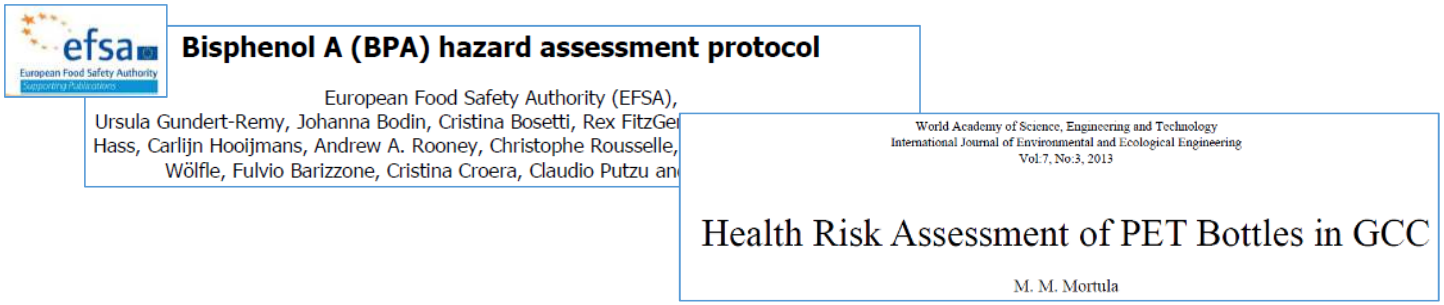
OECD (2018); CONSIDERATIONS FOR ASSESSING THE RISKS OF COMBINED EXPOSURE TO MULTIPLE CHEMICALS; Series on Testing and Assessment No. 296.

RA for MNPs

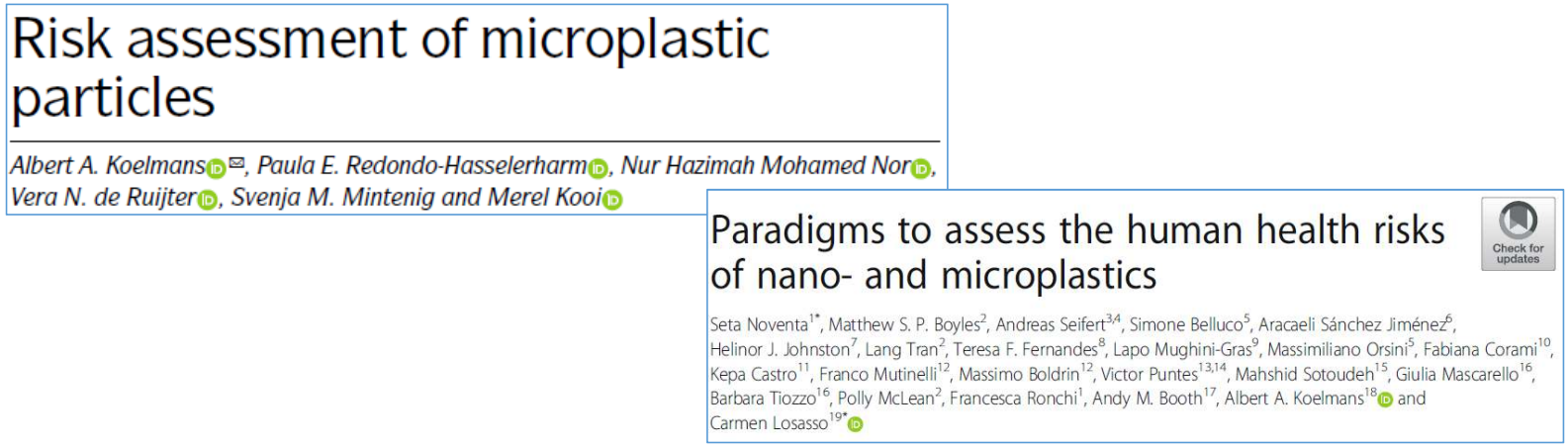
RA for plastics

Single components or MNPs as a whole?

