Regulatory implementation of scientific mixture risk assessment approaches.

Partnership for the Assessment of the Risks from Chemicals

Beltox 07-12-2023

Jacob van Klaveren, with input from ANSES, WR Biomatris and many project partners

PARC

Content

1. Understanding the regulatory process and data gaps

2. Scientific output of the risk of combined dietary exposure to multiple pesticides

3. What is the Partnership for the Assessment of the Risk of Chemicals and how does it work towards filling data gaps

4. Engagement of stakeholders and regulatory readiness

Legal provisions to take account of unintentional mixtures are needed in the relevant legislation, such as REACH, cosmetics, toys, food contact materials, food additives

- *Introducing mixture assessment factor(s) for the chemical safety assessment of substances under REACH*
- *Further development of more specific and targeted methodologies for specific policy areas*

European Commission

Commission Staff Working Document on Combination Effects

Progress report on the assessment and management of combined exposures to multiple chemicals (chemical mixtures) and associated risks
SWD (2020) 250

Peter Korytar, DG ENV, 27 October 2020

What are the knowledge and data gaps?

1. No exposure data covering all routes of exposure (aggregated exposure)

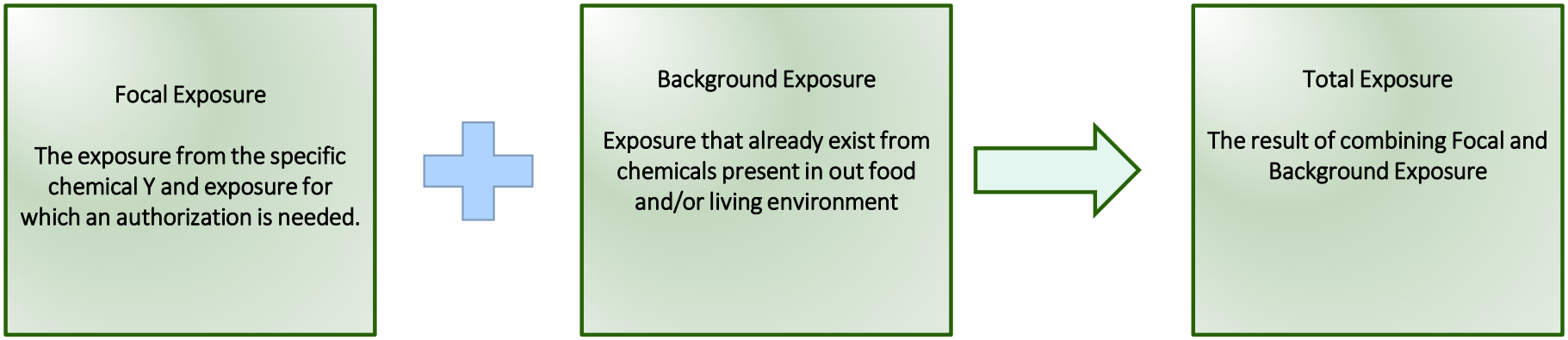
2. IPCHEM is in place, but in 2020 not filled with appropriate exposure data

3. Hazard data and particular toxic prosperities addressing mixture effects is lacking

One substance (mixture), one approach, one health, but what does it mean?

Understanding the regulatory question

Does it relate to a new chemical/ pesticide/ contaminant or is it about the chemicals already present in our living environment (food, air, dermal contact etc.)?



EC-JRC publication using HBM data for MAF

Int J Environ Res Public Health. 2022 May 18;19(10):6121. doi: 10.3390/ijerph19106121.

Chemical Mixtures in the EU Population: Composition and Potential Risks

Sebastian Socianu [1], Stephanie K Bopp [1], Eva Govarts [2], Liese Gilles [2], Jurgen Buekers [2], Marike Kolossa-Gehring [3], Thomas Backhaus [4], Antonio Franco [1]

Affiliations + expand

PMID: 35627658 PMCID: PMC9141134 DOI: 10.3390/ijerph19106121

- Starting point to use HBM data for MRA at the European level using IPCHEM data (due to GPPR restrictions on aggregated data only P50 and P95). Limited HBM data sets.
- Human Biomonitoring Guidance Values for 21 substances available at that time used in the calculations.
- No grouping applied, should be done next time according to the recommendation/discussion (EFSA guidance was just published).
- No Health Impact, calculation based on an algorithm using safety factors

