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Εκτίμηση κινδύνου: Από την έκθεση σε μία χημική ουσία σε συνδυασμό χημικών ουσιών.

Risk assessment for human health from exposure to single towards to multiple chemicals.

Dr Kyriaki Machera,
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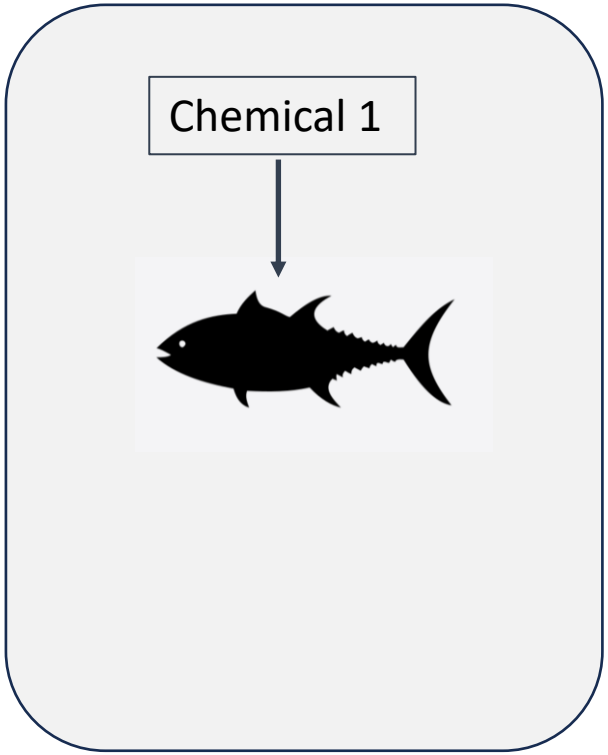
Outline

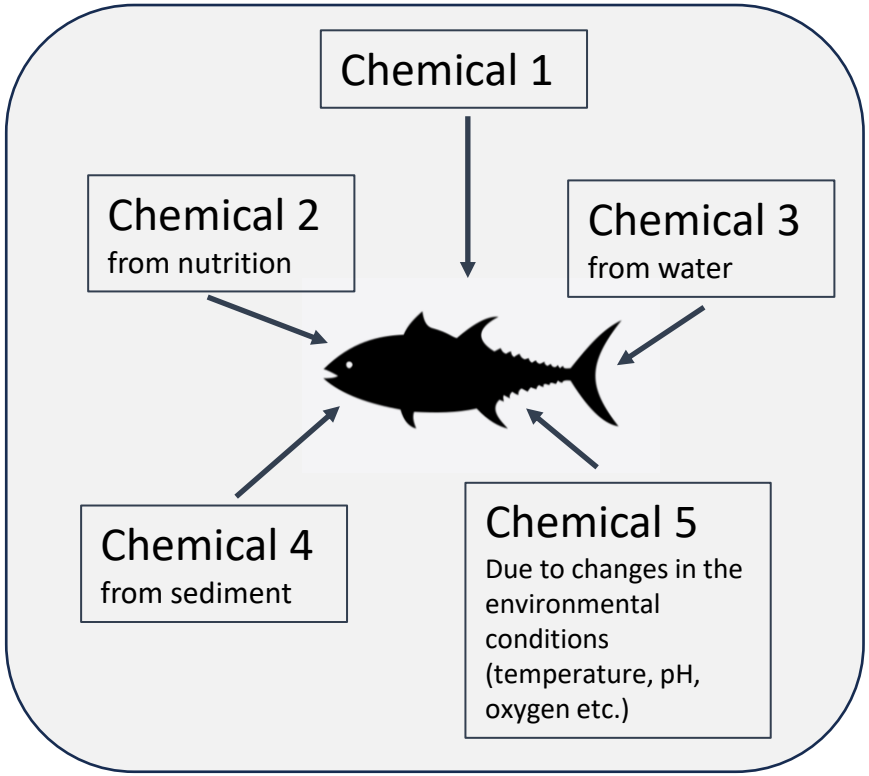
- General & Historical information
- Developments for dietary R.A. from multiple chemicals
- Other approaches (PARC, OECD) & our activities
- The next steps

General information (1)

Focus on chemical
> Reduce exposure



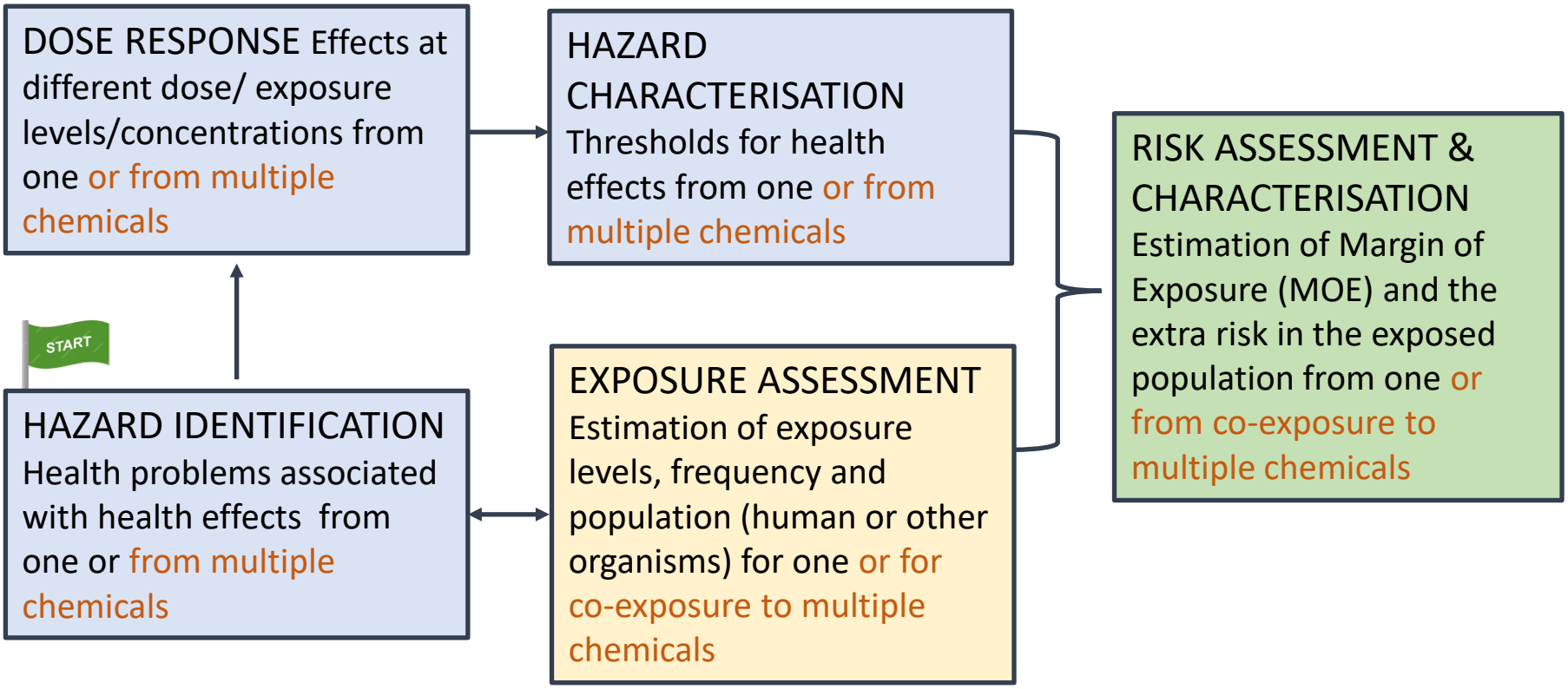
Focus on the organism
> Improve the ecosystem health