Individual components:



MNPs as a whole:



RA for MNPs | RA for plastics

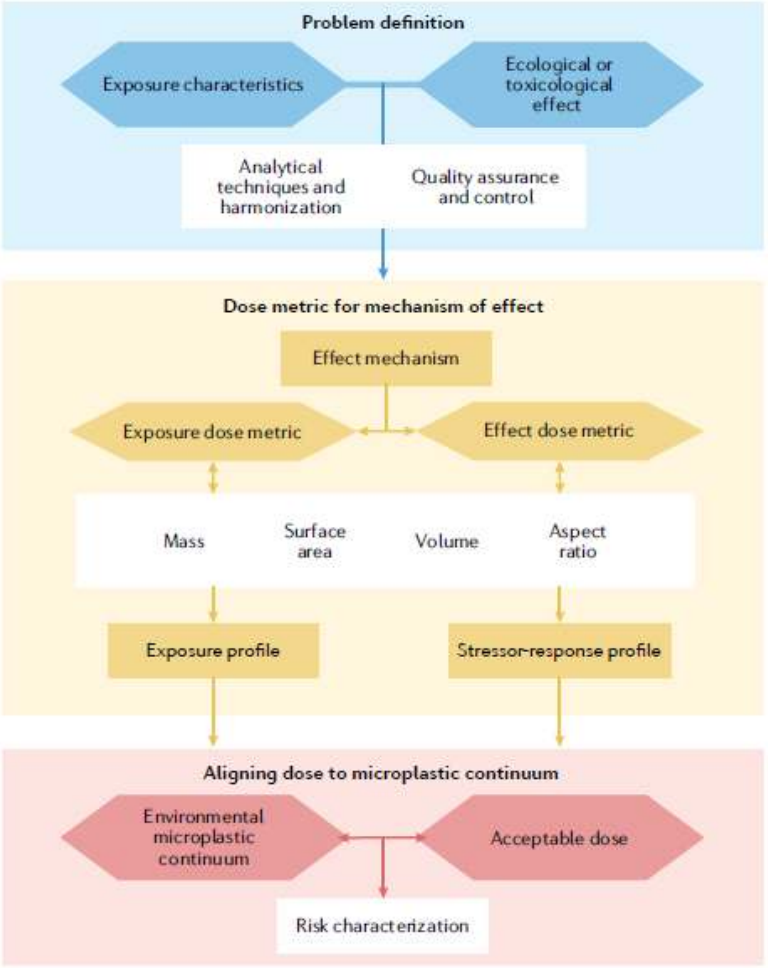
Single components or MNPs as a whole?

MNPs as a whole:

Risk assessment of microplastic particles

Albert A. Koelmans, Paula E. Redondo-Hasselerharm, Nur Hazimah Mohamed Nor, Vera N. de Ruijter, Svenja M. Mintenig and Merel Kooi

- Optimised 'Problem definition' to include a protective objective;
- Uses probability density functions (PDFs) to better define multifaceted risk/toxicity;
- Exposure dose and effect thresholds determined according to predetermined metrics;
- The defined exposure & effect profile aligned to their 'microplastic continuum'



Koelmans 2022; doi.org/10.1038/s41578-021-00411- y.

RA for MNPs | RA for plastics

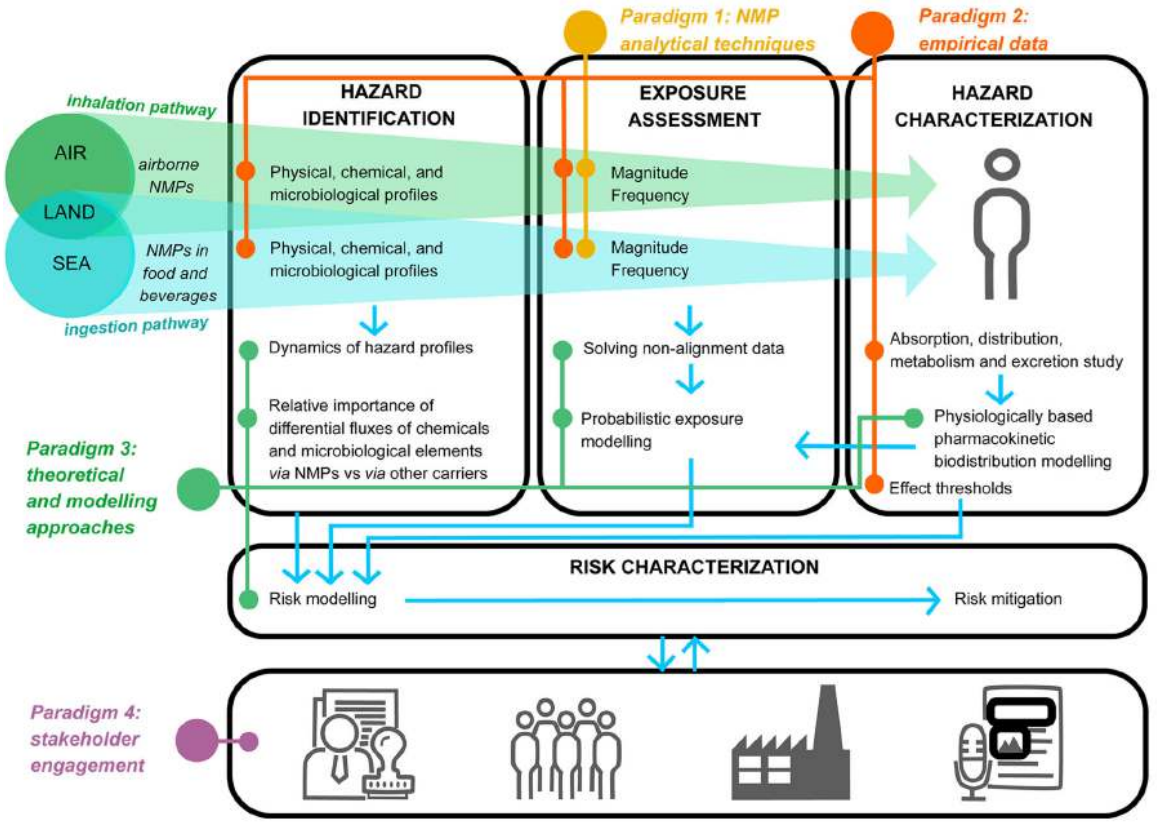
Single components or MNPs as a whole?