CARACAL Statement March 2023

Proposed implementation of MAF

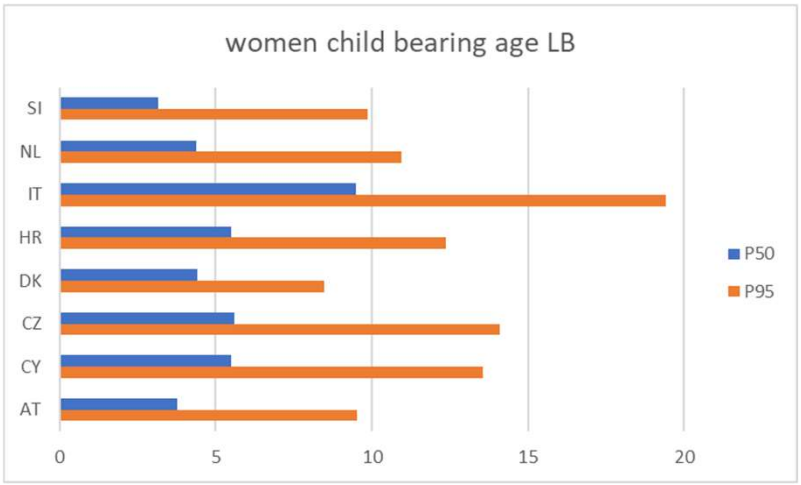
- MAF is risk management tool, proposed value = 5
- Derogation possible if a specific risk assessment is carried out and documented (e.g. workers exposure under CAD)
- Only substances registered at ≥1,000 t/y (covering >99.8% of total tonnage registered)
- Review clause in Article 138

CARACAL Open Questions March 2023

- No sufficient justification provided for the suggested value of 5.
- No sufficient justification provided for the focus solely on high production volume chemicals.
- Application domain(s) unclear.

Targeted retrospective approaches DG SANTE unit contaminants

1. DG SANTE mandates EFSA (and Member States) to perform scientific risk assessments (EFSA scientific opinions on PFAS and heavy metals)
2. Scientific output discussed in DG SANTE working group environmental contaminants



Risk drivers

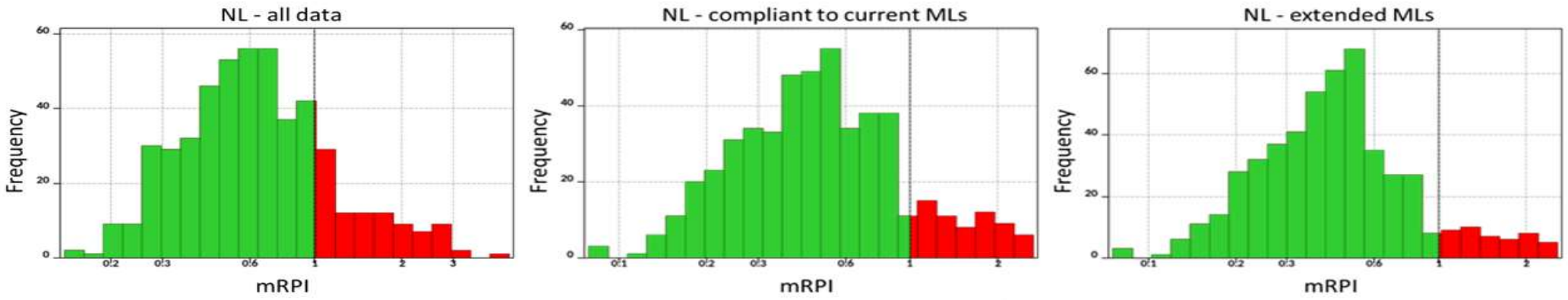
- NDL-PCBs
  - Fish & sea food
  - Dairy
- Lead
  - Grains
  - Fruit
- Methylmercury
  - Fish & sea food
- Fluoride in water

Health impact

Uncertainties

Targeted retrospective approaches DG SANTE unit contaminants

1. Provisions in CONTAM regulation
   - As Low As Reasonable Achievable (ALARA) principle
   - Nutritional impact (e.g. risk drivers in fish highly contaminated with mixtures of heavy metal)
   - Risk-benefit analysis, if health impact is unclear
   - Lowering maximum residue limits (and food availability for all)



Targeted approaches DG SANTE unit pesticides

Protection goals set by DG SANTE unit pesticides

- Threshold of regulatory consideration
- Margin of Exposure Total (MOET) at 99.9th percentile >100
- All pesticides in an assessment group sharing the same adverse outcome