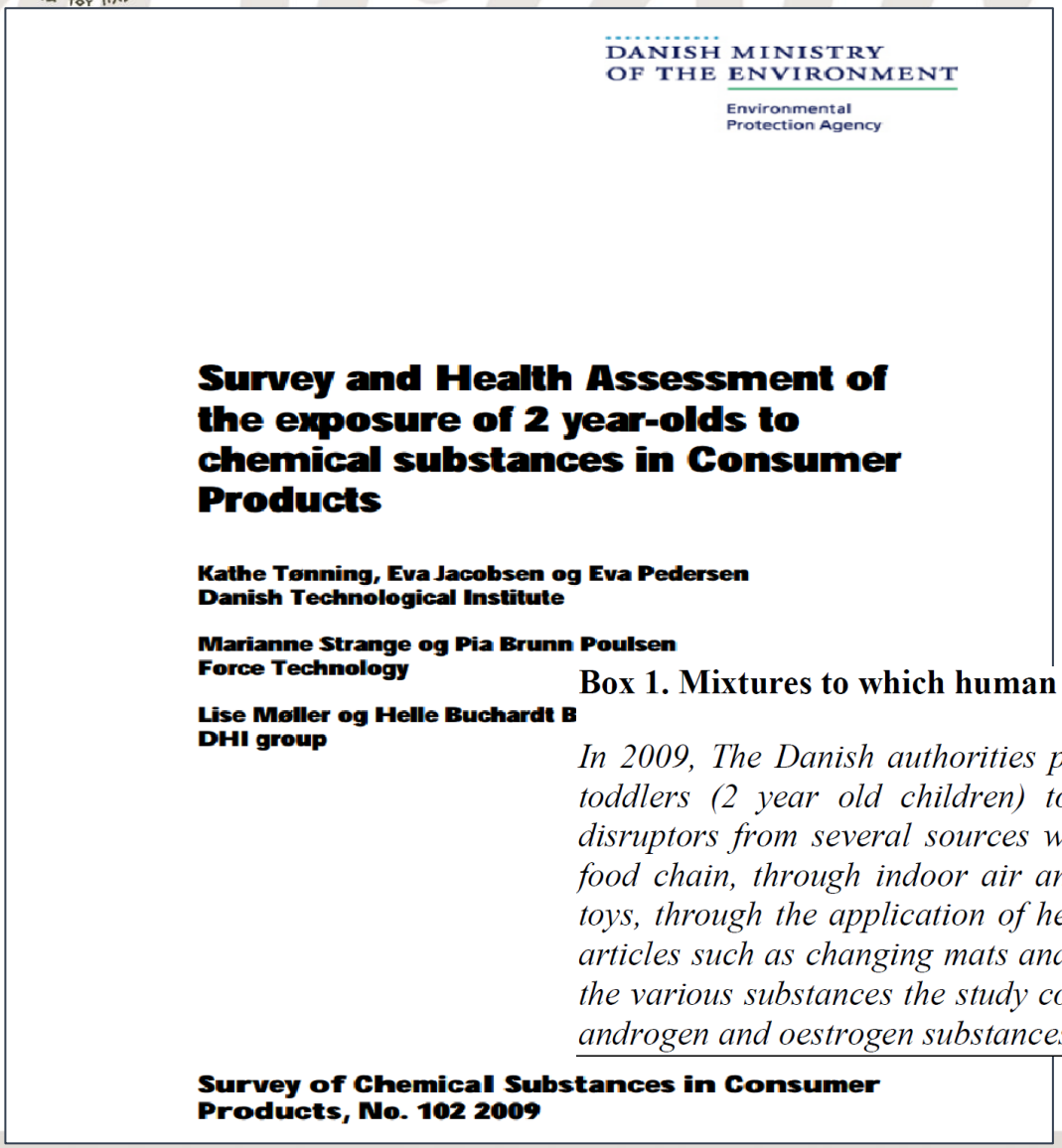
Drawing retrieved from: https://thenounproject.com/

General information (2)

The five steps in Risk Assessment



Historical information (1)



DANISH MINISTRY OF THE ENVIRONMENT
Environmental Protection Agency

Survey and Health Assessment of the exposure of 2 year-olds to chemical substances in Consumer Products

Kathe Tønning, Eva Jacobsen og Eva Pedersen
Danish Technological Institute

Marianne Strange og Pia Brunn Poulsen
Force Technology

Lise Møller og Helle Buchardt B
DHI group

Survey of Chemical Substances in Consumer Products, No. 102 2009

Box 1. Mixtures to which human populations are exposed

In 2009, The Danish authorities published the results of a study[2] in which the exposure of toddlers (2 year old children) to chemical mixtures in the form of multiple endocrine disruptors from several sources were examined. The study examined exposure through the food chain, through indoor air and dust, through clothes and shoes, through contact with toys, through the application of health care and hygiene products and through contact with articles such as changing mats and bath mats. On the basis of the predicted concentration of the various substances the study concluded that there was a need to reduce exposure to anti-androgen and oestrogen substances from food, indoor air and consumer products.

