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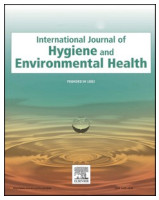

A case study of neurodevelopmental risks from combined exposures to lead, methyl-mercury, inorganic arsenic, polychlorinated biphenyls, polybrominated diphenyl ethers and fluoride

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ABSTRACT

We performed a mixture risk assessment (MRA) case study of dietary exposure to the food contaminants lead, methylmercury, inorganic arsenic (iAs), fluoride, non-dioxin-like polychlorinated biphenyls (NDL-PCBs) and polybrominated diphenyl ethers (PBDEs), all substances associated with declines in cognitive abilities measured as IQ loss. Most of these chemicals are frequently measured in human biomonitoring studies. A component-based, personalised modified reference point index (mRPI) approach, in which we expressed the exposures and potencies of our chosen substances as lead equivalent values, was applied to perform a MRA for dietary exposures. We conducted the assessment for four different age groups (toddlers, children, adolescents, and women aged 18–45 years) in nine European countries. Populations in all countries considered exceeded combined tolerable levels at median exposure levels. NDL-PCBs in fish, other seafood and dairy, lead in grains and fruits, methylmercury in fish and other seafoods, and fluoride in water contributed most to the combined exposure. We identified uncertainties for the likelihood of co-exposure, assessment group membership, endpoint-specific reference values (ESRVs) based on epidemiological (lead, methylmercury, iAs, fluoride and NDL-PCBs) and animal data (PBDE), and exposure data. Those uncertainties lead to a complex pattern of under- and overestimations, which would require probabilistic modelling based on expert knowledge elicitation for integration of the identified uncertainties into an overall uncertainty estimate. In addition, the identified uncertainties could be used to refine future MRA for cognitive decline.

Abbreviations: ESRVs, endpoint-specific reference values; iAs, inorganic arsenic; IQ, intelligence quotients; LB, lower bound; LOD, level of detection; LOQ, level of quantification; metHg, methyl mercury; MRA, mixture risk assessment; mRPI, modified reference point index; NDL-PCBs, non-dioxin-like polychlorinated biphenyls; PBDEs, polybrominated diphenyl ethers; POD, point of departure; SF, scaling factor; UB, upper bound; UF, uncertainty factor.

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1. Introduction

Populations are exposed to unintentional mixtures of chemicals via their diet, drinking water, inhaled air, dust or contact with consumer products. Until recently, the risks of chemicals to human populations were frequently assessed on a chemical-by-chemical basis and for single exposure routes only. However, increasing awareness of the potential risks from mixtures shifted the focus towards combined exposures to multiple chemicals and routes. Depending on the regulatory framework or region, different terminologies are used, such as cumulative risk assessment (e.g. used by the European Food Safety Authority, EFSA, for combined exposure to pesticides, EFSA 2020a; b, 2022), cumulative impact assessment (e.g. United States Environmental Protection Agency; US EPA, 2022) or mixture risk assessment (MRA). Such an assessment can focus on the combined exposure to chemicals only (e.g. pesticides; EFSA 2020a; b, 2022) or include non-chemical stressors (e.g., social determinants as in US-EPA cumulative impact assessment; US EPA, 2022) In this paper, we will focus on the combined exposure to chemicals only and use the wording MRA.

Considerable efforts have gone into developing concepts, methods, and guidance for MRA ((e.g. Boobis et al., 2008; EFSA, 2007, 2008, 2019, 2021a; Fox et al., 2017; WHO, 2008; Bopp et al., 2018; OECD, 2018). To harmonise MRA within the European Union, EFSA developed two pieces of guidance for human risk assessment of combined exposure to multiple chemicals (EFSA 2019, 2021a). In the 2019 report, EFSA elaborated a tiered approach for several aspects of mixture risk assessment across EFSA's domains (EFSA 2019). The EFSA 2021 report developed criteria for the grouping of chemicals for MRA (EFSA 2021a). Mechanistic information (common mode of action or adverse outcome pathway) through a structured weight of evidence approach is regarded as the gold standard. When such mechanistic data are not readily available, EFSA proposes that grouping may be performed using a common adverse outcome (phenomenon) or a common target organ/-system. EFSA used these grouping principles for dietary exposures to pesticides and proposed common assessment groups derived for chronic effects on the thyroid and for those that have acute effects on the nervous system (EFSA, 2020a; EFSA, 2020b, EFSA et al., 2022).

Biomonitoring studies have shown that humans are exposed to mixtures of contaminants from different chemical classes, such as heavy metals and persistent organic pollutants (Haug et al., 2018; Buekers et al., 2021; Julvez et al., 2021). Despite these findings, MRA is often limited to groups of structurally related contaminants, such as dioxins and dioxin-like polychlorinated biphenyls (PCBs), phthalates or polyfluorinated alkyl substances. We therefore became interested in making a leap to a MRA for chemicals that transcend groups of closely related substances and that would facilitate future scientifically based risk management decisions.

In this paper, we present the results of a MRA case study of developmental neurotoxicants in food in which we applied the EFSA approach to assess possible risks of reduced cognitive function in children. Applying this approach to external dietary exposure allows for identification of risk-driving chemical substance combinations. We focused on chemicals with a high occurrence in human biomonitoring matrices of approximately 1300 English, French, Spanish, Lithuanian, Norwegian and Greek mothers and children of the Early-Life Exposome (HELIX) cohorts, and associations with IQ loss in children after maternal or early childhood exposures, as identified by Grandjean and Landrigan (2006, 2014). Accordingly, we selected the food contaminants lead, methyl mercury, inorganic arsenic, non-dioxin-like polychlorinated biphenyls (NDL-PCBs), and polybrominated diphenyl ethers (PBDEs). Fluoride was added to this list because recent evidence suggests it also may affect cognitive development (Grandjean 2019, 2022). In some European countries, fluoride is added to drinking water (EFSA, 2013). The aim of the paper is 1) to investigate the feasibility of MRA for chemicals from different classes that are associated with IQ loss and 2) to identify challenges and major uncertainties in the input data. The results should not be regarded as formal national risk assessments.