Prospective risk assessment and management of pesticides

EXTERNAL SCIENTIFIC REPORT

APPROVED: 23 July 2021

doi:10.2903/sp.efsa.2021.EN-6811

Proposed prospective scenarios for cumulative risk assessment of pesticide residues

Jacob D. van Klaveren[1], Annick D. van den Brand[1], Gerda van Donkersgoed[1], Trijntje van der Velde-Koerts[1], Hilko van der Voet[2], Johannes W. Kruisselbrink[2], Waldo J. de Boer[2], Marco van Lenthe[2], Corinne Sprong[1]

[1]Dutch National Institute for Public Health and the Environment (RIVM)
[2]Wageningen University & Research, Biometris

Full report: here

3 times intensive discussion with regulators of DG SANTE and Member States

Training for regulators

Refined by Mock Assessment

Retrospective risk assessment and management of pesticides

1. Grouping of pesticides into assessment groups based on dossiers, data and scientific knowledge.

2. Probabilistic Exposure Assessment using the MCRA software.

3. Expert Knowledge Elicitation
   - there is always a lack of data (data gaps filled with conservative assumptions or not)
   - what do experts know about possible over-/ underestimation.

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How far is Europe with implementing mixture risk assessment for pesticides from dietary exposure?

2007 — 2011 — 2015 — 2019 — 2023

Regulation 396/2005
Setting of MRLs for pesticides

Regulation 1107/2009
Placing on the market of PPPs

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

Methodological developments → **Pilot assessments** → **Implementation**

EFSA Guidance document on scientific criteria for grouping chemicals into assessment groups for human health risk assessment of combined exposure to multiple chemicals

- Harmonised guidance across regulatory domains of EFSA
- Draft guidance document issued for public consultation in May 2021
- International Workshop (online) took place on 18, 19 & 20th October 2021
- Publication in December 2021

Hazard-driven criteria

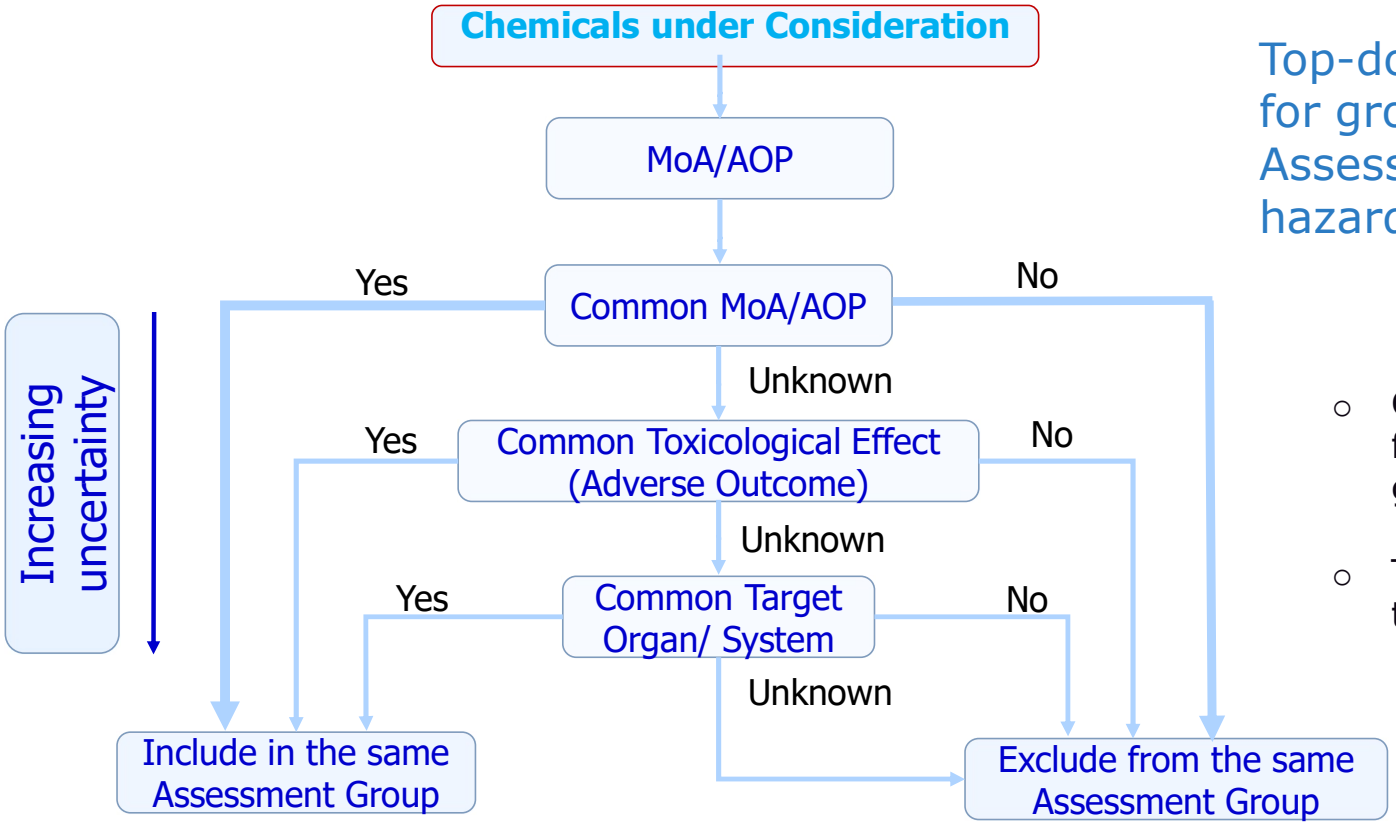
1. Adverse Outcome Pathways
2. Common toxicological effect
3. Common target organ
4. *In silico* methods, structural analysis etc.