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Historical information (2)

COUNCIL OF
THE EUROPEAN UNION

EN

Council conclusions on combination effects of chemicals

2988th ENVIRONMENT Council meeting
Brussels, 22 December 2009

The Council adopted the following conclusions:

"THE COUNCIL OF THE EUROPEAN UNION:

Toxicity and Assessment of Chemical Mixtures

European Commission

Directorate-General for Health & Consumers

Scientific Committee on Health and Environmental Risks

SCHER

EUROPEAN COMMISSION

Brussels, 31.5.2012
COM(2012) 252 final

The Council in particular, invited the Commission, *"... to assess how and whether relevant existing Community legislation adequately addresses risks from exposure to multiple chemicals from different sources and pathways, and on this basis to consider appropriate modifications, guidelines and assessment methods, and report back to the Council by early 2012 at the latest."*

December 2009

The purpose of the present Comm... to respond formally to the invitation from the Council and in particular... whether the current EU legislation which is built predominantly on the as... of single substances and single sources, guarantees the high level of protection requi... by the Treaty. The challenge of dealing with chemical mixtures will also be taken-up in the context of preparing the future priorities for environmental policy.

...OMMISSION TO THE COUNCIL

...ffects of chemicals

...mixtures

...plenary of 22 November 2011

...th plenary of 30 November 2011

...plenary of 14 December 2011

Historical information (3)

Regulation (EC) No 1107/2009: placing of PPPs on the market

"…take into account known cumulative and synergistic effects of pesticides when the methods are available…"

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Developments for dietary R.A. from multiple chemicals (1)

Scientific outputs from EFSA

Methodological development (2007-2014)

- *Methodology for cumulative assessment groups (PPR, 2013)*
- *Opinion on dissimilar mode of action (PPR, 2013)*
- *Guidance for probabilistic exposure assessment (PPR, 2012)*
- *Tiered methodology for cumulative risk assessment (PPR, 2009)*

Data collections (2009-2018)

- *DTU*
- *RIVM/ANSES/ICPS*
- *BfR/RIVM/BPI*

Retrospective CRA (2014-2021)

- *Software development*
  - ✓ *RIVM: MCRA*
  - ✓ *EFSA: SAS®-based*
- *Pilot project (2016-2019): Effects on the **thyroid** and the **nervous system***
- *2020: chronic **AChE inhibition***
- *2021: EFSA-SANTE Action Plan to speed up the development of methods for CRA*

Guidance documents (2019 & 2021) & CAGs 2022…..

MIXTOX (2019); MIXTOX2(2021);

*2021-2023: more CAGs e.g., **craniofacial effects,** 2021, **Ongoing:** grouping for **kidney** effects; grouping for **liver** effects, grouping for effects on **fertility**, update of grouping for effects on **thyroid…***

Developments for dietary R.A. from multiple chemicals (2)

MIXTOX 2 Guidance Document (2021)

MIXTOX2: Guidance on scientific criteria for grouping chemicals into assessment groups for Human Risk Assessment of combined exposure to multiple chemiclas (EFSA 2021)

GUIDANCE

EFSA Journa

ADOPTED: 17 November 2021

doi: 10.2903/j.efsa.2021.7033

Guidance Document on Scientific criteria for grouping chemicals into assessment groups for human risk assessment of combined exposure to multiple chemicals

EFSA Scientific Committee,
Simon John More, Vasileios Bampidis, Diane Benford, Claude Bragard, Antonio Hernandez-Jerez, Susanne Hougaard Bennekou, Thorhallur Ingi Halldorsson, Konstantinos Panagiotis Koutsoumanis, Claude Lambré, Kyriaki Machera, Hanspeter Naegeli, Søren Saxmose Nielsen, Josef Rudolf Schlatter, Dieter Schrenk, Vittorio Silano, Dominique Turck, Maged Younes, Emilio Benfenati, Amélie Crépet, Jan Dirk Te Biesebeek, Emanuela Testai, Bruno Dujardin, Jean Lou CM Dorne and Christer Hogstrand

Cross cutting guidance to support **all EFSA panels dealing with chemical RA**

Grouping Criteria

Hazard-driven criteria
(from different levels of biological organisation & WoE)

Prioritisation methods
(risk based or exposure driven)