2. Methods

2.1. Cumulative assessment group

Food contaminants were included in the assessment group based on the following criteria:

1. A high occurrence rate in human biomonitoring matrices of approximately 1300 English, French, Spanish, Lithuanian, Norwegian and Greek mothers and children of HELIX cohorts, defined as quantifiable in >50% of blood and urine samples, as shown by Haug et al. (2018). Polychlorinated organic pollutants, brominated flame retardants, per- and polyfluoroalkyl substances, heavy metals, phthalate metabolites, phenols, and organophosphates met this criterion.
2. Evidence of associations with cognitive declines, measured as IQ loss as identified by Grandjean and Landrigan (2006, 2014). Lead, methyl mercury, inorganic arsenic, PCBs, PBDEs and organophosphate pesticides fulfilled this criterion. Although not measured in the study of Haug et al. (2018), fluoride was included because high intake levels are associated with IQ loss (Grandjean 2019, 2022).
3. Sufficient data to derive a point of departure (POD) and an endpoint-specific reference value (ESRV) from epidemiological studies. This criterion was met by lead and methyl mercury as their health-based guidance value is based on IQ loss (EFSA 2010a; US EPA 2001). ESRV for PBDEs are extrapolated from developmental neurotoxicity (locomotion and total activity) in rodents. The available epidemiological data for PCBs, inorganic arsenic and fluoride allowed estimations of POD and ESRV, but the data basis for organophosphates was judged to be insufficient. They were therefore not included in the present assessment. Accordingly, the cumulative assessment group for this study was composed of lead, methyl mercury, inorganic arsenic, PCBs, fluoride and PBDEs.

2.2. Estimation of PODs and ESRVs

For all the substances included in the assessment group, we collated quantitative dose estimates for declines in IQ scores and related ESRV for developmental neurotoxicity. The ESRV is defined as the POD of the substance divided by its uncertainty factor (UF) and is used to calculate external exposure. As much as possible, ESRVs were retrieved from existing evaluations of competent authorities (lead, methyl mercury, PBDE). In some cases, however, it was necessary to conduct separate reviews to derive the respective ESRV *de novo* (fluoride, inorganic arsenic). To make the mixture risk assessment as consistent as possible, we attempted to relate all ESRVs to the same effect magnitude, IQ losses by 1 point. However, some studies derived exposures associated with 5-point IQ losses. In such cases, we extrapolated to a 1-point loss. In addition, for some substances an additional UF was applied to take other uncertainties into account.

Table 1 provides an overview of the data used for the derivation of ESRVs. For each substance, details of the derivation of the ESRV are provided below. It should be noted that these ERSVs, unless they are health-based guidance values (e.g. lead), do not have the normative character of such values and should only be used for the purpose of a MRA. Except for iAs, the ESRVs were derived for expected mothers. The same ESRVs were used for all age groups, regardless they were derived from mothers or children.

2.3. Lead

We followed the considerations of EFSA's CONTAM panel (EFSA 2010a). Based on the study by Lanphear et al. (2005) the Panel estimated that a blood lead level of 12 μg/L in children aged 5–10 years old

Table 1
Chemicals in the assessment group, their endpoint-specific reference value (ESRV) used for the scaling factor (SF) calculation and data used for the derivation of the reference dose.

Chemical	Effect	IQ test	Reference point	Sex	Reference type	Species	Conversion to intake dose	Uncertainty factor	ESRV	SF
Lead[a]	IQ loss in children (0–7 years) of exposed mother	FSIQ	1 point IQ loss related to 12 μg/L Pb in blood	Boys and girls	$BMDL_{01}$	Human	Expectant mothers: foetal/maternal Pb blood ratio ~ 0.9	–	0.54 μg/kg bw/d	1
Inorganic arsenic[b]	IQ loss in exposed children, contemporaneous exposure	Raw verbal IQ	2.6 points IQ loss in girls for every 100 μg/L urine	Girls	LOAEL	Human	Conversion to 1 IQ point by linear extrapolation	–	1.3 μg/kg bw/d	0.42
Methyl mercury[c]	IQ loss in children of exposed mothers	Several cognitive test, including FISQ	5 points IQ loss related to 4–25 ppm in maternal hair	Boys and girls	$BMDL_{05}$	Human	Via estimation of blood levels, then kinetic modelling and extrapolation	10	0.1 μg/kg bw/d	5.4
Fluoride[d]	IQ loss in children of exposed mothers	General cognitive index, FSIQ.	0.1–0.2 mg/L urine	Boys and girls	$BMDL_{01}$	Human	With Rugg-Gunn et al., 2011; daily excretion of F at BMDL = 0.1–0.4 mg/d; equivalent to 2.4–12 μg/kg	–	9 μg/kg bw/d	0.06
NDL-PCBs[e]	IQ loss in children of exposed mothers	FSIQ	5 points IQ loss related to 0.63–0.71 μg/g lipid in mother's milk	Boys and girls	$BMDL_{05}$	Human	Via estimation of body burden, kinetic model Factor 2 applied for conversion from 5 to 1 IQ point loss.	2	15 ng/kg bw/d	36
PBDE[f]	developmental neurotoxicity (locomotor, total activity)	–	PBDE-47: 309 μg/kg bw		$BMDL_{10}$	Mice	Via critical body burden in mice and humans to an external dose taking into account kinetic information, except for PBDE 209 since toxicokinetics are assumed to be similar in mice and man[f]. For PBDE-209 the external dose in mice was extrapolated to humans.	PBDE-47: 2.5	PBDE-47: 68.8 ng/kg bw/d	PBDE-47: 7.9
			PBDE-99:12 μg/kg bw/d					PBDE-99: 2.5	PBDE-99:1.68 ng/kg bw/d	PBDE-99: 318
			PBDE-153: 83 μg/kg bw/d					PBDE-153: 2.5	PBDE-153: 3.84 ng/kg bw/d	PBDE-153: 142
			PBDE-209: 1700 μg/kg bw/d					PBDE-209: 100	PBDE-209: 17 μg/kg bw/d	PBDE-209: 0.032

See section 2.2 for explanation. Abbreviations: IQ intelligence quotient; FSIQ full scale intelligence quotient; BMDL Benchmark dose lower limit; LOAEL lowers observed adverse effect level; Pb-lead; F-fluoride; NDL-PCBs non-dioxin-like PCBs; PBDE polybrominated diphenyl ethers; kg kilogram; d day.

[a] Data were retrieved from EFSA (2010a) and were based on Lanphear et al. (2005).
[b] Data were retrieved form Tsuji et al. (2015) and based on Hamadani et al. (2011).
[c] Data were retrieved from Rice et al. (2003).
[d] Data were retrieved from Grandjean (2019).
[e] Data were retrieved from EFSA (2005) and based on Jacobson et al. (2002).
[f] Data were retrieved from EFSA (2011a) and Martin et al. (2017).