Prioritisation methods

1. Risk-based for multiple chemicals
2. Risk-based for individual chemicals
3. Exposure-based (incl. co-exposure)

https://efsa.onlinelibrary.wiley.com/doi/abs/10.2903/j.efsa.2021.7033

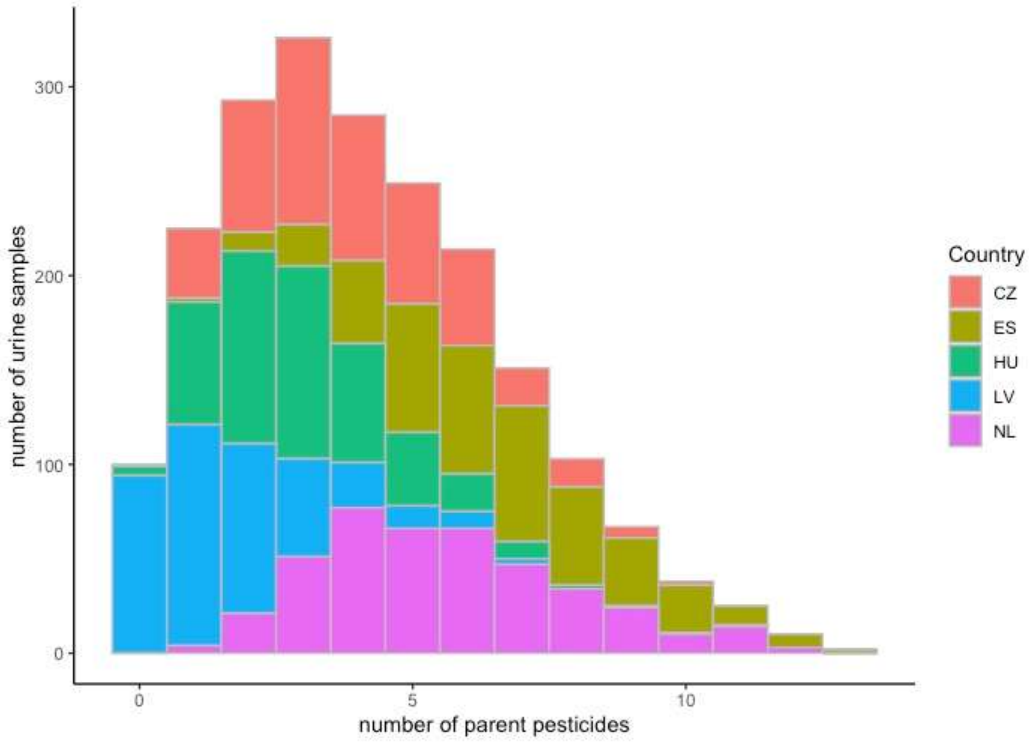
Scientific criteria for grouping based on common effect



