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Full length article

Strategy for mixture risk assessment using European human biomonitoring data: lessons learned from applications to pesticides, per- and polyfluoroalkyl substances and metal(loid)s

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Abbreviations: AChE, Brain and/or erythrocyte acetylcholinesterase; ADI, Acceptable daily intake; AMOE, Acceptable margin of exposure; AOP, Adverse outcome pathway; BKMR, Bayesian kernel machine regression; BMDL, Benchmark dose lower confidence limit; CAG, Cumulative assessment group; CAG NAM, Cumulative assessment group on neurological acute effects on the motor division; CAG NAN, Cumulative assessment group on neurological acute neurochemical effects; CDPC, Common Data Platform on Chemicals; CSS, Chemical Strategy for Sustainability; DNEL, Derived no-effect level; DNT, Developmental neurotoxicity; ECHA, European Chemical Agency; EDI, Estimated daily intake; EEA, European Environment Agency; EFSA, European Food Safety Authority; EU, European Union; ExWAS, Exposome-wide association study; FAIR, Findable, accessible, interoperable and reusable; FAO, Food and Agriculture Organization; FUE, Urinary excretion fraction; GDPR, General data protection regulation; HBGV, Health-based guidance value; HBM, Human biomonitoring; HBM4EU, Human Biomonitoring for Europe Initiative; HBM-EL, Human biomonitoring exposure level; HBM-GV, Human biomonitoring guidance value; HBM-TV, Human biomonitoring toxicological value; IPCHEM, Information Platform for Chemical Monitoring; IQ, Intelligence quotient; ISES, International Society of Exposure Science; JECFA, Joint Expert Committee on Food Additives; JMPR, Joint Meeting on Pesticide Residues; LOD, Limit of detection; LOQ, Limit of quantification; MCRA, Monte Carlo Risk Assessment; MoA, Mode of action; MOE, Margin of exposure; MOET, Total margin of exposure; MRA, Mixture risk assessment; MRL, Maximum residue limits; mRPI, Modified reference point index; NAM, New approach methodology; NOAEL, No-observed-adverse-effect level; NTP, National Toxicology Program; OECD, Organisation for Economic Co-operation and Development; OS-OA, One Substance, One Assessment; PARC, Partnership for the Assessment of Risks from Chemicals; PBK, Physiologically based kinetic; PEH DP, Personal Exposure and Health Data Platform; PFAS, Per- and Polyfluoroalkyl Substance; QSAR, Quantitative Structure Activity Relationship; RAC, Risk assessment committee; RCR, Risk characterisation ratio; RDC, Research Data Centres; REACH, Registration, Evaluation, Authorization and restriction of Chemicals; RIVM, Dutch National Institute for Public Health and the Environment; RPF, Relative potency factor; SCCS, Scientific Committee on Consumer Safety; SCHEER, Scientific Committee on Health, Environmental and Emerging Risks; SEAC, Socio-economic analysis committee; SNMU, Sparse non-negative matrix under approximation; TDI, Tolerable daily intake; US-EPA, Environmental protection agency of the United States; VITO, Flemish Institute for Technological Research; WHO, World health organisation; WQS, Weighted quantile sum.

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ABSTRACT

Humans are exposed daily to mixtures of chemicals from multiple sources and routes, including diet and the environment. These combined exposures may cause adverse health effects that are not adequately captured by conventional substance-by-substance risk assessment, due to the inherent complexity of assessing combined risks. To address this gap, the Partnership for the Assessment of Risks from Chemicals (PARC) Real-life Mixtures project aims to consolidate scientific knowledge regarding mixture risk assessment (MRA).

In synergy with ongoing activities of European agencies and other initiatives, this project developed a strategy to perform MRA using human biomonitoring (HBM) data. The approach consists of five steps: (1) prioritisation of chemical mixtures of interest for human health to guide case-study selection; (2) collection and organisation of the data required for MRA, including exposure, hazard, and toxicokinetic information; (3) development of methods for conducting MRA using HBM data; (4) implementation of these methods within the Monte Carlo Risk Assessment (MCRA) toolbox; and (5) application of the strategy to prioritised case studies.

Three chemical families and four associated adverse health outcomes were selected based on the results of PARC priority process: pesticides affecting the nervous system, per- and polyfluoroalkyl substances (PFAS) affecting the immune system, and metal(loid)s affecting kidney function and neurodevelopment. HBM data from studies conducted across Europe and Greenland were harmonised using the HBM data toolkit. Hazard and toxicokinetic data were compiled to derive internal toxicological values suitable for MRA. The MRA was then performed in a harmonised way for each case study using the MCRA toolbox.

The strategy developed within the PARC Real-life Mixtures project provides a proof-of-concept for conducting HBM-based MRA and for informing policymakers. Future research will focus on reducing uncertainties and expanding the approach to additional chemicals with common health endpoints and co-exposure.

1. Introduction

Chemical risk assessment has mainly been conducted on a substance-by-substance basis by national and European health and safety agencies with limited consideration for chemical mixtures, whereas humans are simultaneously exposed to a diverse range of chemicals from various sources and routes. Thus, there is an urgent need to develop a methodological and practical framework for national and European health and safety agencies to assess the combined impact of chemical mixtures, particularly for chemicals which have a common adverse health effect.

Growing scientific consensus underscores the necessity of comprehensively incorporating the effects of chemical mixtures into risk assessment frameworks. The European Union (EU) Chemical Strategy for Sustainability (CSS) highlighted the current lack of guidance for mixture risk assessment (MRA) and noted that mixture risk management remains insufficiently addressed across regulatory sectors (EC, 2020). Furthermore, the CSS acknowledged that assessing and regulating the almost infinite number of potential chemical combinations is neither realistic nor economically feasible at present. Thus, there is a pressing need to develop a MRA framework based on robust and relevant data and methods and apply it to prioritised mixtures of interest.

European plant protection and biocidal product regulations have already incorporated some aspects of MRA (Regulation (EC) No 1107, 2009; Regulation (EU) No 528, 2012; Regulation (EU) No 284, 2013), which has led to the development of methodologies and their initial application in dietary risk assessment. Specifically, the European Food Safety Authority (EFSA) has developed methods to perform cumulative risk assessment of chemicals in food safety, based on common toxicological effects and applying the dose addition model (EFSA, 2019b). These methodologies have been successfully applied in several cumulative dietary risk assessments for pesticides with effects on the nervous system, thyroid and developing foetus (EFSA, 2019c, 2020a, 2020b, 2020c, 2021a, 2022). Similar approaches, also based on common toxicological effects and the dose addition model, have been applied to other chemical mixtures within a chemical family, such as per- and polyfluoroalkyl substances (PFAS), dioxins, polychlorinated biphenyls, phthalates, metal(loid)s and polycyclic aromatic hydrocarbons (EFSA, 2020c, 2018, 2019c; Lange et al., 2022; Sprong et al., 2023a; Souza et al., 2023; Dai et al., 2024). Moreover, MRA has been extended beyond chemical families to better reflect real-life combined exposures (Sprong et al., 2023a; Crépet et al., 2022; Kortenkamp et al., 2022; Engelhardt, Norström and Weiss, 2023; Willey et al., 2024). Most of these applications relied on dietary exposure assessments, however, other sources of exposure data are now also being applied.

In recent years, human biomonitoring (HBM) data, measuring concentrations of chemicals and/or their metabolites in biological matrices mainly blood and urine, has become more widely available through large-scale biomonitoring programmes. Initiatives such as COPHES/DEMOCOPHES (Schindler et al., 2014) and the Human Biomonitoring for Europe Initiative (HBM4EU) (Gilles et al., 2021) have significantly

enriched the global database on chemical exposure in humans at the European level. These HBM data have been harmonised and the summary statistics have been integrated into the European HBM Dashboard[1] and the Information Platform for Chemical Monitoring (IPCHEM)[2]. Similarly the aligned HBM surveillance programme in the Partnership for the Assessment of Risks from Chemicals (PARC) will generate new HBM data expected in 2027 (Marx-Stoelting et al., 2023). This closely aligns with the European Chemicals Industry Action plan launched by the European Commission in 2025, putting forward the plan to roll out a Common Data Platform on Chemicals (CDPC) as part of the One Substance-One Assessment (OS-OA) initiative (EC, 2025). This platform should be established and managed by the European Chemicals Agency (ECHA) and include, besides HBM data, environmental monitoring data, a repository for reference values, and data on chemicals in articles and products, with the aim to create a monitoring framework for chemicals and chemical risks (Regulation (EU) 2025/2455, 2025).

The analysis of existing HBM data and the generation of new HBM data provide critical insights into human exposure to chemicals (Lobo Vicente et al., 2023; Govarts et al., 2023). HBM data measures internal exposure levels within a study population and enables comparisons of exposure across population groups based on age, sex, nationality or other (demographic) factors. A primary advantage of incorporating HBM data into chemical risk assessment is its ability to directly capture aggregate exposure from multiple sources and routes (Angerer, Ewers and Wilhelm, 2007; Escher et al., 2022; Santonen et al., 2023; Reale et al., 2024). It also allows estimation of real-life co-exposures when several chemicals are measured in the same individuals. In addition, HBM data can be used to explore associations between chemical exposures, biological responses, and health effects, and, when feasible, to derive internal toxicological values, i.e., values defining the level of internal concentration of a specific substance for which no adverse health effect are expected, such as human biomonitoring guidance values (HBM-GV).

Despite its potential, the integration of HBM data into chemical risk assessment frameworks is still under development (Louro et al., 2019). Challenges include addressing uncertainties related to analytical methods, interpreting HBM results in relation to toxicokinetics and health risks, relative attribution of different sources to the overall exposure reflected by HBM data, managing the large number of detectable chemicals and mixtures, and ensuring ethical compliance regarding data protection and privacy (Santonen et al., 2023). The EU CSS emphasised the need to further develop HBM data collection to capture all sources and routes of exposure (EC, 2020). More recently, it was specified that by 2030 ECHA and EFSA, in cooperation with the European Environment Agency (EEA), should commission a comprehensive EU-wide HBM study covering all Member States, and the European Commission should assess the appropriateness of requiring regular HBM studies (Regulation (EU) 2025/2455, 2025). To strengthen the results and interpretation of risk assessment, HBM data should be used in combination with other monitoring data, such as chemical concentrations in air, dust, food and consumer products.