Uncertainty

Recommendations

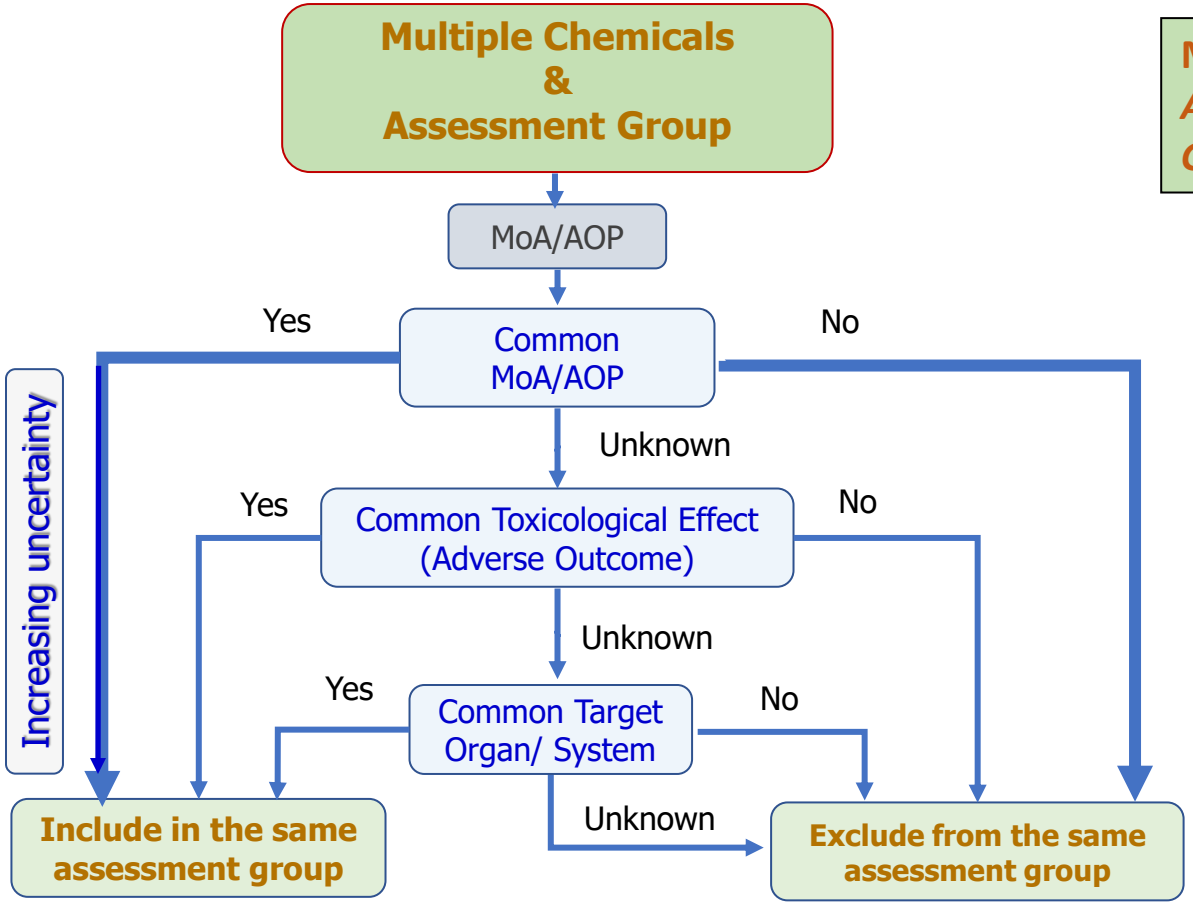
Public Consultation (May-July 2021)

International Workshop (18-20 October 2021)

Published 17-12-2021

Developments for dietary R.A. from multiple chemicals (4)

MIXTOX 2: Hazard-driven criteria for grouping



Multiple chemicals (co-exposure) ***Arrangement in Assessment Groups***

Higher tier:
- Gold standard Common Mode of action (MoA) or Adverse outcome Pathway (AOP) for grouping into assessment group

Next tiers:
- common AO
- common target organ

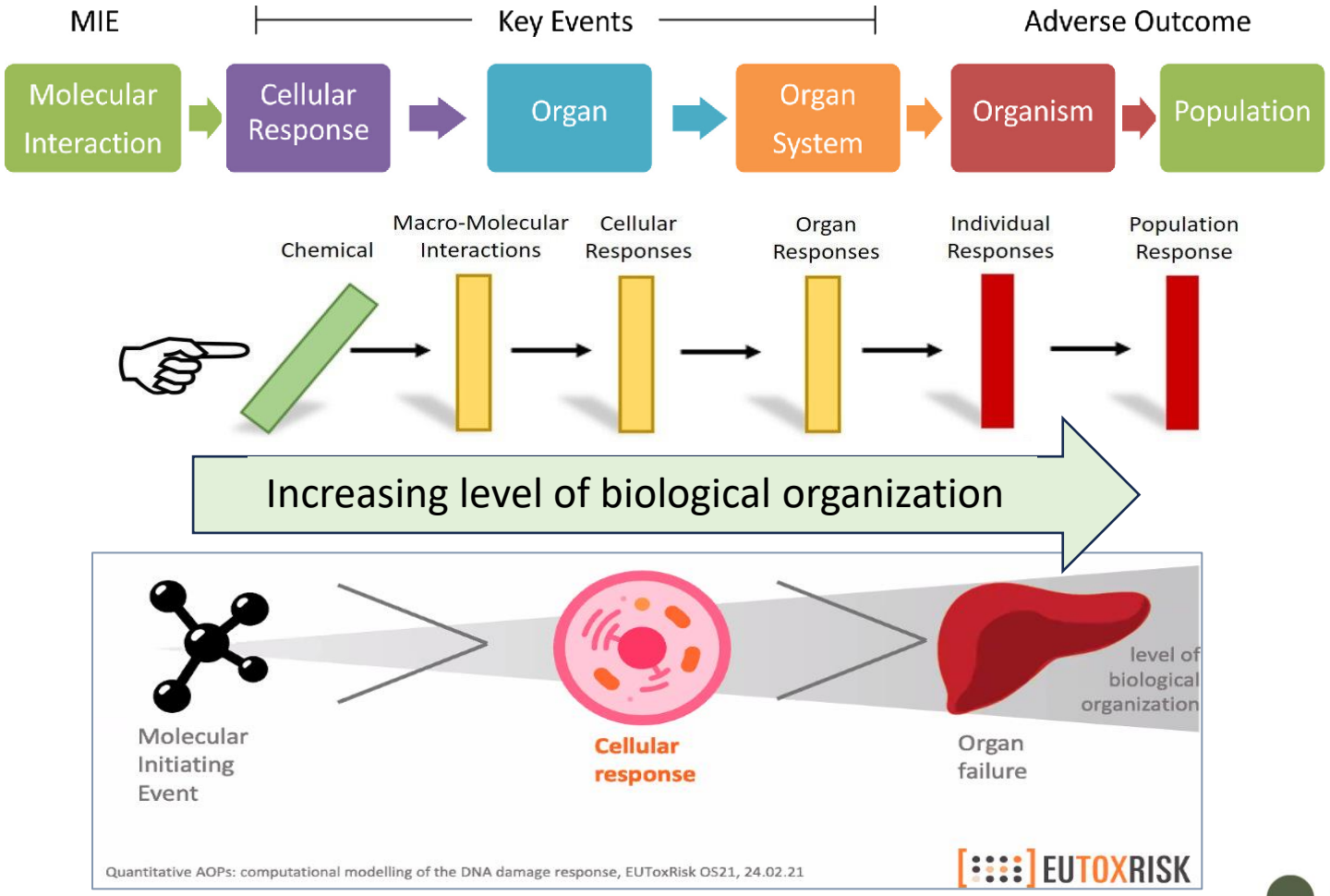
If not hazard criteria for grouping, apply alternative approaches e.g., *in silico/ structure/read across, etc*