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

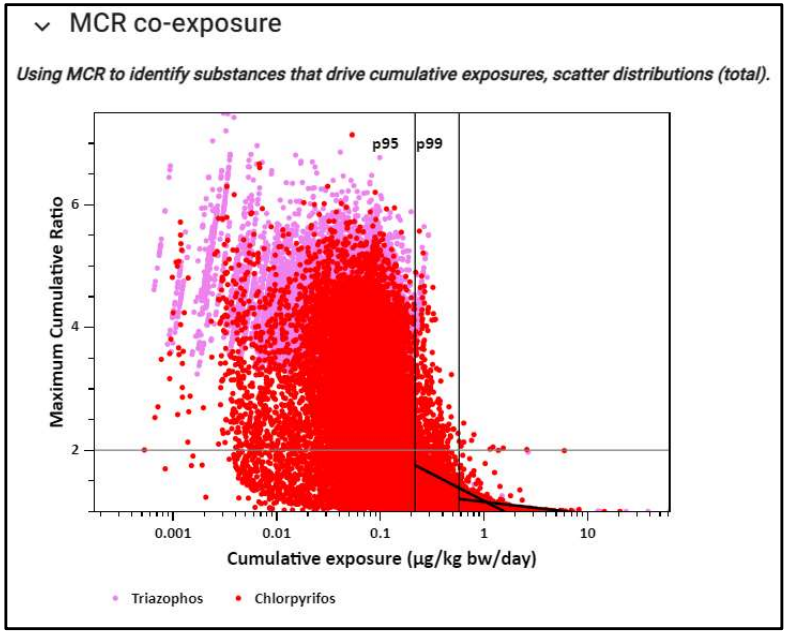
- Gold standard Common MoA/ AOP for grouping into assessment group
- Then move to common toxicity or target organ

Example of mixture risk assessment of pesticides where grouping has not been applied (HBM4EU)



Example where grouping has been applied and where individual data are plotted against the threshold of regulatory consideration

Maximum Cumulative Ratio (MCR)



- MCR > 2 (Y-axis) show mixtures of chemicals
- MCR = 1 represents a single chemical
- The X-axis >1 corresponds with MoE < 100 threshold of regulatory concern
- The X axis > 1 conclusion 75% single chemicals and 25% mixtures

DEVELOPMENT OF THE OPEN MONTE-CARLO RISK ASSESSMENT PLATFORM

Angelo Cafaro
Methodology & Scientific Support Unit at EFSA

Jacob van Klaveren
RIVM National Institute for Public Health and the Environment

Rijksinstituut voor Volksgezondheid en Milieu
Ministerie van Volksgezondheid, Welzijn en Sport

efsa
EUROPEAN FOOD SAFETY AUTHORITY

EFSA-RIVM PARTNERSHIP: FROM MCRA TO OPEN MCRA

Feasibility study issued by RIVM in April 2021

EFSA-RIVM FPA renewed in December 2022

What can be expected?

Transparency: open source, governance.

Interoperability: data connectivity, co-creation.

Accessibility: user groups, dedicated & simplified interfaces.

Harmonisation: standard regulatory actions, capacity building & training.

MAIN DELIVERABLES

- External scientific report describing (available in July 2023):
  1. Open MCRA software governance.
  2. Guidance on accessing published core models in public repository.
  3. Proposal of a design for linking external models.

- Release of MCRA version 10 (June 23rd, 2023):
  - Core models published in openly accessible repository
  - Web application to interface with MCRA core models

Major accomplishment of EFSA-RIVM collaboration available for all MS

MAIN DELIVERABLES

- External scientific report (available in July 2023):
  - Description and integration of SRAs in new MCRA.

- Training sessions:
  - Relevant EFSA networks (Feb-Mar 2023).
  - DG SANTE staff, e-working group, SCoPAFF member and/or appointed experts (May 2023).
  - EFSA staff (June 2023).

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What is PARC and how do we fill datagaps?

- A public-public **partnership** under Horizon Europe
- Avoid duplication of work
- Fill regulatory gaps identified in the Chemical Strategy for Sustainability
- PARC Governance Board are ministries (risk managers)

Public-Public

Co-Fund Budget
EU 50/50 MS,AC
400 M€

Started : 01/05/2022
Duration : 7 years
~200 Partners

29 countries

24 Member States: Austria (AT), Belgium (BE), Croatia (HR), Cyprus (CY), Czech Republic (CZ), Denmark (DK), Estonia (EE), Finland (FI), France (FR), Germany (DE), Greece (EL), Hungary (HU), Ireland (IE), Italy (IT), Latvia (LV), Lithuania (LT), Luxembourg (LU), Netherlands (NL), Poland (PL), Portugal (PT), Slovakia (SK), Slovenia (SI), Spain (ES), Sweden (SE)

3 associated countries: Iceland (IS), Israel (IL), Norway (NO)

2 non-associated third countries: Switzerland (CH), United Kingdom (UK)