Table 2
Description of the food consumption data of nine different European countries, including method of food consumption survey, year(s) in which the food consumption survey was conducted, the name of the survey, the population addressed, the total number of individuals and consumptions days included in the study, and the subpopulation groups and number of individuals included in the cumulative exposure assessment for chemicals relevant for IQ loss.

Country	Food consumption survey						Subpopulation in study	
	Method	Years	Name	Population[a] (years of age)	N total[b]	Consumption days	Subpopulation[c] (years of age)	N[d]
Austria (AT)	24-h dietary recall	2018	ADOLESCENTS-2018-2	10–17	657	2	10–17	657
		2016		18–64	2250	2	F 18-45	1013
		2018	NATIONAL-2016 PREGNANT-2018-2	Pregnant F 19-47	302	2	19–45	299
Croatia (HR)	24-h and 48-h dietary recall	2011–2012	NIPNOP-HAH-2011-2012	18–64	2002	3	F 18-45	629
Cyprus (CY)	24-h dietary recall	2014–2017	2014-2017-LOT1	0–9	848	3	1–2	279
			2014-2017-LOT2	10–76	1016	3	3–9	300
							10–17	274
							F 15-45	287
Czech Republic (CZ)	24-h dietary recall	2003–2004	SISP04	4–64	2353	2	4–9	389
							10–17	298
							F 15-45	419
Denmark (DK)	Food record	2006–2007	IAT 2006-07	0–3	1743	7	1–2	894
		2005–2008	DANSDA 2005-08	4–75	2700	7	3	23
							4–9	298
							10–17	377
							F: 18-45	570
France (FR)	FPQ[e] and 24 h dietary recall	2014–2015	INCA3	General population[f]	4874	3	Toddlers[f]	149
							Other children	921
							Adolescents	1221
Italy (IT)	Food record	2005–2006	INRAN SCAI 2005-06	0–97	3323	3	1–2	36
							3–9	193
							10–17	247
							F 15-45	703
Netherlands (NL)	Food record, 24 h dietary recall	2012–2016	FCS2016_Core	1–80	4313	2	1–2	440
							3–9	853
							10–17	870
							F 18-45	485
Slovenia (SI)	24 h dietary recall	2018	SI.MENU-2018	0.25–75	1981	2	1–2	344
							10–17	493
							F18-45	113

[a] Indicates the age range of the population included in the food consumption survey.
[b] Indicates the number of subjects included in the food consumption survey.
[c] Indicates the age range of the subpopulation included in the case study: toddlers (1–2 years of age), other children (3–9 years of age), adolescents (10–17 years of age) or women in their childbearing age 18–45 years). Unless otherwise stated, the subpopulation included males and females. F means females.
[d] Indicates the number of subjects included per subpopulation in the case study.
[e] FPQ: Food propensity questionnaire.
[f] Due to privacy reasons the French food consumption data contained age groups instead of individual ages.

is associated with an IQ loss of 1 point. By toxicokinetic modelling, EFSA converted this blood lead level into a daily intake of 0.5 μg/kg. Taking account of a foetal/maternal blood lead ratio of 0.9, this is equivalent to a daily intake of 0.54 μg/kg d by expectant mothers, which was used as ESRV in our study. No uncertainty factors were applied.

2.4. Methyl mercury

For our case study, we used the ESRV derived for methyl mercury as described by Rice et al. (2003). Evidence of declines in cognitive ability after maternal methyl mercury exposure during pregnancy comes from three main epidemiological cohorts, those in the Faroe Islands, New Zealand and the Seychelles. Reviewing data from these three cohorts, Rice et al. (2003) used benchmark dose modelling for in-utero exposure for all cognitive effects, including IQ scores of the Faroes cohort and estimated that maternal hair mercury levels of between 4 and 25 ppm are associated with IQ losses by 5 points in their children. Toxicokinetic modelling assuming a hair to blood ratio of 250 and a one compartment model assuming 1) 95% of oral methyl mercury being absorbed, 2) 5.9% of absorbed methyl mercury present in blood, 3) a blood volume of 5 L, 4) an elimination rate of 0.014 day^{-1}, and 5) a fixed body weight of 67 kg for pregnant women (Rice et al., 2003; US EPA 2001) revealed that these hair levels resulted from maternal daily methyl mercury intakes of between 0.447 and 1.9 μg/kg d. It should be noted that this approach assumes a ratio of 1:1 between maternal and cord blood (Rice et al., 2003). By application of an UF of 10 (to account for differences in maternal toxicokinetics and -dynamics), Rice et al. estimated a daily intake of 0.1 μg/kg d as tolerable. We employed this value in our case study. However, it is unclear whether the UF of 10 also caters for an extrapolation to exposures associated with 1 IQ point loss.

2.5. iAs

We adopted the values used by Tsuji et al. (2015) in their systematic review of arsenic-induced developmental neurotoxicity and risk assessment. Tsuji et al. evaluated several epidemiological studies that described associations between inorganic arsenic exposure and verbal IQ scores and rated the data from the Matlab cohort (Bangladesh) communicated by Hamadani et al. (2011) as most suitable for quantitative risk assessments. Hamadani et al. observed a decrease in cognitive ability by 2.6 IQ points in girls for every 100 μg/L increase in speciated urinary arsenic levels. This was related to contemporaneous arsenic exposures; a window of vulnerability for inorganic arsenic and developmental neurotoxicity is poorly defined. Conversion to an IQ loss by 1 point is associated with an increase by 38.5 μg/L speciated urinary arsenic levels. By application of a one-compartment toxicokinetic model, and assuming a urinary excretion rate of 0.4 L/day, 70–90% of oral dose excreted in urine (estimated from monkeys), and a body

weight of 14.9 kg (mean of Matlab cohort) Tsuji et al. (2015) estimated that such urinary arsenic levels result from daily intakes of between 1.1 and 1.47 μg/kg d. We selected the midpoint of this range (1.3 μg/kg d) as ESRV in our study. No UF was applied because the POD was based on human data.

2.6. Fluoride

Grandjean et al. (2022) recently presented a benchmark modelling for IQ losses associated with fluoride exposures in which they used data from two prospective birth cohort studies, the Early Life Exposures in Mexico to Environmental Toxicants (ELEMENT) cohort in Mexico and the Maternal-Infant Research on Environmental Chemicals (MIREC) cohort in Canada. Assuming a benchmark response of 1 IQ point loss, they derived benchmark concentrations (BMCs) of maternal urinary fluoride and benchmark concentration levels (BMCLs). The BMC for maternal urinary fluoride associated with a 1-point decrease in IQ scores of preschool-aged boys and girls was 0.31 mg/L (BMCL, 0.19 mg/L). The BMD was 0.33 mg/L (BMCL 0.20 mg/L) when pooling the IQ scores from the older ELEMENT children and the MIREC cohort. From these two prospective studies the joint data showed BMCL results about 0.2 mg/L.