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

Developments for dietary R.A. from multiple chemicals (5)

MIXTOX 2: Grouping using toxicity information

Essential understanding of the Adverse outcome pathway (AOP)



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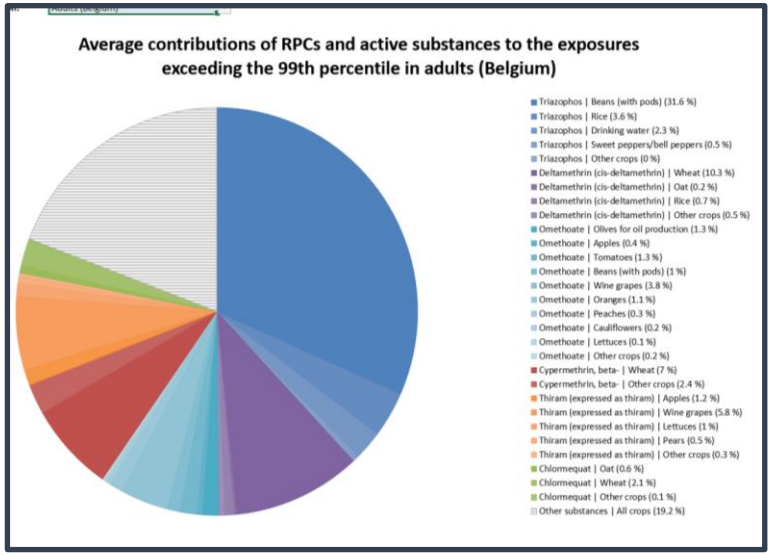
MIXTOX 2: Consumer Risk Assessment for multiple pesticide residues in food

Food consumption & residues of active substances



EFSA 2019, doi: 10.2903/j.efsa.2019.5764

&

Hazard metrics for the individual compounds
ADI, ARfD, HBGV, R*f*P, or PoD

Risk estimation

a. Margin of exposure total (MOET)(> 100)

$$\frac{1}{\mathrm{MOET}} = \sum_i \frac{1}{\mathrm{MOE}_i} = \frac{1}{\mathrm{MOE}_1} + \frac{1}{\mathrm{MOE}_2} + \frac{1}{\mathrm{MOE}_3} \ldots + \frac{1}{\mathrm{MOE}_n}$$

where MOE_i is the margin of exposure for the ith chemical,

$$\mathrm{MOE}_i = \frac{\mathrm{RfP}_i}{\mathrm{E}_i}$$

and RfP is the toxicological reference point (NOAEL in the present report) for chemical i and Ei its exposure.

EFSA 2020, doi: 10 2903/j.efsa.2020.6087

b. Hazard Index estimation (HI) (<1)

Refined Hazard Index approach based on endpoint-specific effect.
HI = HQ1 + HQ2 + … + HQv,
HQ = exposure / HBGV (e.g., ADI/ARfD)

EFSA 2021, doi: 10.2903/j.efsa.2019.5764

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Other BPI Activities in the assessment of risk from multiple chemicals