3 European Agencies :

European Environment Agency

efsa European Food Safety Authority

ECHA EUROPEAN CHEMICALS AGENCY

Co-funded by the European Union

HORIZON EUROPE

PARC

T6.2
Integrative exposure and risk assessment

Partnership for the Assessment of the Risks from Chemicals

ANSES-VITO-RIVM

Amélie Crépet, Katleen De Brouwere, and Jacob van Klaveren

PARC

Integrated exposure assessment

Risk and health impact assessment

Consumption

Chemical occurrence

Determinants of exposure

Dietary Exposure

Non- dietary Exposure

Occupational Exposure

Aggregated External Exposure

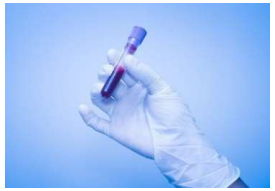
Internal Exposure

Reverse Dosimetry

Forward Dosimetry

anses

Human Biomonitoring



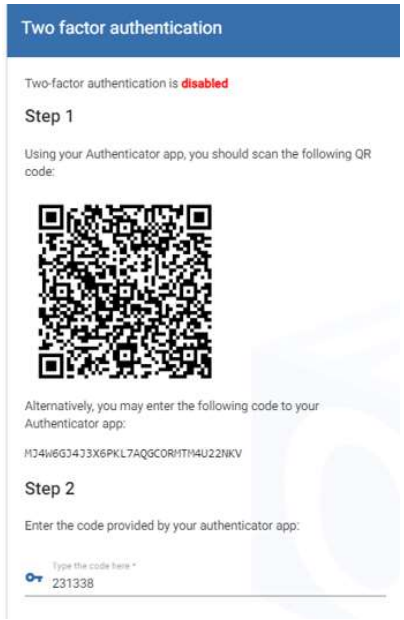
PARC deliverables relevant for future regulatory risk assessment and risk management

Links HBM observation to sources of exposure, health impact and kinetics

Reviewed by EFSA (scientific mandate on these topics) for readiness for regulatory implementation

How will data gaps be filled and how is that related to Legal conditions related to Privacy Regulation and ICT security?

- RIVM legal department agreements with all HBM study owners under the European General Data Protection Regulation (GDPR).
- High level of ICT security required. MCRA is secure by design.
- Engagement and trust in cooperation and solving the issue is beyond expectation (Project Real-life mixtures). All European HBM study owners uploading individual HBM data to MCRA.