Assuming a 24 h urine volume of 1.5 L, this urinary fluoride levels would lead to a daily maternal fluoride excretion of 0.3 mg/d. Rugg--Gunn et al. (2011) have recorded the relationship between total fluoride intake and daily urinary fluoride excretion. Based on 8 studies among adults with a total of 269 data pairs (Fig 3 in Rugg-Gunn et al., 2011) it can be estimated that a daily excretion of 0.3 mg fluoride is to be expected with daily intakes of 0.6 mg. Assuming a body weight of 65 kg, this converts to an intake of 9 μg/kg d which we adopted as ESRV in our study. No UFs were applied.

2.7. NDL-PCBs

From the study of IQ loss in children of PCB-exposed mothers by Jacobson et al. (2002), a benchmark concentration of 0.63–0.71 μg/g lipid in mother's milk is associated with a benchmark response of 5% in terms of full-scale IQ loss (benchmark dose, lower limit, see Table 3 in Jacobson et al.). This value applies to all PCBs. To estimate daily intakes from PCB lipid levels, we followed the assumptions made in EFSA (2005): Adipose tissue constitutes 20% of an adult's body weight, the overall biological half-life of the most persistent PCB congeners is 10 years (3650 days) and the absorbed fraction is 0.9. Based on these assumptions, the daily PCB maternal intakes that will give rise to such PCB lipid levels at steady state can be estimated as 26–30 ng/kg d. For this, the following formula was used: intake [ug/kg/d] = serum lipid level [ug/kg lipid] * 0.138/T1/2 [d]/f, where T1/2 is half-life of excretion, 0.138 a composite of ln 2 and 0.2, and f the absorbed fraction.

Considering that the benchmark concentrations given by Jacobson et al. do not correspond to IQ losses of 1 point, we lowered these values and chose 15 ng/kg d as the ESRV in our study by applying an UF of 2.

PCBs can be split into 12 dioxin-like congeners (DL-PCBS) and 197 NDL-PCBs. We included only NDL-PCBs in our case study for two reasons: 1) According to EFSA, information on neurodevelopmental effects of DL-PCBs is too limited for risk assessment (EFSA 2018) and 2) human body burden in of PCBs in human biomonitoring is frequently assessed based on the sum of three indicator congeners PCB-138, -153 and 180, multiplied by two for inclusion of three additional PCB congeners −28, −52 and −101 (Kraft et al., 2017), which are all NDL-PCBs (EFSA 2005; JECFA 2016).

2.8. PBDEs

We adopted the congener-specific values for PBDE 47, 99, 153 and 209 which EFSA (2011a) used for margin of exposure considerations related to developmental neurotoxicity, applying an UF of 2.5 to PBDE-47, -99 and −153 to account for inter-species difference in toxicodynamics. For PBDE-209 an UF of 100 was applied (Martin et al., 2017). EFSA regarded the available data for other congeners as too unreliable to establish similar values. Therefore, those congeners were not included in the case study. The ESRVs for these PBDE congeners are: PBDE 47–68.8; PBDE 99–1.68; PBDE 153–3.84; PBDE 209–17,000 ng/kg d.

It is noted that these values are derived from motor activity effects observed in a developmental neurotoxicity study in rodents. There is no information how these would relate to IQ loss in humans. However, for the purpose of the present exercise these values were taken as the doses that would lead to 1 IQ point loss in humans.

2.9. Scaling factors

To be able to sum exposures, scaling factors (SF) were used to describe the toxicity of a substance *s* in terms of the toxicity of an index compound and can be used to combine exposures of substances in an assessment group. The SF of substances included in our case study was obtained by dividing the ESRV of lead (Pb) by that of the substance of interest by using the following equation:

$$SF_s = \frac{ESRV_{Pb}}{ESRV_s} \quad \text{(Equation 1)}$$

It should be noted that the scaling factor by definition differs from a relative potency factor (RPF), which is also used to describe the toxicity of a substance s in terms of the toxicity of an index compound to enable combining exposures of substances in an assessment group. Scaling factors can only be called RPFs if chemicals 1) act via a common mode of action; 2) differ only in potency (i.e., their individual dose–response curves should be parallel on log–dose scale), and 3) do not interact (Bosgra et al., 2009; EFSA 2019; Bil et al., 2021). Since this information is lacking for the substances in our case study, we used scaling factors.

2.10. Food consumption data

Food consumption data were obtained from the EFSA data warehouse[1] upon approval of data owners. Consumption data were obtained from nine European Member States and were derived from national food consumption surveys. Table 2 provides an overview of the characteristics of the food consumption data use in this study. Food consumption data were received using the non-hierarchical coding of the harmonized food coding system FoodEx1 (EFSA 2011b) and re-coded in the hierarchical FoodEx1 codes to allow for extrapolation of concentration data.

In their assessments for regulatory purposes, EFSA subdivided the population into age groups, i.e. infants, toddlers, other children, adolescents, adults, elderly and very elderly (EFSA 2011c). In our study, we mirrored the EFSA age groups for children and adolescents as close as possible (i.e. toddlers aged 1–2 years, other children aged 3–9 years, adolescents aged 10–17 years), but selected women aged 18–45 years as proxy for pregnant women. Infants (below the age of 12 months) were not included because the limited availability of food consumption data for this age group among the countries.

2.11. Chemical concentration data in food

Chemical concentration data from the years 2014–2018 were obtained for NDL-PCBs, PBDEs, lead, inorganic arsenic, methyl mercury, and fluoride from the ESFA data warehouse. Data were obtained from 15 European Member States that agreed to share data: Austria, Cyprus, the Czech Republic, Denmark, Estonia, Finland, France, Croatia, Hungary, Ireland, Italy, Luxembourg, the Netherlands, Sweden and Slovenia. Data were formatted according to EFSA standard sample descriptions (SSD1; EFSA 2010b), with food items coded according to the harmonized

[1] https://www.efsa.europa.eu/en/microstrategy/food-consumption-survey.