The Real-life Mixtures project, as part of the PARC work package 6 on Innovation in Regulatory Risk Assessment (Marx-Stoelting et al., 2023), aims to develop a strategy for chemical MRA using HBM data, and to explore its practical application *via* case studies (PARC, 2023a, 2025c), while identifying current limitations and future perspectives. This article presents the developed strategy and its application to a set of prioritised chemical mixtures and associated health effects, using harmonised HBM data from both general and occupational populations across Europe. The strengths and limitations of conducting human health risk assessments for chemical mixtures based on HBM data are discussed, together with the potential of this approach to support and inform chemical regulation.

2. Methods

The strategy was developed by building on approaches and guidance on MRA published in scientific literature and by European and international agencies (Crépet et al., 2022; Dai et al., 2024; EFSA, 2013b, 2018, 2019b, 2021b; Hulin et al., 2020; Kortenkamp et al., 2022; Lange et al., 2022; OECD, 2018; Souza et al., 2023; Sprong et al., 2023a; Nikolopoulou et al., 2023). The component-based approach proposed by EFSA (2019b) was selected as the basis to perform MRA. This approach integrates exposure and hazard data of the individual mixture components to estimate overall risk. The assessment is based on the dose addition model, which considers that components act on the same target organ/system or via a similar mode of action (MoA), but may differ in toxic potency (US-EPA, 2023). The proposed strategy was organised in five steps (Fig. 1) as follows:

1. Prioritisation of mixture(s) based on a chemical group(s) with a common adverse health effect and evidence of co-exposure, within or across regulatory silos (i.e., legal frameworks) (Section 2.1);
2. Collection and organisation of exposure, hazard and toxicokinetic data (Section 2.2);
3. Development of specific MRA methods relevant to the selected case studies (Section 2.3);
4. Implementation of these methods in the Monte Carlo Risk Assessment (MCRA) toolbox (Section 2.4); and
5. Application of the strategy using harmonised European HBM datasets (Section 3).

2.1. Prioritisation of the chemical mixtures

Chemicals can be grouped into mixtures and prioritised considering a combination of regulatory requirements and scientific criteria (EFSA, 2021b). Based on regulatory requirements, chemicals with common toxicological properties can be selected within a regulatory silo (e.g., pesticides, cosmetics, food contact materials). To date, grouping chemicals based on their toxicological properties forms the basis of MRA methods. This strategy was largely developed by EFSA as the hazard-driven scientific criteria for chemical grouping (EFSA, 2021b). It integrates the available lines of evidence on toxicity (i.e., MoA, adverse outcome pathways (AOP), specific effects, and target organ/system toxicity) to group chemicals with common toxicological properties. When the number of chemicals under consideration is vast, as is the case with real-life exposure, exposure-based or risk-based approaches can be used to prioritise chemical mixtures. Exposure-based criteria group chemicals with a high probability of co-exposure (i.e., co-occurrence) and exclude those with low co-exposure likelihood (Crépet et al., 2019, 2022). Risk-based criteria combine hazard information with exposure data (te Biesebeek et al., 2021; Crépet et al., 2019) to exclude chemicals with low *a priori* risk, thereby focusing resources on mixtures of concern. Both approaches lead to the establishment of a priority mixture i.e., a group of chemicals for which, on the basis of their toxicological characteristics, extent of exposure and likelihood of co-exposure, an MRA appears warranted.

As a starting point, the prioritisation of chemical mixtures in this project was largely steered by the priorities set by the PARC Governing Board. This Board serves as the overarching body of PARC, providing the high-level strategic direction to ensure alignment of PARC activities with initiatives undertaken at the European, national and international levels. In 2022, at the beginning of the PARC project, the Governing Board prioritised chemicals and chemical groups to be considered in PARC research. This prioritisation was done in consultation with academia, European agencies, Member State authorities and ministries, and the European Commission. Their expertise and input were collected

[1] https://hbm.vito.be/eu-hbm-dashboard
[2] https://ipchem.jrc.ec.europa.eu

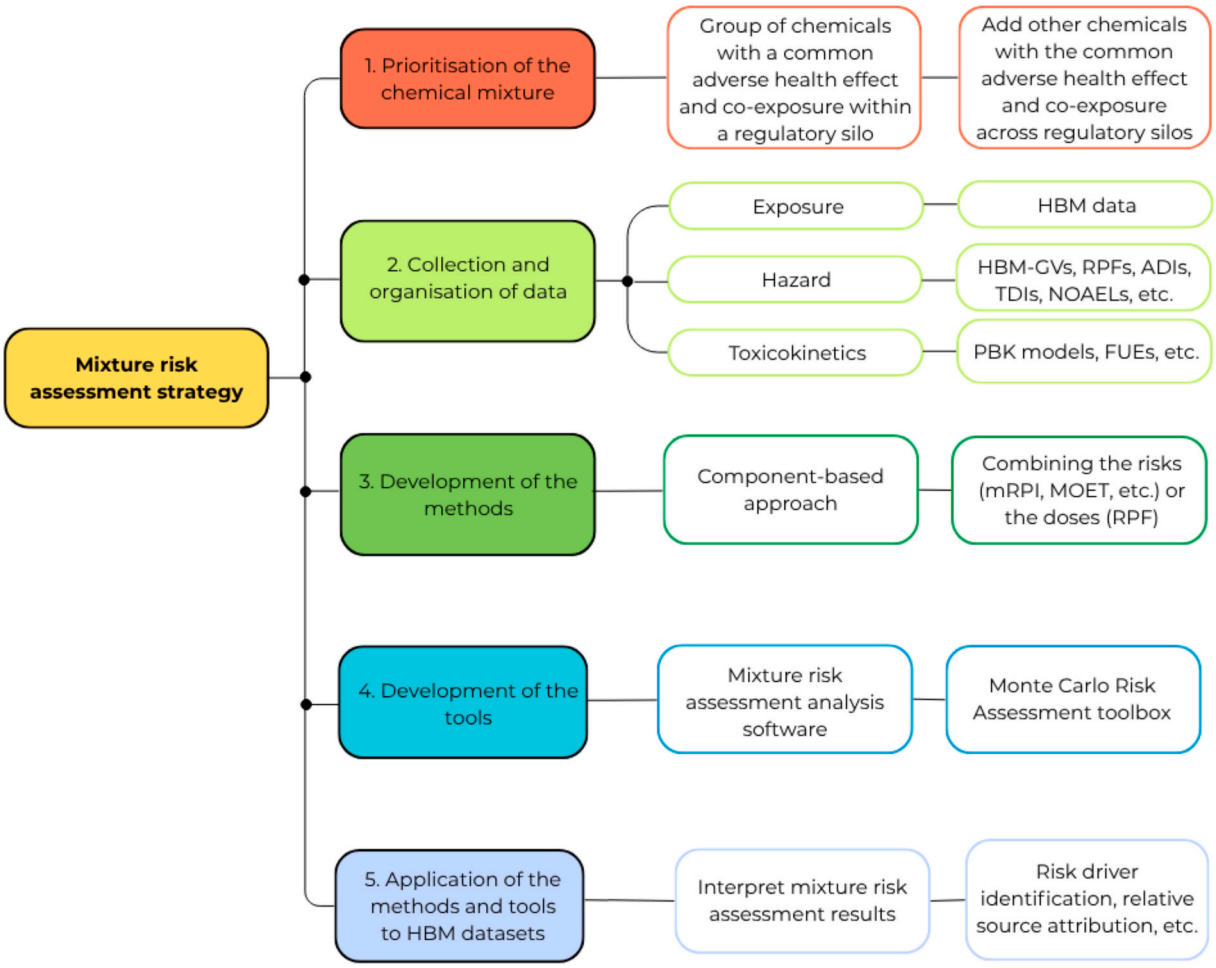


Fig. 1. General strategy for HBM-based MRA developed in the PARC project Real-life Mixtures.

by means of a PARC stakeholder questionnaire regarding exposure, hazard and risk aspects. The specific chemicals and groups prioritised for PARC work package 6 are displayed in Table 1 (Permana et al., 2025; PARC, 2023b).

In the PARC Real-life Mixtures project, the prioritisation process considered not only the chemical groups identified by the PARC Governing Board, but also adverse health effects deemed to be of highest concern and requiring additional research. Consistent with the CSS, priority was given to endpoints including carcinogenicity, mutagenicity, reproductive and developmental toxicity, endocrine disruption, immunotoxicity and neurotoxicity (EC, 2020). Moreover, kidney toxicity was deemed relevant based on the prioritisation of health effects as part of the EFSA-SANTE action plan on cumulative risk assessment (EFSA et al., 2024). Based on prioritised chemical groups, a first set of case studies was developed, focusing on prioritised chemical group and adverse health effect combinations within regulatory silos. Future steps aim to integrate chemicals across regulatory silos. To this end, case studies may be extended by considering combined exposure observed in HBM datasets and common adverse health effects.

Table 1
Overview of the chemicals and topics prioritised by the PARC Governing Board specific to PARC work package 6 on Innovation in Regulatory Risk Assessment (PARC, 2023b).

Priority chemicals / topics
Biocides
Pharmaceuticals/ hazardous medicinal products
Veterinary pharmaceuticals
Plant protection products
Per- and polyfluoroalkyl substances
Bisphenol A, bisphenol A analogues and alternatives, bisphenols
Natural toxins
Metals
Phthalates
Flame retardants
Endocrine disrupting compounds
Mixtures
Food contact materials
Cosmetics
Persistent, bioaccumulative and toxic/ very persistent and very bioaccumulative compounds

2.2. Collection and organisation of the required data

2.2.1. Exposure data from HBM studies

Performing MRA at European level requires the organisation and harmonisation of exposure data and ensuring compliance with the General Data Protection Regulation (GDPR) (EU, 2016). As individual HBM data are required to perform such analysis, these data should be collected and managed using appropriate procedures to ensure data security. Individual HBM data should be harmonised in a common data format in order to facilitate harmonised analysis.