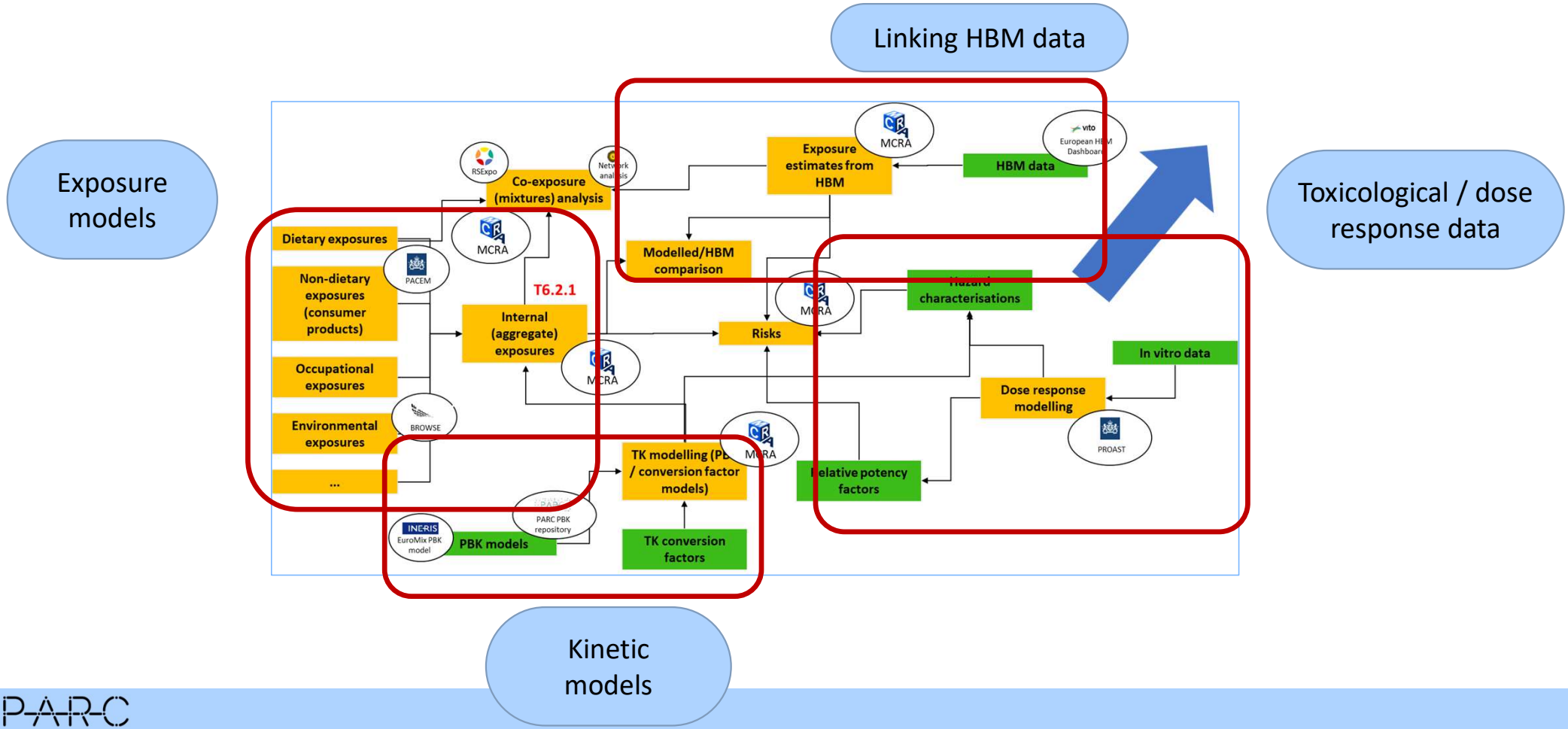


News items integrated risk assessment and PARC project Real-life mixtures using HBM data

Read the news item click here

- 35 institutes from 20 EU Member States are cooperation
- Includes all individual HBM data and many more data sets than elsewhere
- Integrating exposure – hazards and kinetics (following EFSA guidance)

Major development areas for linking models and data



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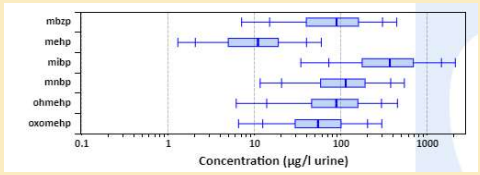
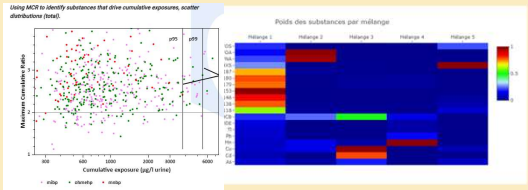
MCRA Integrated risk assessment dashboard available for all stakeholders

HBM observations

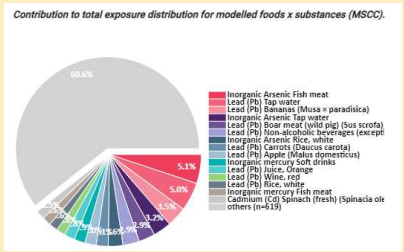
- Exposures
- SNMU co-exposures
- MCR to link with regulatory process





Modelled exposures

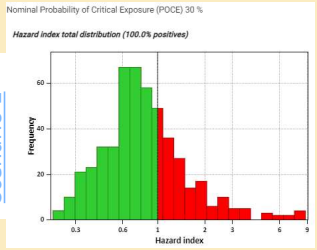
- Calculateted dietary and non-dietary exposure identification sources of exposure
- Provide regulatory perspective to act