Table 3
Personalised modified reference point index) for substances relevant to loss of intelligence scores (lead, methyl mercury, inorganic arsenic, fluoride, non-dioxin-like polychlorinated biphenyls and polybrominated diphenyl ethers) calculated for toddlers (1–2 years), children aged 3–9 years, adolescents (10–17 years) and women in their childbearing age (18–45 years).

	Toddlers		Other children		Adolescents		Women child bearing age	
	LB[b]	UB[c]	LB	UB	LB	UB	LB	UB
P50								
AT[a]	–	–	–	–	1.6 (1.5–1.8)[f]	2.9 (2.7–3.2)	2.0 (1.8–2.1)	3.5 (3.2–3.8)
CY	4.7 (4.3–5.3)	9.2 (8.6–9.8)	3.3 (3.0–3.7)	6.3 (5.9–6.9)	1.8 (1.6–2.0)	3.4 (3.1–3.8)	1.5 (1.3–1.7)	2.6 (2.6–3.2)
CZ	–	–	3.6 (3.0–3.6)	6.0 (5.6–6.4)	2.3 (2.1–2.5)	4.1 (3.8–4.4)	1.6 (1.4–1.7)	2.7 (2.5–3.0)
DK	5.4 (4.8–6.0)	9.7 (9.2–10.5)	3.7[d] (3.2–4.0) 4.3[d] (3.2–6.7)	6.9[e] (6.4–7.5) 7.8[e] (6.8–10)	1.9 (1.7–2.2)	3.6 (3.3–3.9)	2.0 (1.8–2.1)	3.4 (3.2–3.7)
FR	4.5 (3.8–5.4)	9.0 (7.8–10.5)	4.2 (3.7–4.7)	7.3 (6.8–7.8)	2.1 (1.8–2.3)	3.7 (3.4–4.1)	–	–
HR	–	–	–	–	–	–	1.4 (1.2–1.5)	2.7 (2.5–3.0)
IT	7.6 (4.1–11)	12 (8.6–16)	4.7 (4.2–5.6)	8.2 (7.2–9.2)	2.7 (2.3–3.1)	4.7 (4.1–5.2)	2.3 (2.0–2.6)	4.0 (3.6–4.7)
NL	4.1 (3.5–5.1)	8.3 (7.4–9.4)	2.6 (2.4–2.9)	5.4 (5.2–5.9)	1.6 (1.4–1.8)	3.2 (3.0–3.5)	1.5 (1.4–1.7)	2.9 (2.6–3.2)
SI	3.4 (3.1–3.8)	7.1 (6.6–7.6)	–	–	1.5 (1.3–1.6)	2.8 (2.5–3.0)	1.3 (1.1–1.5)	2.5 (2.1–2.8)
P95								
AT	–	–	–	–	4.4 (3.5–5.7)	6.5 (5.8–7.7)	6.0 (4.7–7.6)	7.8 (6.8–9.5)
CY	15 (11–18)	21 (17–25)	11 (9.0–14)	15 (13–20)	6.4 (5.8–8.2)	8.8 (7.9–9.9)	6.5 (5.3–9.4)	8.6 (7.3–11)
CZ	–	–	15 (12–20)	20 (15.4–23.2)	11 (8.1–14)	13.1 (9.9–16.6)	7.9 (6.7–9.9)	9.7 (8.2–12)
DK	21 (18–26)	27 (23–31)	13[d] (9.9–16) 14[d] (9.3–20)	17[e] (14–21) 18[e] (12–25)	5.1 (4.0–6.8)	7.3 (6.3–9.1)	5.0 (4.3–6.1)	7.1 (6.5–8.0)
FR	14 (11–21)	20 (16–29)	13 (11–17)	18 (15–22)	6.8 (5.8–8.4)	9.5 (8.5–11)	–	–
HR	–	–	–	–	–	–	5.0 (4.2–6.3)	6.9 (6.0–8.4)
IT	17 (12–23)	24 (19–31)	14 (11–17)	18 (15–22)	9.7 (8.4–12.9)	12 (10.0–15.3)	10 (8.1–13)	12 (10–15)
NL	11 (8.6–14)	16 (14–19)	8.8 (6.8–10)	12 (11–15)	5.0 (4.0–6.4)	7.2 (6.2–8.8)	5.6 (4.5–7.3)	7.4 (6.3–9.5)
SI	11 (8.5–15)	15 (13–20)	–	–	6.9 (5.5–9.4)	8.5 (7.3–11)	6.7 (4.4–12)	8.0 (6.0–14)

[a] AT-Austria, CY-Cyprus, CZ-Czech Republic, DK-Denmark, FR-France, HR-Croatia, IT-Italy, NL-Netherlands, SI-Slovenia.
[b] LB is lower bound scenario. In this scenario analytical values below the limit of detection or limit of quantification were assumed to equal 0.
[c] UB is upper bound scenario. In this scenario analytical values below the limit of detection or limit of quantification were assumed to equal the value of the particular limit.
[d] DANSDA 2005–08 food consumption survey; children aged 4–9 years old.
[e] IAT 2006–07 food consumption survey; children aged 3-years old.
[f] Values between brackets indicate the upper and lower boundaries of the uncertainty interval quantified for uncertainties in food consumption and food occurrence data due limited sample sizes.

FoodEx1 coding system (EFSA 2011b). Wherever possible, food concentration data were used at FoodEx1 level 4, the most detailed level. For example, if sufficient concentration data, defined as at least 50 measurements, were available at the FoodEx1 level 4 code 'cow milk, <1% fat (skimmed milk)' concentration data at this level were used. If sufficient concentration data were not available, concentration data were grouped at a less detailed level. For example, 'cow milk, <1% fat (skimmed milk)' was then recoded into to cow's milk (level 3), liquid milk (level 2) or milk and dairy products (level 1), wherever relevant.

Data with empty cells in any important field of the SSD file, such as level of detection, level of quantification and analytical value, or invalid concentration units, were omitted. If a FoodEx code was missing, but the product name was available, the corresponding FoodEx code was added manually. Only data obtained from random sampling and convenient data were included. For each substance and composite food combination in the dataset it was decided to use the analytical data as such or to convert the food into its ingredients (see matching food consumption and concentration data). Complexity of the food (e.g. the FoodEx1 code represents a broad range of composite foods rather than a single food, such as meat-based dishes), availability of recipe data, and number of measurements for the composite food and its ingredients were important criteria for this decision. Once decided to convert a composite food into its ingredients, the analytical data of the composite food were removed from the data set. Supplemental material A provides information on the decisions made for the foods, and Supplemental material B shows the FoodEx1 level used for each substance in the concentration dataset, together with the number of measurements, the percentage left-censored data, i.e. measurements below the level of detection (LOD) or level of quantification (LOQ) and mean concentrations per food and substance. Below some particularities for the different substances are provided.