In this work, HBM studies covering both general and occupational populations across Europe were inventoried and harmonised into an MCRA compatible format. First, an inventory of the HBM studies accessible through partners of the PARC Real-life Mixtures project was created. Then, data harmonisation was conducted following the approach and criteria outlined in the Personal Exposure and Health Data Platform (PEH DP) by the Flemish Institute for Technological Research (VITO) and using the HBM data toolkit (https://hbm.vito.be/tools/data-harmonization) (Peeters et al., 2025). This harmonisation process comprises the following steps: identifying the biomarkers measured in the corresponding matrix using the biomarker list, harmonising the data using the provided data template according to the codebook, and running the data validation tool to check compliance with the formats and rules specified in the codebook.

To enable processing of the harmonised HBM datasets in the MCRA toolbox (https://mcra.rivm.nl/mcra/#/), bilateral data controller-data processor agreements were established between the HBM study data partners (data controllers) and the Dutch National Institute for Public Health and the Environment (RIVM), the host of the MCRA software (data processor), in compliance with the GDPR.

2.2.2. Hazard data collection

To apply the component-based approach (EFSA, 2019b), it is essential to obtain hazard data for each individual chemical in the mixture for the selected common adverse health effect.

For the PARC Real-life Mixtures project, an array of available hazard data was gathered for each component in the mixture from authoritative sources, including institutional scientific reports from EFSA, ECHA, the Environmental Protection Agency of the United States (US-EPA), and the Food and Agriculture Organization (FAO)/ World Health Organisation (WHO) Joint Expert Committee on Food Additives (JECFA), as well as peer-reviewed scientific publications such as those from the HBM4EU project (Apel et al., 2020, 2023).

2.2.2.1. Internal toxicological values. Where available, HBM-GVs should be selected if their associated critical effect corresponded to the common adverse effect under assessment. An HBM-GV is a concentration of a chemical or its metabolite in a human biological matrix (e.g., blood or urine) that indicates a level below which no health concern is expected. HBM-GVs are derived using health-based data and scientific principles and methodologies (Schulz et al., 2007; Apel et al., 2020; Hopf et al., 2025). In this context, the term HBM-GV is reserved for a critical effect of a chemical in a target population.

Where no established HBM-GVs are available, internal reference points for the common effect should be gathered. These reference points are often obtained from epidemiological studies that examine associations between exposure biomarker concentrations and adverse health effects (e.g., through the measurement of biomarkers of effect) in human populations. Statistical models are typically applied to estimate the exposure biomarker concentration associated with a specific increase in health risk (e.g., 10% increase in the risk of a given effect). These internal reference points can be directly used in MRA or serve as the basis for deriving HBM-GVs or human biomonitoring toxicological values (HBM-TV). An HBM-TV is defined here as a derived concentration of a chemical or its metabolite in a human biological matrix that indicates a level below which no relevant health concern is expected for the specific effect under assessment, distinct from substance's critical effect, in a target population. When HBM-GVs and HBM-TVs are derived from reference points, such as a benchmark dose lower confidence limit (BMDL), then uncertainty factors can be applied to the internal reference point to account for intra- and interindividual variability (e.g., sensitive sub-populations), data quality, and uncertainty in the exposure-response relationship (EFSA, 2012a), where needed.

2.2.2.2. External toxicological values. Where no internal toxicological values are available, external health-based guidance values (HBGV), such as the tolerable daily intake (TDI; typically applied to contaminants) or the acceptable daily intake (ADI; used for regulated chemicals) should be used when the critical effect corresponds to the selected common effect. In the absence of established HBGVs, external reference points, such as a no-observed-adverse-effect level (NOAEL) or BMDL can be considered. External toxicological values are being used to interpret HBM data after the conversion of internal exposure levels to external exposure levels using reverse dosimetry. Alternatively, they can serve as reference points for the derivation of HBM-GVs or HBM-TVs using forward dosimetry. Both reverse and forward dosimetry rely on toxicokinetic models, such as physiologically based kinetic (PBK) models, or at least on toxicokinetic parameters to convert an external dose into an internal concentration in a specific biological matrix (e.g., blood or urine) and *vice versa* (Section 2.2.3).

2.2.2.3. Relative potency factors. Relative potency factors (RPF) are used to estimate a potency-related exposure. RPFs are scaling factors that express the toxicological potency of individual chemicals in a mixture relative to a selected index compound (Meek et al., 2011; EFSA, 2019b). They are calculated for each component as the ratio of equipotent doses of the index compound and the respective mixture components (Equation (1)). Internal and external RPFs are derived from internal and external reference points and requires precise criteria (e.g., parallel curves, etc.). The used of these data require a toxicological value for the index compounds.

$$RPF_k = \frac{RP_{index}}{RP_k} \quad (1)$$

Where:

RPF_k = Relative potency factor of chemical k;
RP_{index} = Reference point of the index compound;
RP_k = Reference point of chemical k.

2.2.2.4. Read-across. Where the abovementioned hazard data are not available, read-across approaches offer a pragmatic alternative by inferring hazard or potency information for data-poor chemicals based on structurally or toxicologically similar substances for which robust data exist (Rorije et al., 2018). Read-across assumes that chemicals within a defined group share comparable modes of action or toxicokinetic profiles established through application of new approach methodologies (NAMs). It requires data from NAMs e.g., Quantitative Structure Activity Relationship (QSAR) modelling, *in vitro* assays, omics strategies, and combinations thereof, allowing for the extrapolation of toxicological profiles. Although associated with uncertainty, this approach enables the progression of MRA for data-poor substances.

2.2.3. Toxicokinetic data collection

Although HBM measurements provide information on internal exposure, their direct application in risk assessment is often limited by the lack of corresponding internal toxicological reference values. Therefore, HBM may be converted to external exposure levels using reverse dosimetry and thereafter be compared to external toxicological values in a risk assessment. Substance-specific toxicokinetic information on absorption, distribution, metabolism and excretion (e.g., half-life and

fraction of urinary excretion (FUE)) is therefore needed to support the translation between internal to external exposure metrics. Depending on data availability, reverse dosimetry approaches may range from simple mass-balance or steady-state models to more comprehensive PBK models (Šulc et al., 2022; Apel et al., 2020; Angerer et al., 2011; Hays et al., 2007; Apel et al., 2023; Pouillot et al., 2022; Sams and Jones, 2012).

Alternatively, external toxicological values can serve as reference points for the derivation of HBM-GVs or HBM-TVs using forward dosimetry. Similarly, substance-specific toxicokinetic information is needed for the translation of external to internal exposure metrics.

Toxicokinetic data and models can also facilitate conversion between biomarker or biological matrices when the biomarker or biological matrix used to derive an internal toxicological value differs from that measured in an HBM study. In such cases, conversion factors can be applied to the HBM data to align them with the relevant biomarker of exposure and biological matrix. Such conversion factors are gathered from the scientific literature and/or established from existing HBM or toxicokinetic studies. In this work, for example, urinary compound concentrations were converted to corresponding blood concentrations where relevant, or biomarkers representing multiple chemical forms, such as total arsenic, were converted to a toxicologically relevant fraction (i.e., toxicologically relevant arsenic), enabling comparison with the relevant toxicological value.

2.3. Mixture risk assessment methods

The selection of the best suitable MRA approach largely depends on the quality, quantity, and type of hazard data available. A decision tree depicting the selection process based on hazard data availability for the MRA methods has been developed (Fig. 2). Where applicable, the RPF method is the preferred approach, followed by the modified reference point index (mRPI) method, and the total margin of exposure (MOET) method.

2.3.1. Risk characterisation ratio based on relative potency factors

When HBM data are used as the basis for exposure assessment, the RPF approach can be applied provided that internal RPFs are available for the mixture components, alongside an HBM-GV (or an HBM-TV) for the index compound for the common adverse health effect.

The internal RPFs are multiplied by the internal exposure levels of each component and then summed to estimate the cumulative exposure expressed as index compound equivalents (Cum HBM-EL_{Index}) (Equation (2)).

$$CumHBM\text{-}EL_{Index} = \sum_{k} HBM\text{-}EL_k \times RPF_k \quad (2)$$

Where:

Cum HBM-EL_{Index} = Cumulative index compound equivalent exposure;

HBM-EL_k = Internal exposure for chemical k (e.g., HBM concentrations);

RPF_k = Relative potency factor of chemical k;

Finally, the Cum HBM-EL_{Index} is then compared to the HBM-GV (or HBM-TV) of the index compound to generate the risk characterisation ratio (RCR) (Equation (3)).

$$RCR = \frac{CumHBM\text{-}EL_{Index}}{HBM\text{-}GV_{Index}} \quad (3)$$

Where:

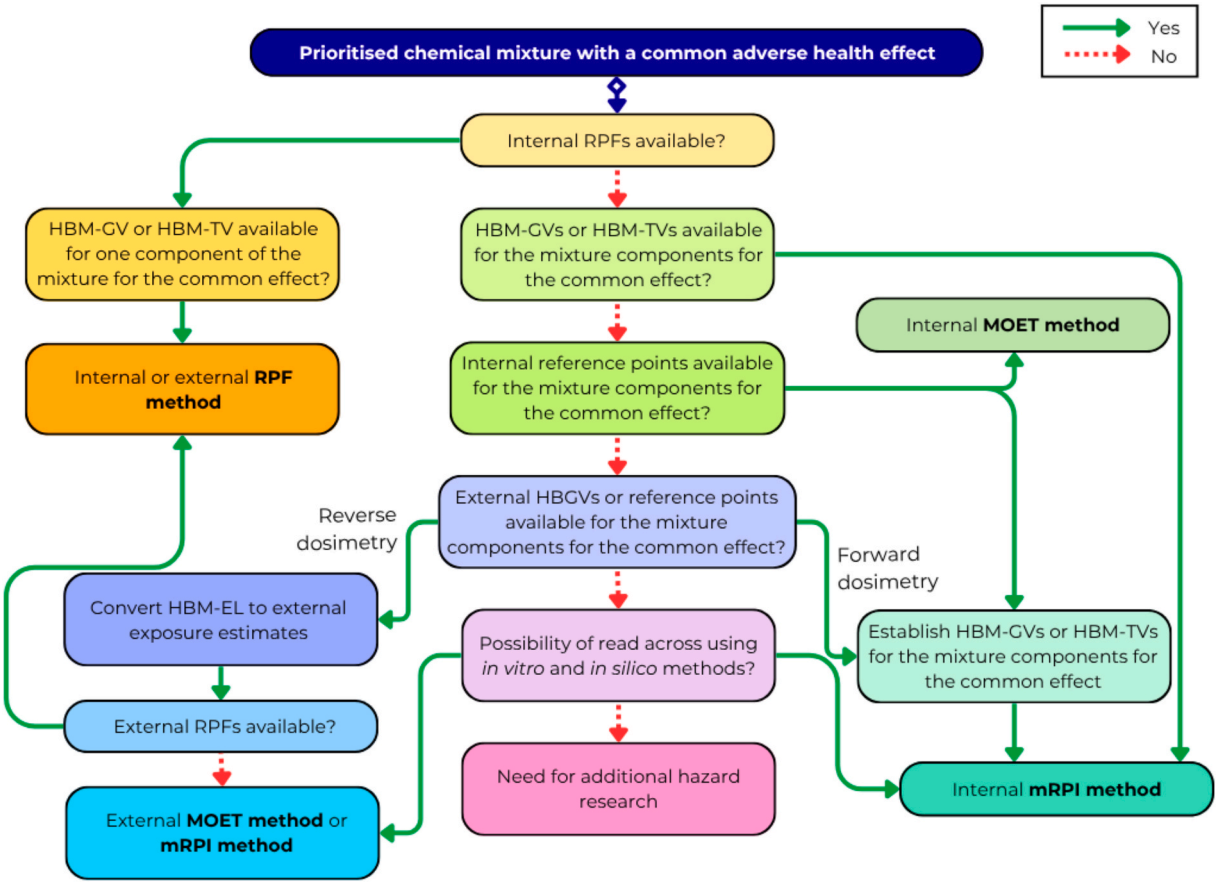


Fig. 2. Decision tree for selecting MRA methods (Section 2.3) based on the availability of hazard data (Section 2.2). The green full arrows depict 'yes' and the red dashed arrows depict 'no'.

RCR = Risk characterisation ratio;

Cum HBM-EL_{Index} = Cumulative index compound equivalent exposure;

HBM-GV_{Index} = Human biomonitoring guidance value for the index compound (to note, HBM-TVs could also be applied).

If the RCR ≤ 1, the risk of adverse health effects in the study population is considered low. In contrast, if the RCR > 1, adverse health effects in the study population cannot be excluded.

Where external RPFs are available alongside an external toxicological value (e.g., TDI or ADI), the RPF method can also be applied. In this case, internal exposure levels are first converted into external exposure estimates (e.g., estimated daily intake (EDI)) using reverse dosimetry. The RPFs are then applied to these external estimates to calculate the cumulative index compound equivalent exposure, which is compared with the external toxicological reference value of the index compound to derive the RCR, which is interpreted as described above.

2.3.2. Modified reference point index (mRPI)

The mRPI method is applicable where no RPFs are available, but internal toxicological values (e.g., HBM-GVs or HBM-TVs) for the common adverse health effect are defined (or can be derived) for each component in the mixture (Vejdovszky et al., 2019; Crépet et al., 2022; Sprong et al., 2023a, 2023b). For each component, the internal exposure level is divided by the respective internal toxicological value. These ratios are then summed to obtain the mRPI (Equation (4)).

$$mRPI = \sum_{k=1}^{n} \frac{HBM\text{-}EL_k}{HBM\text{-}GV_k} \quad (4)$$

Where:

mRPI = Modified reference point index;

HBM-EL_k = Internal exposure level of chemical k (i.e., HBM concentration);

HBM-GV_k = Human biomonitoring guidance value of chemical k (to note, HBM-TVs could also be applied)

n = Number of chemicals in the mixture.

If the mRPI ≤ 1, the risk of adverse health effects in the study population is low. In contrast, if the mRPI > 1, the possibility that adverse health effects in the study population cannot be excluded.

Alternatively, when external toxicological values (e.g., TDI, ADI or endpoint-specific reference values) are available for each mixture component, the mRPI method can be applied. In this case, internal exposure levels are first converted into external exposure estimates (e.g., EDIs) using reverse dosimetry based on available toxicokinetic data and/or models. For each component, the external exposure estimate is divided by its respective external toxicological value, and the resulting ratios are summed to derive the mRPI, which is interpreted as described above.

2.3.3. Total margin of exposure (MOET)

The MOET can be used as a risk metric when internal reference points (e.g., BMDL for a 10% response ($BMDL_{10}$)) are available. First, the margin of exposure (MOE) is calculated for each single substance as the ratio of the internal reference point and the corresponding internal exposure level. The MOE expresses the margin between the dose at which an adverse effect is observed and the actual internal exposure (Equation (5)).

$$MOE_k = \frac{RP_k}{HBM\text{-}EL_k} \quad (5)$$

Where:

MOE_k = Margin of exposure of chemical k;

RP_k = Internal Reference point of chemical k;

HBM-EL_k = Internal exposure level of chemical k (i.e., HBM concentration);

For MRA, the reciprocals of the individual MOEs are summed, and the MOET is then calculated as the reciprocal of this sum (Equation (6)).

$$MOET = 1/\sum_{k=1}^{n} \frac{1}{MOE_k} \quad (6)$$

Where:

MOET = Total margin of exposure;

MOE_k = Margin of exposure of chemical k;

If the MOET is higher than the acceptable margin of exposure (AMOE), the risk of adverse health effects in the study population is considered low. In contrast, if the MOET $<$ AMOE, the possibility of adverse health effects in the study population cannot be excluded. The AMOE depends on the toxicological properties of the substances under consideration (US-EPA, 2012). For mixtures of non-genotoxic substances, an AMOE value of 100 is relevant, based on the default uncertainty factors of 10-fold for interspecies variability and 10-fold for intraspecies variability, as used in EFSA pesticides acute MRA (EFSA, 2020a, 2019b). If one or more components of a mixture are genotoxic carcinogens, a higher AMOE (e.g., 10,000) could be used (EFSA, 2019b).

Alternatively, when only external reference points (e.g., NOAEL or BMDL) are available, the MOET approach can also be applied. In this case, internal exposure levels are converted into external exposure estimates (e.g., EDI) using reverse dosimetry based on available toxicokinetic data and/or models. These external exposure estimates are compared with the corresponding external reference points to derive individual MOEs, which are then summed to determine the MOET, interpreted as described above.

2.4. Implementation in MCRA toolbox and data protection

2.4.1. Uncertainty and variability in mixture risk assessment methods

To enable application of the MRA strategy across a broad range of HBM studies in Europe, the MCRA toolbox (van der Voet et al., 2020), originally developed for dietary exposure and risk assessment, was adapted to support risk assessment using HBM data (Engel et al., in prep). The probabilistic MRA methods described in Section 2.3 were implemented using the software's two-dimensional Monte Carlo framework, which allows inter-individual variability and multiple sources of uncertainty to be treated separately (van der Voet and Slob, 2007). The framework consists of an inner and an outer loop. The inner loop quantifies variability by using individual-level biomarker values in the dataset to generate a population exposure distribution. Where relevant, this includes sampling from distributions of biomarker conversion factors to account for biological variability. The outer loop quantifies uncertainty by repeatedly running the inner loop on bootstrap samples of the HBM dataset. Additionally, it accounts for parameter uncertainty by (independently) sampling from uncertainty distributions defined for internal RPFs, toxicological values, and toxicokinetic factors. The outer loop was run for 1,000 iterations to generate uncertainty intervals. Uncertainty in toxicological values can be addressed by defining an HBM-TV range or a distribution, from which values are sampled in the outer loop to propagate this uncertainty into the final risk estimates (Vrijenhoek et al., submitted).

2.4.2. Criteria for generated outputs

Handling individual-level personal data requires strict measures to protect the privacy of the participants. In this work, individual values are kept confidential, and a certain percentile can only be presented if enough cases contribute to the percentile segment. In this project, recommendations from the Research Data Centres (RDC) of the Federal Statistical Office and Statistical Offices of the Länder (2022) were followed to ensure anonymity. Specifically, results were only presented when the number of individuals included in the analysis was sufficiently large. Equations (7) summarise the rules applied to calculate the minimum sample size required to display a certain percentile. For example, the 2.5^{th} to 97.5^{th} percentiles could only be calculated when datasets

included at least 120 individuals. For smaller datasets, smaller percentile ranges were applied to protect confidentiality (see Table 2). These thresholds were applied to protect data confidentiality and to ensure that high-end exposure estimates remain statistically robust while preventing the potential identification of individuals in the tails of the distribution (Table 2).

$$\forall P < 50, \quad N_{min}(P) = \left\lceil \frac{300}{P} \right\rceil$$

$$\forall P \geq 50, \quad N_{min}(P) = \left\lceil \frac{300}{(100 - P)} \right\rceil \tag{7}$$

Where:

P = Percentile

N_{min} = Minimum number of individuals in a dataset to display percentile P

3. Results

3.1. Human biomonitoring studies

In total, data from 35 HBM studies across 20 European countries covering both general and occupational populations were harmonised and organised with the HBM data toolkit (Peeters et al., 2025). Of these 32 studies from 13 European countries represented the general population (two were Greenlandic studies and thus not geographically located in Europe), while the remaining three studies involved occupationally exposed individuals from 10 European countries. A map summarising the general population HBM studies, including study names, is shown in Fig. 3, and full name of the studies are available in the Supplementary Material, Table S1. Specific characteristics of all organised studies (e.g., study acronym, country, and level of representativity) are provided in Table 3, in alphabetical order. The selected studies enabled measuring a variety of chemicals across diverse target populations, including children, adolescents, women of childbearing age, adults or occupationally exposed individuals. More information on the substances measured by dataset is available in the Supplementary Material, Table S2. It should be noted that not all data from the entire HBM studies were used, only data relevant to the Real-life Mixtures project were organised.

3.2. Prioritised chemical mixture-effect combinations

Four case studies, each combining a specific group of chemicals with a common adverse health effect were established (Table 4). Notably, PFAS, pesticides and metal(loid)s were the primary chemical families prioritised by the PARC Governing Board (Table 1). For pesticides, neurotoxicity is a well-established adverse health effect associated with both acute and chronic exposure. Several EFSA reports have established cumulative assessment groups (CAGs) of pesticides affecting the nervous system and have previously performed cumulative risk assessment for neurotoxic endpoints (EFSA, 2019a, 2020a). For PFAS, immunotoxicity has been identified as the critical effect by EFSA (EFSA, 2020c). Both nephrotoxicity and developmental neurotoxicity have long been associated with exposure to certain metal(loid)s, and previous MRAs for these endpoints have been performed using dietary exposure data (Sprong et al., 2023a, 2023b).