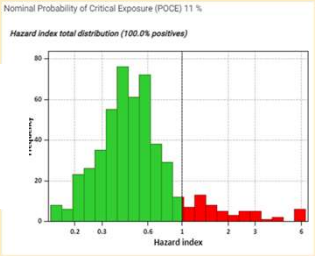
Risk scenarios

e.g. exploring effect maximum limits on risk

Scenario 1



Scenario 2

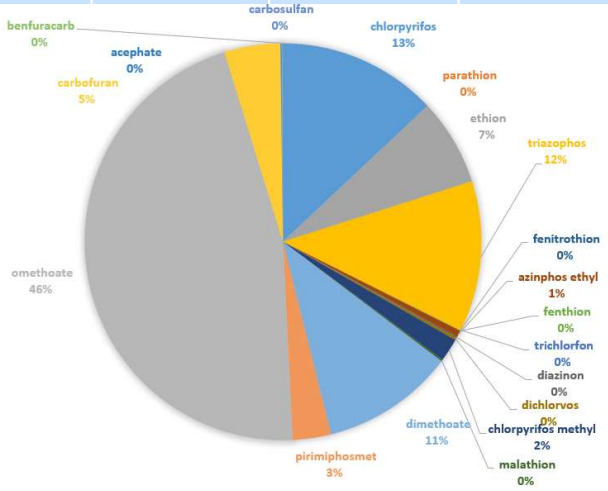


Risk decreases

The MCRA Dashboard example for mixtures of pesticides

Data	Assumption	Approach			MOET, 95th percentile	MOET, 99th percentile	MOET, 99.9th percentile	% of individual with MOET<100
Dietary exposure assessment		Tier II			782	287	59.1	0.3%
HBM data for 19 pesticides (OP and carbamates)	Allocation of metabolites considering potential presence of the residue	Best case scenario						0.99
HBM data for 19 pesticides (OP and carbamates)	Allocation of metabolites considering potential presence of the residue	Worst case scenario						5.94

Preliminary results only for illustration purpose



Overview of chemicals contributing the most

Perspectives to reduce risk by risk drivers

5 case studies with regulatory impact based on PARC priorities

	PFAS-Immune	Pesticides CAG-NAN-NAM	Metals – Nephrotox Pb, Cd, i-As, i-Hg	Metals-DNT (e.g. IQ loss) Pb, i-As, MeHg
Approach taken with HBM data risk assessment	Ready to proceed 32 scenarios proposed	Almost ready Need agreement of the approach and validation	Ready to proceed	Ready to proceed Scenario need to be defined
Understanding sources of exposure	Not yet, but doable via EFSA for dietary exposure and some PARC project non-dietary	Yes, by comparing with EFSA results	Yes, published in Sprong et al. 2023 10 countries	Yes, published in Sprong et al. 2023 10 countries
Implementation in MCRA (new models)	Ready For 16 scenarios	In progress	Ready	Ready
Compared to 21 Human Biomonitoring Guidance Values for critical effects used for MAF, hazard data gaps are filled with relevant hazard data for the relevant mixture endpoint				
Hazard data based on grouping	9 or 13 PFAS internal toxicological threshold values. Many more to come based on NAMs and SNMU	30 pesticide internal toxicological threshold values Many more to come based on NAMs and SNMU	4 internal threshold values more Many more to come based on NAMs and SNMU	4 internal threshold values more to come using NAMs Many more to come based on NAMs and SNMU

Applicability in future risk management

- DG SANTE Working Group on Environmental and Industrial Contaminants (maximum residue limits and risk mitigation options)
- DG SANTE Standing Committee on Plant Animal, Feed and Food (pesticide authorisation)
- DG ENVI (Refinement of the MAF) depending on the outcome of REACH revision

Roadmap for regulatory readiness

- 5 PARC Case studies prioritised chemicals and effects
  - Pesticides with effect neuro system (2 effects)
  - PFAS and immune toxicity
  - Heavy metals and nephrotoxicity
  - Chemicals with possible effect on IQ loss

- PARC Governing Board agreed on PARC Integrative risk assessment webinar understanding how mixture risk assessment using HBM data can be used by them
  - ministries Public Health and ministries Environment

- Integrated risk assessment based on HBM data for EFSA and ECHA aiming to collect their feedback for improvement

- Regulatory understanding by DG SANTE, DG ENVI and regulators at Member State level

Synergies between PARC task 6.2 and EFSA

- Scientific knowledge and mandate (e.g. grouping) useful cooperation with experts engaged in EFSA panels participating in PARC projects.

- PARC projects integrative risk assessment and EFSA's strategic agenda ExpoAdvance (aggregated exposure, HBM data streams, kinetics) and RACEMiC (mixtures).

- Link to European infrastructures laboratoria to fill hazard data gaps (either based on animal or NAM testing).

Summary

- Regulatory requirements and possibilities to implement are diverse and not similar.
- It helps to understand retrospective and prospective risk management needs and dilemmas.
- The PARC projects integrative risk assessment is filling the hazard data (endpoints specific based on grouping) and exposure data (using HBM data from all HBM study owners) gaps highlighted in the Chemical Strategy for Sustainability.
- Synergies should be further explored. Synergies between Member States has highly been appreciated.
- Regulatory readiness will be further explored in first half of 2024.