PARC

INSIGNIA-EU

INSIGNIA-EU

EuroMix

A tiered strategy for risk assessment of mixtures of multiple chemicals

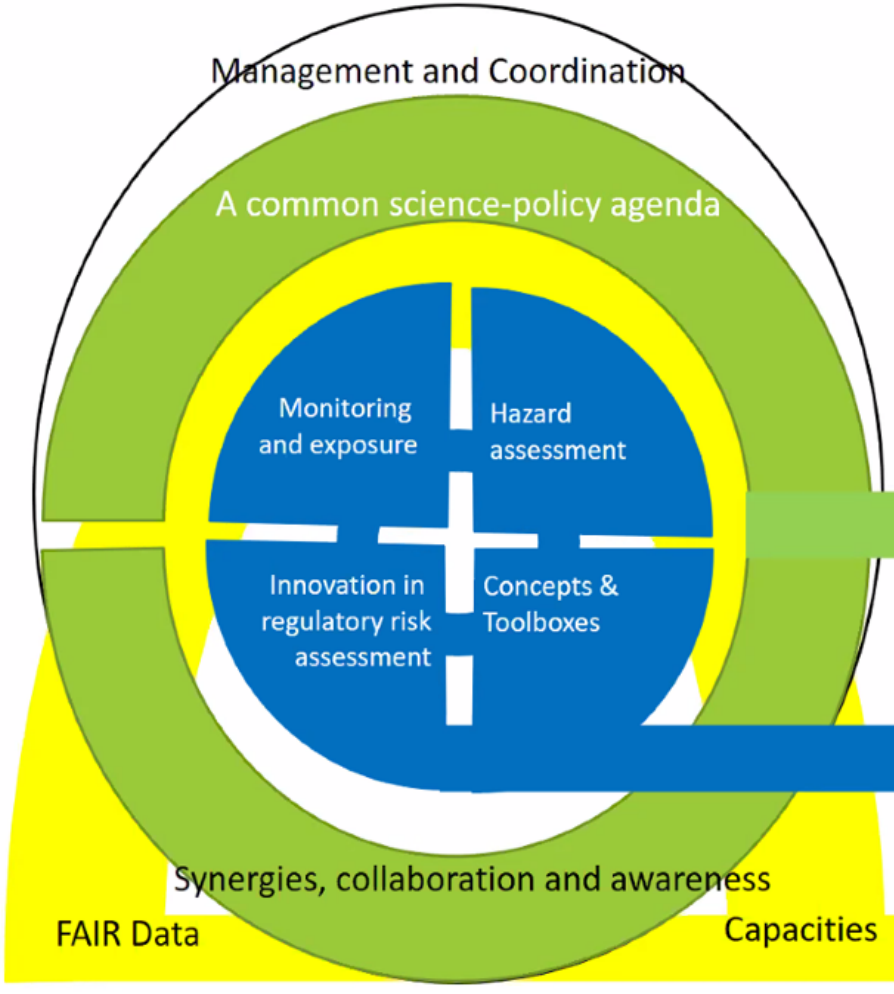
OECD

BETTER POLICIES FOR BETTER LIVES

The European Partnership for the Assessment of Risks from Chemicals

https://www.eu-parc.eu/

The European Partnership for the Assessment of Risks from Chemicals



PARC Objectives

Our general objective is to **consolidate and strengthen** the EU's Research and Innovation capacity for chemical Risk Assessment to **protect human health and the environment**

1. High level network for regulatory science interface
2. Research & Innovation towards Next Generation Risk Assessment
3. Capacities and Platforms

The European Partnership for the Assessment of Risks from Chemicals

WP 6: Innovation in regulatory risk assessment

Project: P6.2.3.a_Y1: New risk assessment and exposome methodologies to reduce exposure and risk of real-life mixtures

Project objective: Development of the strategy for mixture risk assessment using HBM data on prioritized chemicals from different European populations.

Five case studies prioritized chemicals and effects

- Pesticides with acute effect on nervous system (AChE inhibition)
- Pesticides with effects on the motor division of the nervous system
- PFAS and immune toxicity
- Heavy metals and nephrotoxicity
- Chemicals with possible effect on Developmental Neurotoxicicty (IQ loss)

WP 6: Innovation in regulatory risk assessment
Case studies: Pesticides and nervous system

Estimation of risk from external exposure (dietary route) for all pesticide residues

+ Reliable monitoring data
- only dietary exposure
- only pesticide a.s. considered

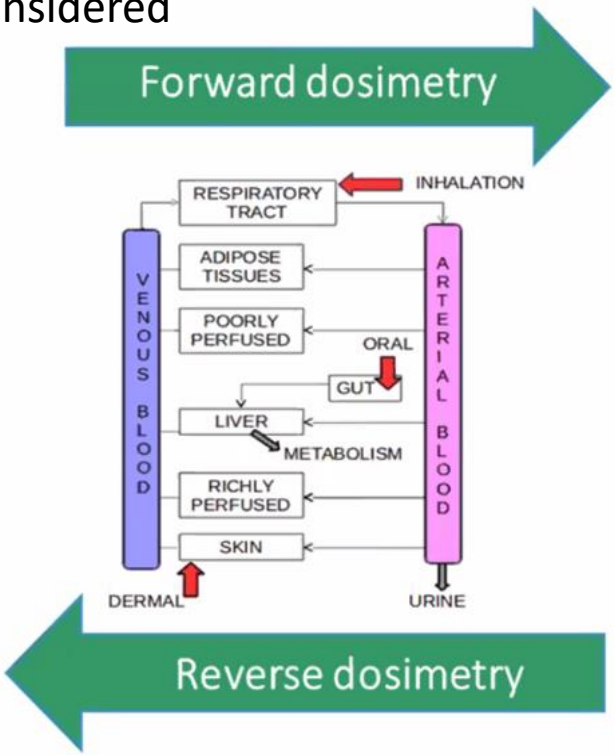
EFSA Dietary exposure

?

Total Margins of Exposure (MOET)

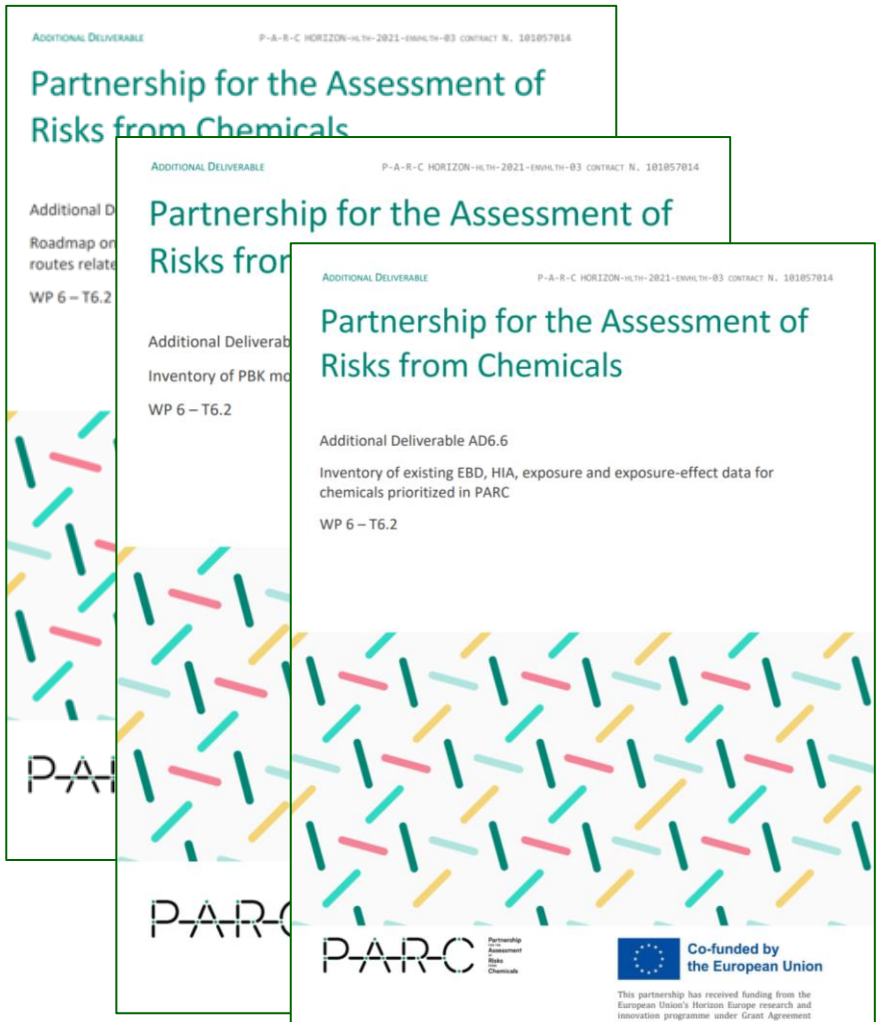
PARC HBM all routes & sources

Biomarkers of pesticide exposure for all routes & sources (HBM studies)