MNPs as a whole:

Paradigms to assess the human health risks of nano- and microplastics

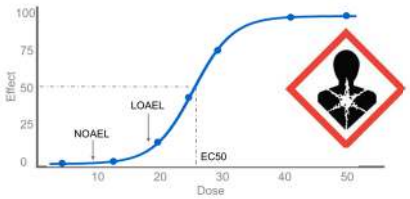
Seta Noventa[1*], Matthew S. P. Boyles[2], Andreas Seifert[3,4], Simone Belluco[5], Aracaeli Sánchez Jiménez[6], Helinor J. Johnston[7], Lang Tran[2], Teresa F. Fernandes[8], Lapo Mughini-Gras[9], Massimiliano Orsini[5], Fabiana Corami[10], Kepa Castro[11], Franco Mutinelli[12], Massimo Boldrin[12], Victor Puntes[13,14], Mahshid Sotoudeh[15], Giulia Mascarello[16], Barbara Tiozzo[16], Polly McLean[2], Francesca Ronchi[1], Andy M. Booth[17], Albert A. Koelmans[18] and Carmen Losasso[19*]

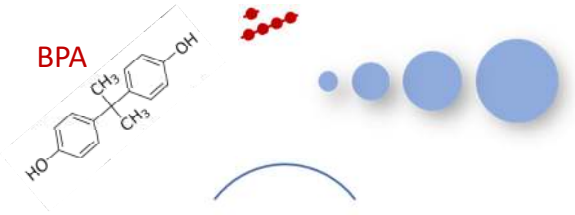
- Follows the traditional 4 pillars of RA
- Introduces 4 paradigms to better define/measure MNP HH continuum;
  - Advancing methods for MNP detection,
  - Empirical data on occurrence and effects of MNPs,
  - Modelling – exposure and effect, and uncertainty,
  - Engagement with e.g. government & regulators.