2.12. Lead

Of all obtained samples, two aberrant samples (outliers) were removed from the FoodEx1 category 'wine'; one with 14 mg lead/kg and the other 21 mg lead/kg. Of all substances, lead concentration data were most abundantly available, 39,959 entries were obtained from 13 EU countries and for 358 different FoodEx1 codes, after clean-up of the data.

2.13. Methyl mercury

Data for methyl mercury were obtained for fish and sea food (60 foods) from 12 EU countries. Analytical results for both methyl mercury and total mercury were available. Fewer numbers of analytical values were available for methylmercury (n = 165) than for total mercury (n = 6,542). Therefore, we decided to include methyl mercury concentrations calculated out of total mercury concentrations using conversion factors established by EFSA (EFSA 2012a):

- 1 for fish meat, fish products, fish offal and unspecified fish and seafood;
- 0.8 for crustaceans, molluscs and amphibians, reptiles, snails and insects;
- 0 for all other food categories not containing fish or seafood.

For the samples with measured methyl mercury concentrations, total mercury concentrations were also available, allowing comparisons of measured and calculated methyl mercury concentrations. To do this, the mean of positive samples, i.e. samples with an analytical value of methyl mercury or total mercury above the LOQ value, was calculated. The mean calculated methyl mercury concentration was generally slightly higher than mean measured methyl mercury concentration (see Supplementary Material C). Given the smaller number of measured methyl mercury data and the slightly higher concentrations of calculated methyl mercury, it was decided to include only calculated methyl mercury data. After data cleaning, the dataset for methyl mercury contained 6,473 entries.

2.14. Inorganic arsenic

From the EFSA data warehouse, samples containing 'arsenic' between 2014 and 2018 were retrieved. Since we focused on the exposure to inorganic arsenic (iAs), 'organic arsenic' samples were omitted from the data and samples coded as 'arsenic and derivatives' and 'arsenic' were recoded to 'total arsenic' samples, following the approach taken by EFSA (2021b). Of samples for which both 'total arsenic' as well as 'inorganic arsenic' values were reported, the 'total arsenic' samples were omitted from the database. In addition, after closer examination of the original data, samphire ("*zeekraal*") samples analysed for 'arsenic' from the Netherlands were originally coded as 'leafy vegetables' and were consequently recoded as 'sea weeds'. The fraction of iAs was translated from the remaining 'total arsenic' samples according to the median ratios described in EFSA's Scientific Opinion (2021b). Similar to EFSA, total arsenic was not converted into iAs for fish. Supplemental material F lists the factors used for the conversion of total arsenic into iAs. Like EFSA, we used an additional LOQ-cut off of 100 μg/kg for iAS in cereal-based food for infants and young children.

The original dataset also contained 3104 entries for drinking water (tap and bottled). High concentrations of iAs in tap water (typically up to 7920 μg/litre), especially originating from one country, were present in the data set. In addition, the dataset contained non-detects with high LOQs (up to 900 μg/kg). A maximum level of 10 μg/L has been established for water intended for human consumption, without distinguishing among different arsenic forms (EU, 2020). In addition, a maximum level of 10 μg/L was established for total arsenic in natural mineral water (EC, 2003). In the most recent EFSA opinion on iAs, EFSA used concentration data over the years 2013–2018 and excluded values obtained from analytical methods with LOQs higher than 10 μg/L for that reason (EFSA, 2021b). To perform calculations using representative European iAs in drinking water, we did not use the received data from the Data Warehouse but used the mean values for the lower and upper bound as reported by EFSA in 2021. After data cleaning, 3,021 entries for iAs were obtained from 13 EU countries and for 117 different FoodEx1 codes.

2.15. Fluoride

Only fluoride concentrations in drinking water were available. Data were obtained from the EFSA data warehouse for bottled water, carbonated mineral water, still mineral water, well water and drinking water. Because of food conversions containing water, such as soft drinks and liquid infant formulae which are converted to water and other ingredients (see matching food consumption data and concentration data), all types of water were recoded into drinking water (A.15). Within the EFSA data warehouse information from limited countries was available. Therefore, additional fluoride concentration data obtained from the Dutch monitoring program for drinking water between 2014 and 2018 were included. It should be noted that those data were provided as mean values per pumping station. Mean values were calculated using a middle-bound scenario, in which samples below the limit of detection were substituted with a value equal to half the value of the level of detection. After data cleaning, 2011 entries for fluoride in drinking water were available.

2.16. NDL-PCBs

Concentration data were obtained for 6 NDL-PCBs, which are regarded as indicator congeners for the exposure to NDL-PCBs via food (EFSA 2005; JECFA 2016). Concentration data (n = 3,363 samples) for each of the 6 NDL PSBs were obtained from 9 countries. For many samples, the sampling type was not specified. To enlarge the number of observations, those samples were included. NDL-PCB concentrations in food were expressed on a whole weight- or on a percentage fat weight-basis. If for a sample data were available for both whole weight and percentage fat weight, the data expressed on whole weight were selected. If data were expressed based on percentage fat weight, the percentage fat in the original sample was provided in the SSD format. However, the original percentage fat in the sample was not always provided or higher than expected (up to 100%). To calculate the NDL-PCB concentration in those samples, the percentage fat weight according to the Dutch food composition database (NEVO; accessed November 2021)[2] was used. If NEVO provided two or more values for the percentage fat, the average fat weight was used for the calculations. After an initial run, high exposure estimates were obtained for NDL-PCBs in vegetable oil. This was mainly due to extreme NDL-PCBs concentrations analysed in one country. Average concentrations were approximately 250 times higher than those described for vegetable oil in the EFSA opinion (EFSA, 2012b). We therefore omitted the extreme NDL-PCBs concentrations analysed in one country. The mean concentration of the sum of 6 congeners now fell within the range published by EFSA (EFSA, 2012b).

As the sum of 6 indicator congeners comprises 50% of the total exposure to NDL-PCBs (EFSA 2012b), the 6 NDL-PCBs were summed per sample assuming equipotency (see paragraph scaling factors) and multiplied by 2 as a proxy for the total concentration of NDL-PCBs in food. In total, 20,103 data entries for the sum of NDL-PCBs in 60 food categories were used in the case study.