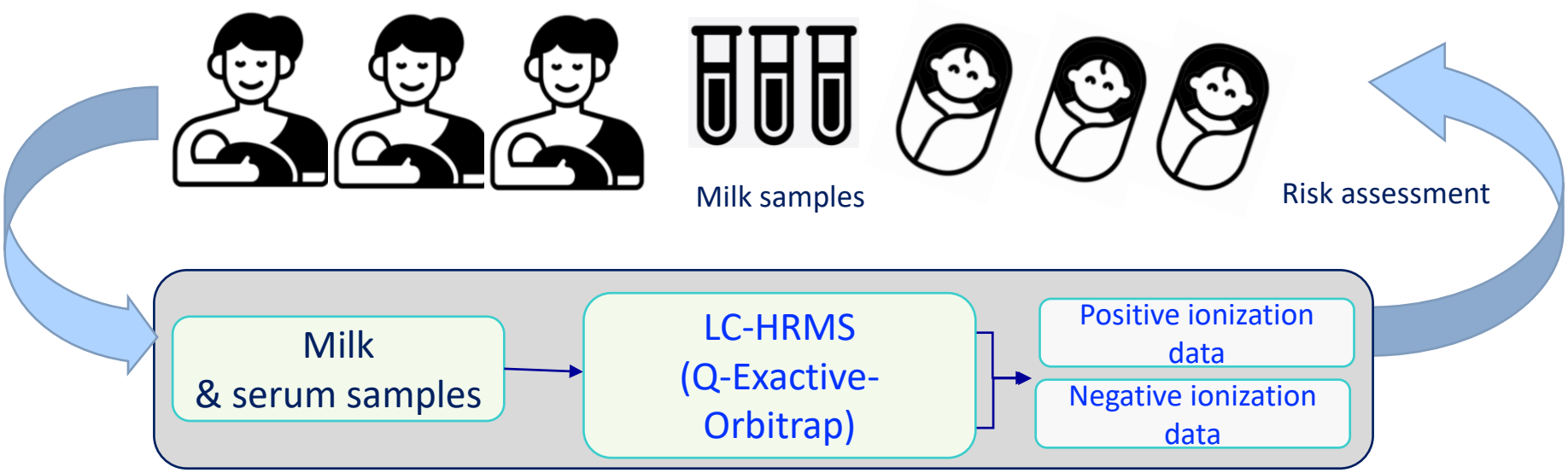
+ all routes and sources of exposure
- limited data cohorts with many limitations
- targeted analysis

Partnership for the Assessment of Risks from Chemicals (PARC)
WP 6 - Innovation in regulatory risk assessment



https://www.eu-parc.eu/news/risk-assessment/parc-supports-regulatory-risk-assessment-four-new-reports-are-now-published

Partnership for the Assessment of Risks from Chemicals (PARC)
WP4: Multiple chemicals in the maternal milk and serum



- **Milk and serum samples from Greek population (+ other countries)**
- **Untargeted chemical analysis**
- **Targeted chemical analysis (LC-MS/MS, GC-MS/MS)**
- **Statistical analysis and evaluation of the results**
- **Reverse dosimetry for external exposure estimation (maternal)**
- **Risk assessment (maternal and newborn)**
- **Risk communication**

Drawings retrieved from: https://thenounproject.com/

Partnership for the Assessment of Risks from Chemicals (PARC) WP4, WP5 & WP6

- **WP 4 :** Human Biomonitoring studies in mixtures of chemicals

- **WP5 :** AOP development & effect markers.

- **WP5:** BPA alternatives and associated mixtures (data gaps, effect biomarkers and NAM development) [*use of vertebrate (e.g., zebrafish), invertebrates (e.g., daphnia magna, C. elegance, insects) and in vitro models by applying classical, molecular and OMICs technics*]

- **WP 6:** Workflow for Human Relevance Assessment of AOPs, Associated Biomarkers of effect and New Approach Methodologies

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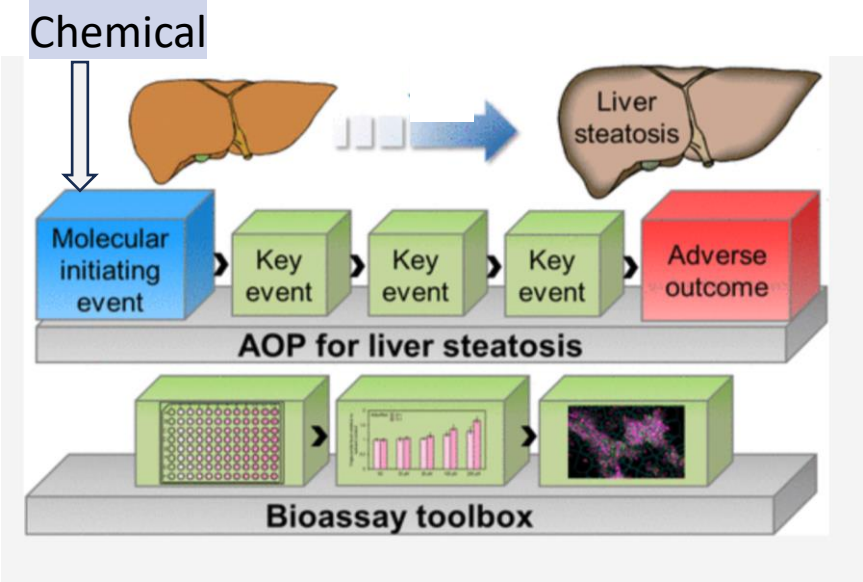
Other BPI Activities in the assessment of risk from multiple chemicals