Table 2
Percentiles used to display HBM results according to the number of individuals in the dataset to protect data privacy.

Number of individuals	Lower percentile	Upper percentile
N ≥ 120	2.5	97.5
60 ≤ N < 120	5	95
N < 60	10	90

3.3. Application of the MRA to case studies

3.3.1. Pesticides and neurotoxicity

The starting point for this case study was the work previously conducted by EFSA on the cumulative exposure and risk assessment of pesticides causing acute effects on the nervous system (EFSA, 2020a; van Klaveren et al., 2019). Two CAGs were defined by EFSA, namely, CAG NAN (neurological acute neurochemical effects), populated with 47 pesticides associated with brain and/or erythrocyte acetylcholinesterase (AChE) inhibition, and CAG NAM (neurological acute effects on the motor division), populated with 100 pesticides which are associated with functional alterations of the motor division. The goal of this case study was to perform a MRA for both CAGs based on urinary concentrations (e.g., morning, spot or 24-h urine samples) of pesticide metabolites, as parent compounds are rarely detectable in urine, and compare the results with EFSA's dietary-based assessment (2020a). All methodological details and results can be found elsewhere (Palmont et al., 2026). In summary, the review of the available hazard data revealed that internal toxicological values (HBM-GVs and HBM-TVs) for pesticide metabolites measured in urine were limited. Consequently, external reference points (namely, the NOAELs values for each specific effect derived from experimental animal studies following oral exposure and used in EFSA cumulative risk assessment) were extracted (EFSA, 2020a). Using these NOAEL values, the MOET approach was applied. As a first step, urinary concentrations of pesticide metabolites were converted into external exposure estimates for each parent compound using reverse dosimetry equations adapted from Šulc et al. (2022). Across the HBM datasets, from two to 11 metabolites were included in the analysis, resulting in 12 to 39 parent compounds being represented. For each parent compound, the NOAEL values were compared with the estimated external exposure (i.e., EDIs) to derive individual MOE values. Then, the reciprocals of these MOEs were summed to calculate the reciprocal of the MOET for the pesticide mixture for each individual participant. A MOET value exceeding the AMOE of 100 indicated the possibility of adverse health effects cannot be excluded.

3.3.2. PFAS and immunotoxicity

This case study was built on the work performed by Bil et al. (2023), where internal RPFs were derived for several PFAS using PFOA as the index chemical. The target populations for this MRA were in children, woman of childbearing age, adults and workers. Owing to limited data availability, no functional immunotoxicity endpoint could be established, and immunotoxicity parameters were entirely lacking for some PFAS (e.g., PFBA, PFDoDA). Consequently, a pooled distribution of internal RPF based on hepatotoxicity and immunotoxicity effects observed in male rats was established for ten PFAS, namely, PFBA, PFHxA, PFOA, PFNA, PFDA, PFDoDA, PFBS, PFHxS, PFOS, and HFPO-DA (Bil et al., 2022, 2023). Blood concentrations (i.e., measured in whole blood, plasma or serum) of the ten aforementioned PFAS when available were multiplied by internal RPF distributions and then summed to calculate the sum of PFOA equivalents. To estimate the RCR, the sum of PFOA-equivalent blood concentrations was then compared to an age dependent HBM-GV based on the PBK modelling and the internal $BMDL_{10}$ value for the sum of four PFAS set up by EFSA for immunotoxicity (EFSA, 2020c). All methodological details and results can be found elsewhere (Bil et al., submitted).

3.3.3. Metal(loid)s and nephrotoxicity

This case study assessed the risk of nephrotoxicity related to exposure to metal(loid)s, as detailed in Schillemans et al. (2026), for adult populations using urinary and blood concentrations for arsenic, cadmium, lead, and mercury. Since RPFs for nephrotoxicity were not identified for these metal(loid)s, the mRPI method was applied. Internal toxicological values (e.g., HBM-GVs or HBM-TVs) or internal reference points for nephrotoxicity were already available or could be derived for each metal(loid). Where established values were unavailable, internal

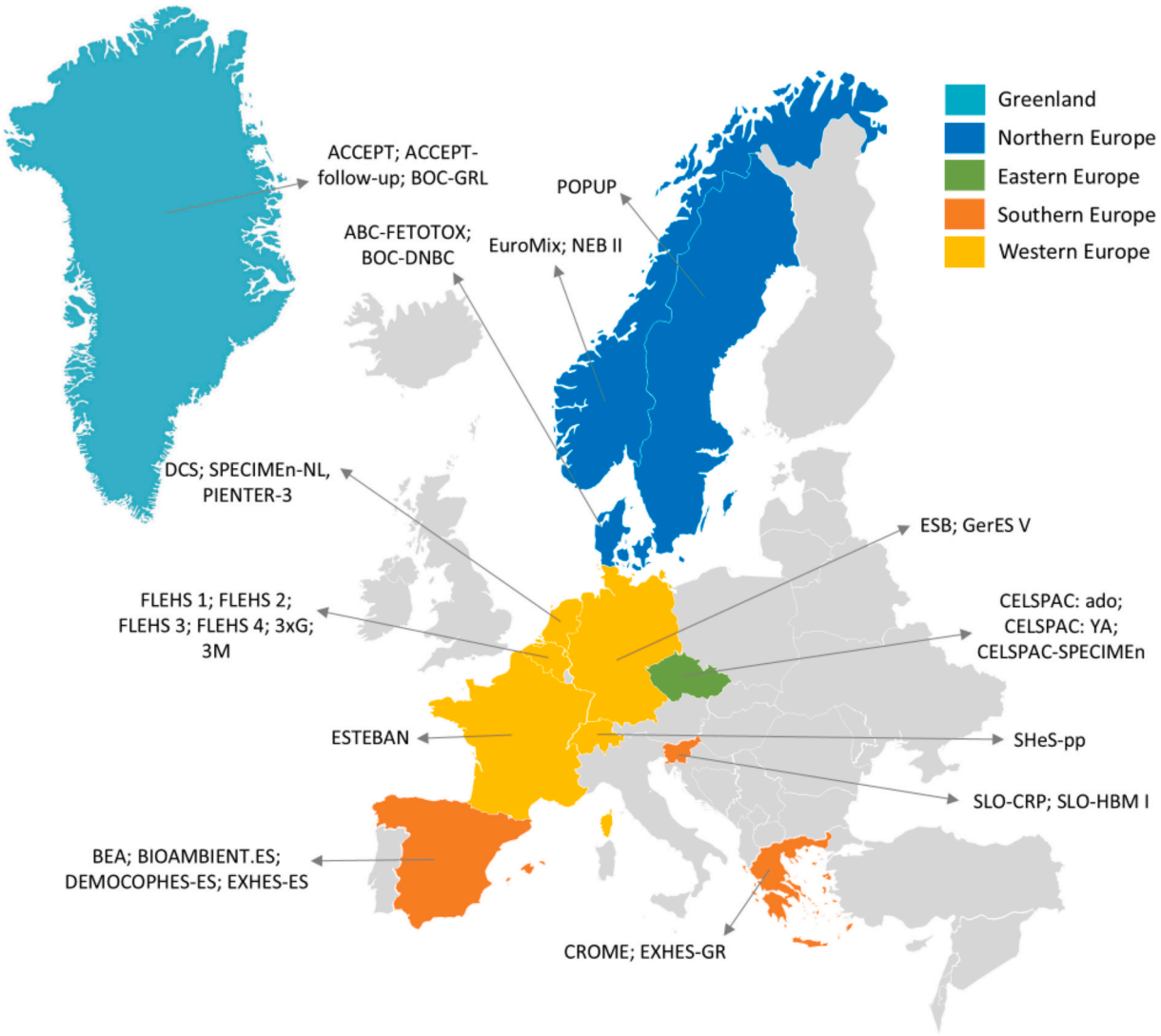


Fig. 3. General population HBM studies (n = 32) from 13 European countries and Greenland, harmonised and organised within the PARC Real-life Mixtures project, with study names displayed per country. Occupational studies are not presented in the Figure but are described in Table 3.

references points were used to derive HBM-GVs and HBM-TVs by applying appropriate uncertainty factors (details provided in Vrijenhoek et al. (submitted). The measured biomarker concentrations of arsenic, cadmium, lead, and mercury were compared with their respective internal toxicological values, and the resulting risk ratios were summed to calculate the mRPI. All methodological details and results can be found elsewhere (Carsique et al., submitted).

3.3.4. Metal(loid)s and developmental neurotoxicity

This fourth case study assessed the risk of developmental neurotoxicity (DNT) through Intelligence Quotient (IQ) loss due to exposure to a mixture of arsenic, lead, and methylmercury in children, adolescents and woman of childbearing age using urinary, blood and hair concentrations (Smirnova et al., 2014; McVey et al., submitted). As in the nephrotoxicity case study, RPFs were not identified for developmental neurotoxicity. Nevertheless, HBM-GVs were available for lead and methylmercury, and an HBM-TV was derived for toxicologically relevant arsenic. Thus, the mRPI method was applied by comparing the measured biomarker concentrations in the appropriate biological matrices with their respective HBM-GVs or derived HBM-TV. The resulting risk ratios were then summed to calculate the mRPI. All methodological details and results can be found elsewhere (McVey et al., submitted).

4. Discussion

This study presents a strategy developed to perform MRA based on current knowledge and using HBM data across Europe. It proposes a coherent framework for integrating exposure, hazard and toxicokinetic data with MRA methods, targeting end-users such as EFSA Scientific Panels and working groups, ECHA committees and expert groups, European Commission Scientific Committees (e.g., Scientific Committee on Consumer Safety (SCCS), Scientific Committee on Health, Environmental and Emerging Risks (SCHEER), etc.), FAO/WHO expert committees (JECFA, Joint Meeting on Pesticide Residues (JMPR)), national experts responsible for risk assessment of mixtures, and other stakeholders. The development of this strategy within the context of the PARC Real-life Mixtures project resulted in the organisation and harmonisation of data from 35 HBM studies across 19 European countries and Greenland. From the list of prioritised chemicals and chemical groups established by the PARC Governing Board, four chemical mixture-adverse health effect pairs were selected as case studies to perform MRA. The following sections discuss the main lessons learned from the application of the proposed strategy to the four case studies.