[2] Nederlands Voedingsstoffenbestand (NEVO) | RIVM. https://nevo-online.rivm.nl/Home/En

2.17. PBDEs

Concentration data were obtained from 4 countries and for 24 foods of animal origin (meat and meat products, fish and other seafood, eggs and milk). Like the NDL PCBs, PBDE concentrations in food were expressed based on whole weights or on percentage fat weight. Again, concentrations expressed on a whole weight basis were preferred over those expressed on percentage fat weight. In addition, the fat weight of the original sample was not always available, and the fat weights provided in the Dutch NEVO database was used to calculate PBDE concentrations expressed on whole weight. After data cleaning, the data set contained 1557 measurements for each of the four PBDEs.

Because some exposome studies or aggregated external exposure studies express the sum of PBDEs, concentration data for the four PBDEs −47, −99, −153 and −209 were summed per sample as lead-equivalents thus considering their SFs compared with lead (see paragraph scaling factors). Summing was performed following the lower bound and upper bound scenario (see Exposure scenarios).

2.18. Matching food consumption data and concentration data

As much as possible, food consumption data was linked to concentration data at the same level of detail. If that was not possible, food consumption was linked to a less detailed level FoodEx1 coding using the hierarchical FoodEx1 system. For example, consumption of turnips was linked to concentration data in root vegetables. As concentrations of substances are often available in raw agricultural products rather than processed products, a food translation table was used to link consumed processed food to substance concentrations in its raw agricultural commodity ingredients. For this we used the Dutch food translation table (Boon et al., 2015), which was based on Dutch recipes and contained conversion factors to convert foods classified according to FoodEx1 into their edible raw agricultural commodity ingredients (e.g. 167 g raw spinach is needed to produce 100 g cooked spinach). As this food translation table was developed for pesticide exposure calculations, it focused on fruit and vegetables. As such, the food translation table did not include animal-derived ingredients (fish, meat and milk) in composite food. Therefore, we updated the food consumption table with animal-derived ingredients as much as possible using Dutch recipes for composite foods.

2.19. Exposure scenarios

For each subpopulation the lower and upper bound scenarios following EFSA practice regarding handling concentrations below LOD LOQ EFSA, 2010c) were used for the exposure assessments. In the lower bound scenario, concentration values below the LOD or LOQ, as indicated accordingly in the SSD files, were assumed to equal 0. In the upper bound scenario, concentrations below the LOD or LOQ were assumed to equal the value of the respective limit.

2.20. Mixture risk assessment

Mixture risk assessment was performed using the MCRA tool version 9.1 (https://mcra.rivm.nl) for each country and subpopulation listed in Table 2, assuming dose additivity. Chronic (long-term) exposure was calculated using the Observed Individual Means (OIM) model. For each substance *s* in the assessment group and for each individual *i* in the food consumption data base, the consumed amount of a certain food *f* averaged over the total number of consumption days q_{if} was multiplied with the average concentration present in that food c_{ifs}. This was done for all consumed foods per individual. The subsequent obtained exposures per food were summed for each chemical *s* per individual over the *F* numbers of food consumed and divided by the bodyweight of the individual bw_i, which yielded the chronic exposure E_{is} to chemical *s* of the individual *i*.

$$E_{is} = \frac{\sum_{f=1}^{F} q_{if} c_{ifs}}{bw_i} \quad \text{(Equation 2)}$$

The chronic exposure of each chemical *s* in the assessment group E_{is} was then multiplied by the SF of the chemical (SF_s) and summed per individual to obtain the cumulative exposure per individual *Cum* E_i. As we used lead as the index chemical for deriving the SF, *Cum* E_j is the cumulative exposure of each individual expressed as lead equivalents:

$$Cum\ E_i = \sum_{s=1}^{S} E_{is} * SF_s \quad \text{(Equation 3)}$$

where *s* relates to the chemical considered. This yielded a distribution of the cumulative exposure, from which the median (P50) and the 95th exposure percentile were obtained.

Fold-exceedance of combined potency weighted tolerable exposures to the chemicals in the assessment group were characterised by dividing each individual's combined exposure in lead equivalents (*Cum* E_j) by the ESRV of the index compound lead ($ESRV_{Pb}$). We called the metric obtained in this way a *personalised modified reference point index* (mRPI).

$$personalised\ mRPI_i = \frac{Cum\ E_i}{ESRV_{Pb}} \quad \text{(Equation 4)}$$

This approach is similar to the mRPI introduced by Vejdovszky et al. (2019), as outlined in supplemental material D, and mathematically equivalent to the Hazard Index (Teuschler and Herzberg 1995). According to the EFSA guidance on harmonized methodologies, the hazard index is used in the context of health-based guidance values for the critical effect (such as the acceptable daily intake or the tolerable daily intake), whereas the reference point index (RPI), also known as the point of departure index, could be used for ESRVs that are not necessarily based on the critical effect (EFSA 2019). The RPI could typically use a single group UF (either a default or chemical-specific assessment factor) to assess the risk (EFSA 2019). Since UFs may vary depending on the derivation of the reference points, Vejdovszky et al. (2019) finetuned the RPI approach by applying chemical-specific uncertainty factors and named this the modified RPI (mRPI) approach. Because the reference points for IQ loss are not always based on the critical effect of a chemical and different UFs were applied, the mRPI approach was best suited to estimate the risk related to IQ loss.

Our approach yielded distributions of the personalised mRPI, of which the median and the 95th percentile of personalised mRPI were obtained. The personalised mRPI distributions obtained in this way were evaluated in terms of exceedances of combined "acceptable" exposures to lead equivalents relative to a value of 1. A personalised mRPI larger than 1 either means that a risk of the combined exposure cannot be excluded or that refinement is needed, depending on the direction of the uncertainties.

In addition to the calculation of percentiles, the contribution of substances to the personalised mRPI of the total population was assessed. For a particular substance *s,* the sum of the exposure *E* to that substance (expressed as lead-equivalents) of all individuals (n) in the food consumption database relative to the sum of the cumulative exposures of all individuals was calculated:

$$\%\ contribution\ s = \frac{\sum_{i=1}^{n} E_s}{\sum_{i=1}^{n} Cum\ E_i} * 100 \quad \text{(equation 5)}$$

Calculating the contributions for combinations of foods and substances is done in a similar way.