The EuroMix project



Adverse outcome pathway- driven (AOP) analysis of liver steatosis in vitro, identification of KE/biomarkers of effect and bioassays for measurement (NAMs), Luckert et al, 2018 (The Euromix, FP7 project). https://www.euromixproject.eu/

The INSIGNIA-EU project

"Preparatory action for monitoring of environmental pollution using honey bees"

Honeybee colonies for the detection of pesticides, microplastics, heavy metals, and air pollutants.

https://www.insignia-bee.eu/

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OECD Expert Group on Effect Biomarkers

Working Party on Exposure Assessment and Working Party on Hazard Assessment (WPEA/WPHA)

Project "Using Adverse Outcome Pathways (AOP) to address combined exposures to chemicals with relevant effect-biomarkers" https://aopwiki.org/

Drafting new HBM methodologies for the following adverse outcomes:

- Carcinogenicity
- Genotoxicity and Oxidative stress
- Endocrine Disruption (mainly estrogenicity),
- Neurotoxicity
- Developmental Neurotoxicity,
- Reproductive toxicity.

The way forward….

EFSA

PARC

OECD

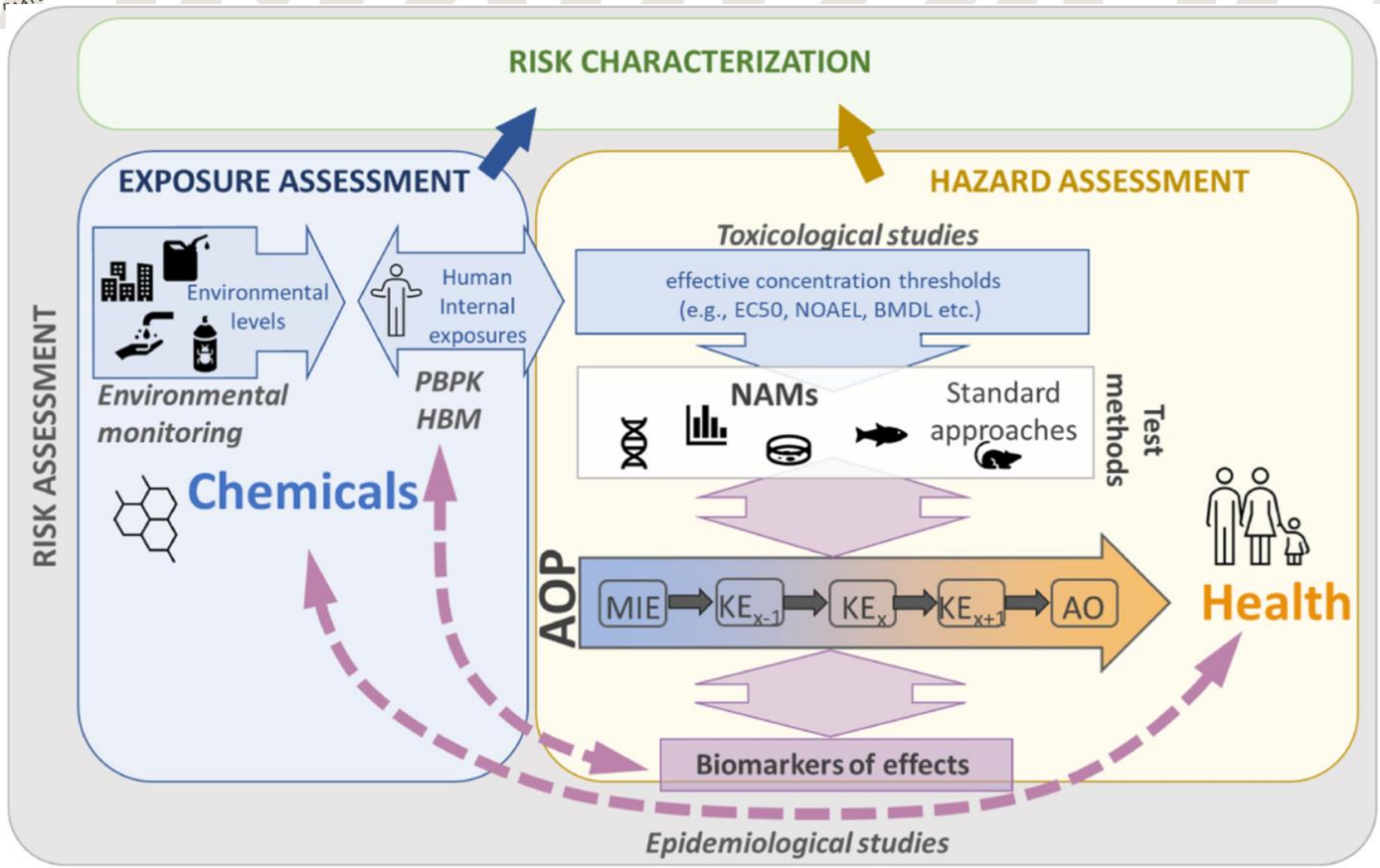
EuroMix

…

- Construction of the AOP/AON
- Identification and characterization of KE
- Interrelation of KE to biomarkers of effect
- Development and evaluation of NAMs
- Regulatory acceptance of NAMs

- Enhanced
  - human relevance
  - accuracy and specificity in grouping of chemicals
  - readiness & high thruput methods
- Reduced
  - uncertainty
  - vertebrate testing

Graphical presentation integrating the different parts for the next generation risk assessment (NGRA)



Bajard , et al, Application of AOPs to assist regulatory assessment of chemical risks – Case studies, needs and recommendations Environmental Research, 2023

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Our team

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Thank you