Table 3
Characteristics of the HBM studies harmonised and organised within the PARC project Real-life Mixtures. This table includes both general population and occupational studies. Please note that not the full original data were organised and thus some data represent only a subset of the original full dataset.

Study acronym	Country code	Level of representativity	Region	Study design	Sampling period (year)	Study population	Age range (years)	Sample size	Reference(s)
General population									
ABC-FETOTOX	DK	National	-	Cross sectional	2008-2014	Pregnant women	18-45	1533	Mortensen et al., 2013; Bjerregaard-Olesen et al., 2019
ACCEPT	GRL	National	-	Cross sectional	2010-2015	Pregnant women	18-48	580	Long et al., 2015; Terkelsen et al., 2018
ACCEPT-follow-up	GRL	National	-	Longitudinal	2013-2020	Children Women	3-6 20-55	97 266	Wielsøe et al., 2022, 2024
BEA	ES	National	-	Cross sectional	2017-2018	Adolescents	13-17	300	-
BIOAMBIENT.ES	ES	National	-	Cross sectional	2009-2010	Adults	18-66	1892	Castaño et al., 2011; Pérez-Gómez et al., 2013
BOC-DNBC	DK	National	-	Cross sectional	2011	Pregnant women	20-42	412	Olsen et al., 2001; Bonefeld-Jørgensen et al., 2014
BOC-GRL	GRL	National	-	Cross sectional	2000-2014	Adults	18-81	245	Bonefeld-Jørgensen et al., 2011; Wielsøe, Gudmundsdottir and Bonefeld-Jørgensen, 2016; Wielsøe, Kern and Bonefeld-Jørgensen, 2017
CELSPAC: TE	CZ	Regional	South Moravia	Longitudinal	2019	Adolescents	11-17	332	Govarts et al., 2023
CELSPAC: YA	CZ	Regional	South Moravia	Longitudinal	2019	Adults	20-37	300	Piler et al., 2017; Sharma et al., 2025
CELSPAC-SPECIMEn	CZ	Regional	South Moravia	Cross sectional	2020	Children Adults	5-12 31-54	110 110	Ottenbros et al., 2023; Šulc et al., 2022; Vlaanderen et al., 2019
CROME	GR	Regional	Thessaloniki	Cross sectional	2020-2021	Children Adolescents Adults	6-11 12-18 19-69	161 150 258	Vogel et al., 2023; Gerofke et al., 2024; Bil et al., 2023; Gabriel et al., in prep
DEMOCOPHES-ES	ES	Regional	Toledo, Madrid	Cross sectional	2011-2012	Children Adults	6-11 26-48	120 120	Esteban López et al., 2015
DCS	NL	Regional	Doetinchem	Cross sectional	2018-2019	Adults	52-91	336	Picavet et al., 2017; Mengelers et al., 2024; McKeon et al., 2025
ESB	DE	Regional	Münster, Greifswald, Halle/Saale, Ulm	Cross sectional	2015-2022	Adults	20-29	2589	Kolossa-Gehring et al., 2012; Lermen et al., 2014; Lemke et al., 2021
ESTEBAN	FR	National	-	Cross sectional	2014-2016	Children Adolescents Adults	6-11 12-17 18-75	526 552 2478	Balicco et al., 2017; Fillol et al., 2021
EXHES-GR	GR	Regional	Thessaloniki	Longitudinal	2020-2023	Pregnant women Fathers	23-52	99 99	Errahmani et al., 2025; Sarigiannis et al., 2026
EXHES-ES	ES	Regional	Tarragona	Longitudinal	2018	Pregnant women	18-45	60	Martínez et al., 2020; Bocca et al., 2020
EuroMix	NO	Regional	Oslo, Akershus	Cross sectional	2016-2017	Adults	24-72	144	Husøy et al., 2023
FLEHS 1	BE	Regional	Flanders	Cross sectional	2002-2005	Newborns Adolescents Adults	0 13-16 49-65	1196 1679 1583	Schroijen et al., 2008; Den Hond et al., 2011; Sioen et al., 2013; Croes et al., 2015; Reynders et al., 2017; Schoeters et al., 2017; Govarts et al., 2020
FLEHS 2	BE	Regional	Flanders	Cross sectional	2008-2011	Newborns Mothers of newborns Adolescents Adolescents (HS G) Adolescents (HS M) Adults	0 18-42 13-16 13-16 13-17 21-40	255 255 210 197 199 204	Den Hond et al., 2009, 2013; Kiciński et al., 2012; Schoeters et al., 2012a, 2012b, 2017; Baeyens et al., 2014; Vrijens et al., 2014; Croes et al., 2014, 2015; Franken et al., 2014, 2017; Reynders et al., 2017; Colles et al., 2020; Govarts et al., 2020; Van Larebeke et al., 2023
FLEHS 3	BE	Regional	Flanders	Cross sectional	2013-2014	Newborns Mothers of newborns Adolescents Adolescents (HS GH)	0 18-44 13-16 13-16	281 281 208 200	Schoeters et al., 2012b, 2017; Reynders et al., 2017; Govarts et al., 2020; Colles et al., 2020; Van Larebeke et al., 2022, 2023

(*continued on next page*)

Table 3 (*continued*)

Study acronym	Country code	Level of representativity	Region	Study design	Sampling period (year)	Study population	Age range (years)	Sample size	Reference(s)
						Adults	49-65	209	
FLEHS 4	BE	Regional	Flanders	Cross sectional	2017-2018	Adolescents	13-16	428	Bastiaensen et al., 2021; Buekers et al., 2021; Verheyen et al., 2021; Schoeters et al., 2022
GerES V	DE	National	-	Cross sectional	2014-2017	Children Adolescents	3-11 12-18	956 1327	Murawski et al., 2020; Schulz et al., 2021
NEB II	NO	National	-	Longitudinal	2016-2017	Children	7-14	668	Paulsen et al., 2025
PIENTER-3	NL	National	-	Cross sectional	2016-2017	Children Adolescents Adults	0-11 12-17 18-87	106 127 1254	Bil et al., 2025b
POPUP	SE	National	-	Longitudinal	2015-2019	Children Women	4-12 22-48	59 203	Glynn et al., 2012; Gyllenhammar et al., 2015, 2025
SHeS-pp	CH	Regional	Vaud, Bern	Cross sectional	2020-2021	Adults	20-69	638	Bourqui et al., 2023; Jaus et al., 2025
SLO-CRP	SI	Regional	Mura	Cross sectional	2018	Children Adolescents	7-10 12-15	149 97	Stajnko et al., 2020
SLO-HBM I	SI	National	-	Cross sectional	2008-2014	Adults	18-49	617	Perharic and Vracko, 2012; Snoj Tratnik et al., 2019; Runkel et al., 2020; Joksić et al., 2022
SPECIMEn-NL	NL	Regional	-	Cross sectional	2020	Children Adults	6-11 30-56	102 105	Vlaanderen et al., 2019; Ottenbros et al., 2023
3xG	BE	Local	Dessel, Mol, Retie	Longitudinal	2011-2015 2019-2021 2011-2025	Newborns Children Pregnant women	0 6-8 23-44	301 212 301	Govarts et al., 2023
3M	BE	Regional	5 km radius of the 3M site in Zwijndrecht and neighboring municipalities	Cross sectional	2022	Adolescents	12-16	303	van Larebeke et al., 2025
Occupationally exposed individuals									
CELSPAC-FIREexpo	CZ	National	-	Cross sectional	2019-2020	Workers	18-35	165	Říhářková et al., 2023
Chromate	BE, FI, FR, IT, LU, NL, PL, PT, UK	-	-	Cross sectional	2018-2020	Workers Controls	31-43 34-54	399 203	Santonen et al., 2019, 2022
E-waste	BE, FI, LU, LV, NL, PL, PT, UK	-	-	Cross sectional	2021	Workers Controls	18-64 21-60	195 73	Scheepers et al., 2021; Cseresznye et al., 2024

Abbreviations: BE = Belgium; CH = Switzerland; CZ = Czech Republic; DE = Germany; DK = Denmark; ES = Spain; FI = Finland; GR = Greece; GRL = Greenland; HS G = hotspot study in Genk; HS GH = hotspot study Ghent Harbor; HS M = hotspot study in Menen; IT = Italy; LU = Luxembourg; LV = Latvia; NL = The Netherlands; NO = Norway; PL = Poland; PT = Portugal; SE = Sweden; SI = Slovenia; UK = United Kingdom

Table 4
Overview of the established case studies regarding the prioritised chemical mixture and adverse health effect in the PARC Real-life Mixtures project.

Chemical mixture and adverse health effect
Pesticides and neurotoxicity
PFAS and immunotoxicity
Metal(loid)s and nephrotoxicity
Metal(loid)s and developmental neurotoxicity

4.1. Choice of the chemical mixtures and adverse health effects

The prioritised mixtures and their selected adverse effects on human health were based on the PARC priority integrating stakeholder needs and data availability (e.g., exposure and hazard data). While the selection of specific substances is a necessary step to make MRA feasible and realistic, it may lead to an underestimation of the risk if other substances contributing to the same adverse health effect are excluded. In the current case studies, and in regulatory practice, mixtures are often composed of chemicals from the same chemical family to align with regulatory silos.

To better represent real-life mixtures, the prioritised mixtures can be expanded across regulatory silos by adding substances that share the relevant adverse effect and show co-exposure in populations (EFSA, 2021b; Crépet et al., 2022). An approach for defining mixtures is to use real-life co-exposure observations from HBM data. In that case, mixtures are defined based on the probability of co-exposures, and when possible, their relative contribution to combined risk. Statistical methods have been applied to identify these co-exposure patterns from HBM data, such as network analysis (Ottenbros et al., 2021; Rodriguez Martin et al., 2023; Loh et al., 2023) or sparse non-negative matrix under approximation (SNMU) (Gillis and Plemmons, 2013; Traoré et al., 2016, 2018; Crépet et al., 2019; Mancini et al., 2021; Crépet et al., 2022). This co-exposure-based approach will be applied in the next steps of the PARC Real-life Mixtures project to enlarge current mixtures with substances from other chemical families across regulatory silos. In recent years,

epidemiological studies (such as HELIX, ATHLETE and ELFE) have provided a growing body of evidence regarding the effects of real-life mixtures using advanced mixture modelling approaches (e.g., weighted quantile sum (WQS), Bayesian kernel machine regression (BKMR) and Exposome-wide association study (ExWAS)) (Vrijheid et al., 2014, 2021; Charles et al., 2020; Güil-Oumrait et al., 2024; Ghozal et al., 2024; Wang et al., 2026).