Noventa *et al.* 2021; https://doi.org/10.1186/s43591-021-00011-1

Next steps for RA within the AURORA project



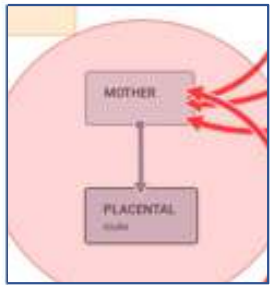


Substance of concern

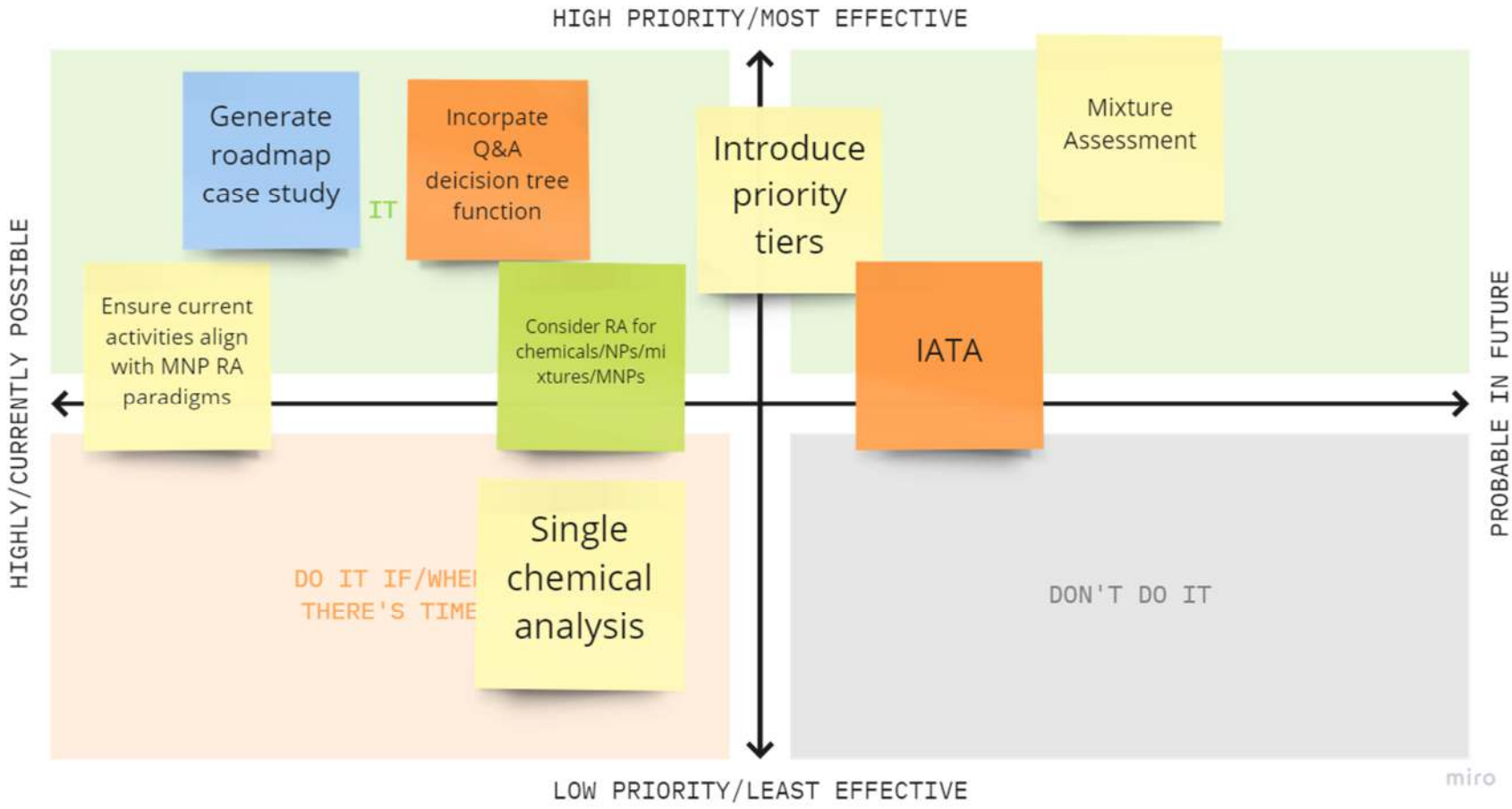
Hazard characterisation

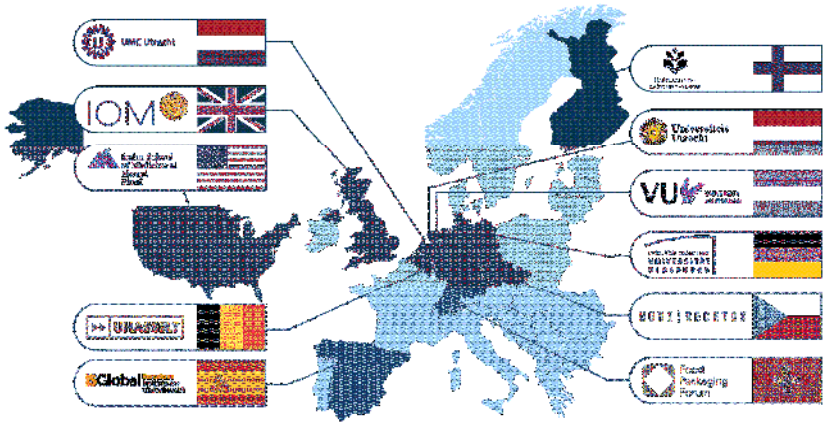
Exposure assessment

Risk characterisation



Next steps for RA within the AURORA project





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