4.2. A component-based approach considering dose addition model

Two different ways of performing MRA are currently proposed by EFSA (EFSA, 2019b), whole mixture-based approaches and component-based approaches. In the whole mixture approach, the mixture is treated as a single entity. This requires dose-response information for the specific mixture or a sufficiently similar reference mixture using read-across or statistical methods. This approach has the advantage of directly capturing potential interactions between components (e.g., synergism, antagonism, potentiation) when they are present. It is particularly useful for well-characterised mixtures, with a stable composition over time, such as commercial formulations. The main limitation is that the results are specific to the assessed mixture, or to mixtures with very similar compositions. Consequently, they cannot be extrapolated to mixtures with different compositions and do not account for potential variations in effects and risks associated with varying ratios of the same components within a mixture.

Our proposed strategy is based on component-based approaches where the mixture is assessed by combining exposure and hazard data for its individual components (EFSA, 2013b, 2019b). These approaches are more flexible and allow application of MRA irrespective of mixture compositions. The mixture risk is predicted, under the dose addition model, by summing the exposures of all components present in the mixture, weighted by their toxic potential (van den Berg, Birnbaum and Bosveld, 1998). Scientific literature supports dose addition as the default model for MRA (Faust et al., 2001, 2003; Jonker et al., 2004; Junghans et al., 2006; Kortenkamp et al., 2009; Backhaus and Faust, 2012; EFSA, 2013b, 2013a; Altenburger et al., 2013; EFSA, 2019b; Martin et al., 2021; van der Ven et al., 2022; Kortenkamp et al., 2022), and is recommended by several scientific committees and regulatory bodies with risk assessment in their remit (WHO, IPCS, 2009; Meek et al., 2011; SCHER, SCCS and SCENIHR, 2012; EFSA, 2013b; Altenburger et al., 2013). Importantly, the dose addition model accurately estimates the combined effects of substances sharing similar MoA and remains protective when substances act independently, as it generally predicts higher combined risks than those obtained under the assumption of statistical independence (Faust et al., 2003).

Moreover, at relevant exposure levels (i.e., those around the NOAEL adjusted by uncertainty factors or at maximum residue limits (MRLs) for dietary exposure to pesticide residues), toxicologically relevant interactions (e.g., synergy) are considered uncommon (EFSA, 2019b). The dose addition model is therefore applicable at low levels of exposure, when information on the MoA or detailed dose-response relationships is lacking. Consequently, it has been widely applied in MRA based on both dietary exposure data (EFSA, 2020a; Sprong et al., 2023a, 2023b; EFSA, 2020c) and HBM data (Crépet et al., 2022; Kortenkamp et al., 2022; Engelhardt, Norström and Weiss, 2023; Willey et al., 2024).

4.3. Collection and harmonisation of HBM data for mixture risk assessment

The collection, organisation and harmonisation of HBM data constituted a central component of this work. However, the compiled datasets present important limitations, as the original studies were not designed for MRA and therefore do not always provide the information required for such analyses. First, the datasets were highly heterogeneous in terms of research objectives and study design, making comparisons of MRA results across studies challenging and often infeasible. Key sources of variability included sampling years, sample sizes, participants age groups, sampling matrices (e.g., morning, spot or 24-h urine; whole blood, plasma or serum), analytical methods (including analytical techniques and method sensitivity, such as limit of detection (LOD) and limit of quantification (LOQ)), and the specific biomarkers of exposure measured. In addition, the number of chemicals included in the mixtures varied substantially across datasets. For instance, in the PFAS and immunotoxicity case study, some datasets included all ten target PFAS, whereas others contained only two, leading to differences in mixture coverage and consequently in the estimated mixture risk.

Second, biomarkers of exposure and their associated biological matrices in the HBM studies were selected based on physicochemical, toxicokinetic and toxicodynamic properties according to criteria reviewed in HBM4EU (Vorkamp et al., 2021). Nevertheless, biomarkers were not always measured in the biological matrix most relevant for risk assessment, requiring assumptions and conversion factors that introduced uncertainty in the MRA. In certain cases, the optimal (or target) biomarker of exposure for a chemical is unknown or non-specific due to limited toxicokinetic information. Specifically, in the pesticides and neurotoxicity case study, the lack of specific biomarkers for pesticide exposure required assumptions to link measured biomarkers of exposure to individual parent compounds. In the absence of compound–specific toxicokinetic models, these assumptions introduce additional uncertainty into the exposure assessment. For instance, some pesticides (e.g., pyrethroids) are metabolised into several non-specific metabolites; therefore, the detection of a specific metabolite in urine does not allow unambiguous identification of the ingested parent compound. Assumptions were therefore required to back-calculate exposure to parent compounds, often utilising external information such as food residue data, which introduces significant uncertainty into the exposure assessment and consequently into the MRA.

Finally, to conduct MRA effectively, it is imperative to have individual-level measurements of several substances within the same subjects and ideally substances across regulatory silos. This allows correlations between exposures to be directly integrated into the calculations. However, in some HBM studies (e.g., ESTEBAN (France)) substances were measured in different subsets of the population rather than the whole study population, reducing the effective sample size for MRA analysis. Therefore, a future challenge is to define the optimal subdataset to be used to identify mixtures from the largest possible set of substances (Luijten et al., 2023).

The progress made in COPHES/DEMOCOPHES and HBM4EU to develop aligned HBM data across Europe is continuing in the framework of PARC. This will help address the above-mentioned issues and improve comparability of the datasets by applying a common protocol (PARC, 2025a). Overall, the harmonisation of individual HBM and accompanying data is essential to meet Findable, Accessible, Interoperable and Reusable (FAIR) principles and improve the comparability and reliability of MRA results.

4.4. Collection of hazard data and derivation of toxicological values

The reliability of MRA depends directly on the availability, quality, and relevance of hazard data. Incomplete or uncertain hazard data can lead to an under- or overestimation of cumulative risk. Applying a component-based approach requires collecting relevant toxicological values for each chemical in the mixture, associated with the selected common effect. When mixtures include many substances, this process is time and resource intensive. Therefore, there is an urgent need to gather available hazard information in databases following FAIR principles to facilitate access for risk assessors (Regulation (EU) 2025/2455, 2025). Key information includes target organs, effect types, MoA, and quantitative dose response functions to derive internal or/and external toxicological values. Traditionally, risk assessment compared exposure from a single source (e.g., diet) with an external HBGV (e.g., ADI or TDI). In general, HBGVs are established on a substance-by-substance basis and

are mainly derived from animal studies by applying appropriate uncertainty factors to a reference point (e.g., NOAEL or BMDL) for the critical effect. Recently, HBGVs were compiled in EFSA's OpenFoodTox database (Kovarich et al., 2022). This database could be expanded to include reference points as well as RPFs, where available, for additional effects, which is crucial when the common effect for MRA differs from the critical effect identified for individual substances. SCHEER recently recommended to make more extensive use of the Registration, Evaluation, Authorization and restriction of Chemicals (REACH) registration database (i.e., ECHA chemicals dataset) for derivation of RPFs for PFAS (SCHEER, 2025). This database includes publicly available study summaries and derived no-effect levels (DNEL). Publicly available information from the ECHA chemicals database and other sources (EFSA OpenFood, ToxRefDB, EXOTOX) has recently been combined and harmonised in the ToxValDB database developed by the US-EPA, that includes reference points, HBGVs, and media-specific exposure guidelines. The ToxValDB database is accessible, among other platforms, via Zenodo and the CompTox Chemicals Dashboard (Wall et al., 2025).

As the use of HBM data to perform risk assessment is relatively recent, the establishment and collection of internal toxicological values, such as HBM-GVs, is still at an early stage. In the HBM4EU project, HBM-GVs were derived for a set of prioritised substances (e.g., bisphenol A, cadmium, deltamethrin, cyfluthrin, phthalates) for the general population and/or workers. These values were established through a consultation process involving all partner countries to reach a broad scientific consensus (Apel et al., 2020, 2023; Lamkarkach et al., 2021; David et al., 2021; Lange et al., 2021; Ougier et al., 2021). Furthermore, the international Human Biomonitoring Working Group affiliated with the International Society of Exposure Science (ISES) has developed an open-access database[3] of HBM-GVs, including those derived from HBM4EU (Nakayama et al., 2023).

With specific regard to the RPF approach, it is considered a higher tier approach for MRA (van den Brand et al., 2022; Zilliacus et al., 2019). However, in some cases, the mRPI approach can be more applicable than the RPF approach, for instance when toxicity data for all components in the mixture are equally data-rich. That is, the mRPI approach integrates all toxicity studies and information available for each substance to derive an appropriate reference point, whereas the RPF approach there is a focus on a specific toxicity study design and endpoint (Bil et al., 2025a). Indeed, suitable toxicity information that allows for external or internal RPF derivation requires several stringent conditions to be met, including: 1) the same toxicological endpoint should be considered; 2) dose response curves should be parallel on a log-dose scale; 3) mixture components should not exhibit interactions such that dose addition applies; and 4) RPFs should be derived from experiments with (very) similar experimental setups to avoid or minimise confounding factors (Fournier et al., 2016, 2017; Bil et al., 2025a). Hence, effective application of the RPF approach requires data from studies conducted according to standardised test protocols. For instance, T-cell dependent-antibody response assays for PFAS, which are still considered the gold standard for assessing the effects of chemicals on humoral immunity, are lacking for most PFAS. The ones that are available could not be reliably used for RPF derivation because these studies used different test species and strains, exposure routes and durations, and sensitisation protocols, all of which influence potency estimates (Bil et al., 2023). In contrast, studies conducted according to standard test guidelines, such as Organisation for Economic Co-operation and Development (OECD) test guidelines or the National Toxicology Program (NTP) study protocols, are better suited for RPF derivation. As suggested by SCHEER (2025), studies performed within the context of (EU) chemical legislation such as REACH, where compliance with OECD test guidelines is commonly required, represent a potentially underutilised source of relevant information. However, such studies are owned by REACH registrants and are not freely available for use by third parties (Borchert, Beronius and Ågerstrand, 2022). PARC itself also plays a role by developing NAM and generating hazard data for groups of prioritised chemicals working under harmonised study protocols, which aid in filling data gaps related to MoA and toxicity *in vitro* and *in vivo* for substances such as bisphenols, PFAS, mycotoxins (Marx-Stoelting et al., 2023; PARC, 2024).

To address the absence of HBM-GVs in the pesticide case study, reverse dosimetry was applied to convert internal exposure levels into estimated external exposure (i.e., EDIs). Alternatively, forward dosimetry could have been used to translate external hazard data (e.g., NOAELs) into internal concentrations suitable for comparison with HBM data. Both approaches require toxicokinetic information for the parent chemicals and their (main) metabolites. However, this information was sparse for this case study. Very few PBK models for pesticides are available in the literature and data on the metabolic profile of pesticides are often incomplete or missing. Thus, equations based on the FUE and molecular weight of each substance were applied; however, due to the lack of FUE values for many compounds, assumptions had to be made, introducing additional uncertainty that may lead to either over- or underestimation of the risk. The development, harmonisation, and accessibility of kinetic information, such as FUEs and PBK models, is essential for performing robust MRA.

Although experimental studies have traditionally formed the basis for hazard characterisation, there is a clear shift toward integrating NAMs and robust human epidemiological evidence, particularly when internal exposure metrics and real-life mixture exposures are of interest (Marx-Stoelting et al., 2023). NAMs offer opportunities to refine hazard data and reduce reliance on animal testing; however, further validation and regulatory guidance are needed to support their consistent application in risk assessment (Cattaneo et al., 2023; Miccoli, Marx-Stoelting and Braeuning, 2022; Schmeisser et al., 2023; Corsini et al., 2024; Bearth et al., 2025). Complementing this methodological evolution, work on mixture-health effect modelling in the Real-life Mixtures project has demonstrated the feasibility of applying advanced multi-pollutant statistical methods to HBM data to quantify combined health effects of chemical mixtures and identify influential mixture constituents (Govarts et al., 2025; Zhang et al., 2026). In the next phase, applying these methods to pooled HBM data of the PARC Aligned studies, with harmonised questionnaires and effect biomarker data across cardio-metabolic, neurodevelopmental/neurological, renal, and immune/respiratory endpoints, will enable estimation of internal dose-response relationships under real-life exposure conditions, with explicit consideration of confounding by co-exposures and potential interactions. Such analyses can support the derivation of: 1) mixture-level guidance values using a whole-mixture approach, and 2) component-level metrics, including RPFs and internal reference points or HBM-GVs, depending on data availability and methodological feasibility. Advancing these applications will require further methodological development and regulatory dialogue to ensure alignment with risk assessment practices and decision-making needs, and may contribute to strengthening and extending existing guidance on the use of epidemiological data in risk assessment (EFSA, 2024a).

4.5. Regulatory acceptance and application

In June 2025, the European Parliament and the Council adopted the OS-OA legislative package. This initiative aims to align methodology and underlying information for risk assessments across different legislative frameworks and chemical domains, by consolidating relevant information within a common data platform on chemicals. Furthermore, the OS-OA approach mandates the systemic collection of HBM data generated within research and development programmes (EC, 2023). In response to this need, numerous partners involved in in the PARC Real-life Mixtures project organised individual-level data from their HBM studies on numerous substances, including metals, PFAS and pesticides in a harmonised manner. This effort resulted in a unique cross-

[3] https://www.intlexposurescience.org/i-hbm/

institutional, and interoperable collection of datasets with shielded raw data, providing wide coverage of chemical exposures across European countries/geographical regions, population groups, and time periods, and enabling analysis via the MCRA toolbox. These activities directly align with the European Commission's call to make HBM data 'as open as possible, as closed as necessary' (Council of the EU, 2024; Regulation (EU) 2025/2455, 2025). It is important to note that individual-level HBM data constitute personal data and are therefore subject to GDPR requirements. Accordingly, strict handling and processing is required, including bilateral data controller-data processor agreements. The HBM datasets were not pooled, but were processed solely by the respective data partners.

In current regulation frameworks, standard methods for performing single-substance and MRA predominantly rely on external exposure data derived from sources such as food consumption and dietary residues (EFSA, 2020b, 2020c, 2021a, 2022, 2024b). To verify the regulatory relevance of using internal exposure (i.e., HBM) for MRA, the proposed strategy should be applied to additional case studies beyond those proposed here (Palmont et al., 2026; Bil et al., submitted; Carsique et al., submitted; McVey et al., submitted) and results should continue to be compared with those obtained from dietary exposure assessment when applicable (EFSA, 2020a, 2020c; Sprong et al., 2023a, 2023b). The MRAs performed on HBM data can inform stakeholders on the health concern for a given population and identify the principal risk drivers (i.e., the substances contributing the most to the risk metric). However, unlike traditional dietary assessment, HBM-based MRA does not inherently provide information on exposure sources or routes. Therefore, internal (HBM-based) and external exposure-based approaches are complementary and must be developed in parallel. The identification of the main sources and routes of exposure for the risk drivers identified in these case studies is currently being addressed within the PARC Aggregate Exposure project (PARC, 2025b). Additionally, EFSA's ExpoAdvance roadmap enable integration and coherence between both approaches (Lamon et al., 2024). All these new developments are expected to further enhance the regulatory relevance of HBM-based MRA.

Finally, risk mitigation measures may ultimately be addressed through restriction measures. For instance, currently ECHA scientific committees (risk assessment committee (RAC) and socio-economic analysis committee (SEAC)) are evaluating a restriction proposal submitted by several Member States to restrict the use of PFAS as a chemical group. The outcomes of the PFAS case study strongly support restricting the use of this chemical group to limit further emissions into the environment and prevent prolonged human exposure.

5. Conclusion

This work demonstrates the feasibility and added value of performing MRA based on harmonised HBM data across Europe, and presents a structured and transparent strategy aligned with current scientific guidance and regulatory needs. By integrating exposure, hazard, and toxicokinetic information within a component-based MRA approach assuming dose addition, the proposed strategy offers a pragmatic and protective approach that is applicable to a wide range of real-life mixtures and adaptable to diverse data availability. Its application to four case studies within the PARC Real-life Mixtures project illustrates both the strengths of the approach and the key methodological challenges that must be addressed to support routine regulatory implementation. Overall, this research represents an important step toward the operationalisation of HBM-based MRA in Europe. Continued application to additional case studies, further methodological refinement, improved data systems, and sustained interaction between scientists and regulators will be necessary to consolidate regulatory acceptance and to fully realise the potential of this approach for protecting human health from exposure to chemical mixtures.

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For this manuscript, ethics committee approval was not required under relevant laws and institutional guidelines. The human biomonitoring data partners/ co-authors provided human biomonitoring metadata provided from multiple (already published) studies. The reference of each human biomonitoring study is available in the manuscript, where study-specific ethical considerations can be found. For the purposes of this manuscript, for each human biomonitoring study, a Data Controller-Data Processor agreement for the use of the HBM data in the MCRA software was signed.

CRediT authorship contribution statement

Amélie Crépet: Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. **Hannah McKeon:** Writing – review & editing, Writing – original draft, Visualization, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Karine Angeli:** Writing – review & editing, Methodology. **Wieneke Bil:** Writing – review & editing, Methodology, Conceptualization. **Bianca Cox:** Writing – review & editing, Methodology, Data curation. **Eva Govarts:** Writing – review & editing, Methodology, Data curation. **Emily McVey:** Writing – review & editing, Methodology, Conceptualization. **Philippe Palmont:** Writing – review & editing, Methodology, Conceptualization. **Nanette Vrijenhoek:** Writing – review & editing, Methodology. **Johannes Kruisselbrink:** Writing – review & editing, Software. **Eva Cecilie Bonefeld-Jørgensen:** Writing – review & editing, Data curation. **Pavel Čupr:** Writing – review & editing, Data curation. **Deepika Deepika:** Writing – review & editing, Data curation. **Marta Esteban-López:** Writing – review & editing, Data curation. **Clémence Fillol:** Writing – review & editing, Data curation. **Céline Fragnière Rime:** Writing – review & editing, Data curation. **Catherine Gabriel:** Writing – review & editing, Data curation. **Sergio González-Ruiz:** Writing – review & editing, Data curation. **Trine Husøy:** Writing – review & editing, Data curation. **Tomáš Janoš:** Writing – review & editing, Data curation. **Spyros Karakitsios:** Writing – review & editing, Data curation. **Jana Klánová:** Writing – review & editing, Data curation. **Helle Katrine Knutsen:** Writing – review & editing, Data curation. **Klára Komprdová:** Writing – review & editing, Data curation. **Vikas Kumar:** Writing – review & editing, Data curation. **Manhai Long:** Writing – review & editing, Data curation. **Ruth Moeller:** Writing – review & editing, Data curation. **Nina Pálešová:** Writing – review & editing, Data curation. **Nafsika Papaioannou:** Writing – review & editing, Data curation. **Anja Remškar:** Writing – review & editing, Data curation. **Tiina Santonen:** Writing – review & editing, Data curation. **Dimosthenis Sarigiannis:** Writing – review & editing, Data curation. **Phillipp Schmidt:** Writing – review & editing, Data curation. **Line Småstuen Haug:** Writing – review & editing, Data curation. **Janja Snoj Tratnik:** Writing – review & editing, Data curation. **Maria Torres Toda:** Writing – review & editing, Data curation. **Nina Vogel:** Writing – review & editing, Data curation. **Carolina Vogs:** Writing – review & editing, Data curation. **Natalie von Goetz:** . **Maria Wielsøe:** Writing – review & editing, Data curation.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Ethics declaration

Informed consent and patient details

Written informed consent to take part in the human biomonitoring studies has been obtained from all participants. Consent to publish this manuscript has been obtained from the human biomonitoring study representatives. The privacy rights of participants have been observed.

Studies in Human

The human biomonitoring studies were performed in compliance with relevant laws, regulatory frameworks and guidelines where the research took place.

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Other activities

Given his role as Editor for this journal, Dr Spyros Karakitsios had no involvement in the peer review of this article and had no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to another journal editor.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2026.110560.

Data availability

The authors do not have permission to share data.

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