2.21. Uncertainty

The bootstrapping approach was used to quantify sampling uncertainty in food consumption and concentration data caused by a limited sampling size (Efron 1979; Efron and Tibshirani 1993). This approach

re-samples (with replacement) the original food consumption and concentration dataset to obtain a bootstrap of n observations. In the present calculation, we performed an uncertainty analysis using 100 re-sampling cycles with 10,000 iterations. This yielded 100 alternative exposure distributions, which might have been obtained during sampling from the population of interest and during sampling of foods. The mean and P95 were estimated for each of those 100 alternative exposure distributions, yielding 100 alternative exposure statistics. The median value (regarded as the best estimate) and its 95% uncertainty interval around the exposure estimates were obtained from those 100 alternative exposure statistics.

3. Results

3.1. Personalised modified reference point index

We calculated distributions of the potency weighted lead-equivalent exposures for substances relevant to IQ loss relative to the acceptable level of lead exposure, which we termed personalised modified reference point index (mRPI). Fig. 1 shows the personalised mRPI-distributions of women of child-bearing age from 8 European countries, calculated for the lower bound scenario, where analytical non-detects were set to zero. For the majority of the populations, personalised mRPIs were larger than 1. To make our findings comparable with risk assessments usually performed at the median (P50) or the 95th percentile (P95) of exposures, we additionally listed the P50 and P95 personalised mRPIs in Table 3. In the lower bound scenario, P50 personalised mRPI exceeded the ESRV of lead by between 1.3-fold for Slovenian women in their childbearing age and 7.6-fold for Italian toddlers. Approximately twofold higher P50 personalised mRPI were observed for the upper bound scenario in which we set analytical non-detects to the limit of detection. At P95, the personalised mRPI ranged from 4.4 for Austrian adolescents to 21 for Danish toddlers in the lower bound scenario. In the upper bound scenarios, 1.5-fold higher personalised mRPI were obtained. There was no exposure scenario, population subgroup or country, where the personalised mRPI stayed at or below the value of 1 for the entire population.

3.2. Main substances contributing to the personalised mRPI

Fig. 2 shows the contribution (expressed as percentages) of the different substances to the combined lead-equivalent exposures relative to the acceptable exposure to lead, personalised mRPI, of the various populations we examined in the selected countries.

Lead was an important contributor to the personalised mRPI in both the LB (non-detects set to zero) and UB scenarios (non-detects set at the level of quantification) in most of the countries and for several age groups. Lead alone made up between 15% of the personalised mRPI in Slovenian toddlers and 40% in Austrian adolescents in the LB scenario. In the UB scenario, this rose to between 35% for Danish toddlers and 52% for Austrian adolescents.

Non-dioxin-like PCBs also had a significant impact on the personalised mRPI, ranging from 17% for Austrian adolescents to 57% for Danish toddlers in the LB scenario and 14% for Austrian adolescents to 44% for Danish toddlers in the UB scenario.

For some countries, methyl mercury had a considerable influence on the personalised mRPI while for others its contribution was relatively small. It varied from 8% for Danish toddlers to 38% for Italian women in their childbearing age in the LB scenario. For the UB scenario it ranged from 6% in Austrian adolescents to 27% for Italian women in their childbearing age.

Fluoride showed differing impacts to the personalised mRPI, ranging from 4% for Slovenian toddlers in the LB scenario to 24% for Austrian women in their childbearing age. For the UB scenario, fluoride contributions varied between 4% (Italian toddlers) to 17% (Austrian women in their childbearing age).

Inorganic arsenic did not contribute strongly to the personalised mRPI, making up only 5–10% in the LB scenario and 8–11% in the UB scenario.

The sum of 4 PBDEs were of minor importance to the personalised mRPI in all countries. Their contribution amounted to only 2% or less in both the LB and UB scenarios.

3.3. Risk-driving food-substance combinations

Next, we analysed which food-substance combinations made up most of the intake of chemicals that considerably contributed to the personalised mRPI in the different countries (Table 4).

In all countries, and under both the lower and upper bound assessment scenarios, fluoride in drinking water contributed significantly to the personalised mRPI, varying from 6 to 24%. Methyl mercury in fish and seafood strongly impacted the personalised mRPI in all countries and age groups. This ranged from 8% (Denmark) to 38% (Italy). Lead derived from grains and grain products made up 5–11% of the personalised mRPI. Other notable sources of lead intake were vegetables and products thereof with a contribution to the personalised mRPI of up to 10% and fruit and fruit products (up to 12%). The most important source of NDL-PCB intake was from fish and seafood (8–38% of the personalised mRPI). Dairy products also significantly contributed to NDL-PCB intake (5–10% of personalised mRPI). In some countries, special foods were an important source of NDL-PCBs. This was due to fish oil supplements.

4. Discussion

Our case study shows that the component-based approach for performing MRA following EFSA guidance for grouping and exposure-based prioritisation of chemicals (EFSA 2021a) provides powerful information to risk managers on mixtures of different classes of dietary contaminants. Those mixtures have a high co-occurrence rate in biomonitoring studies. Apart from information on exceedances of the acceptable combined exposures, it provides information of sources of exposure, which could feed into re-evaluations of legal limits of substances in food. Considering chemicals relevant for IQ loss, the median and P95 personalised mRPIs exceeded the value of 1 in all populations. Lead and NDL-PCBs contributed strongly to the personalised mRPI, followed by methylmercury, fluoride and iAs. PBDEs only marginally influenced the combined risk. We also show that the food-substance combinations that contributed most to the combined risk are dairy, fish and seafood for NDL-PCBs, grains and fruits for lead, methyl mercury in fish and seafood, fluoride in drinking water and iAS in grains. There are some strengths and weaknesses in our case study which we discuss below.

4.1. Strengths and limitations of the study

4.1.1. Strengths

A major strength of our case study is in the use of combinations of food consumption data and data on the occurrence of our selected chemicals in food. This allowed us to establish country-specific distributions of personalised mRPIs. This level of detail was not achieved in MRA studies that relied on summary statistics of exposures at the median or the P95 (see for example Vejdovszky et al., 2019, EFSA 2019, Boberg et al., 2021, Sprong et al., 2020, Evans et al., 2016, Martin et al., 2017). The use of such summary statistics cannot deal with the fact that individuals highly exposed to one chemical will not necessarily experience high exposures to another substance. For example, in our study a vegetarian with high lead exposures due to large consumption of vegetables will not also be highly exposed to methyl mercury and NDL-PCBs in fish. The summing of lead exposure equivalents derived from high exposure percentiles is over-conservative. Distributions of personalised mRPIs for MRA provide rather realistic assessments and can therefore be regarded as a high tier MRA. Similar observations were made recently by

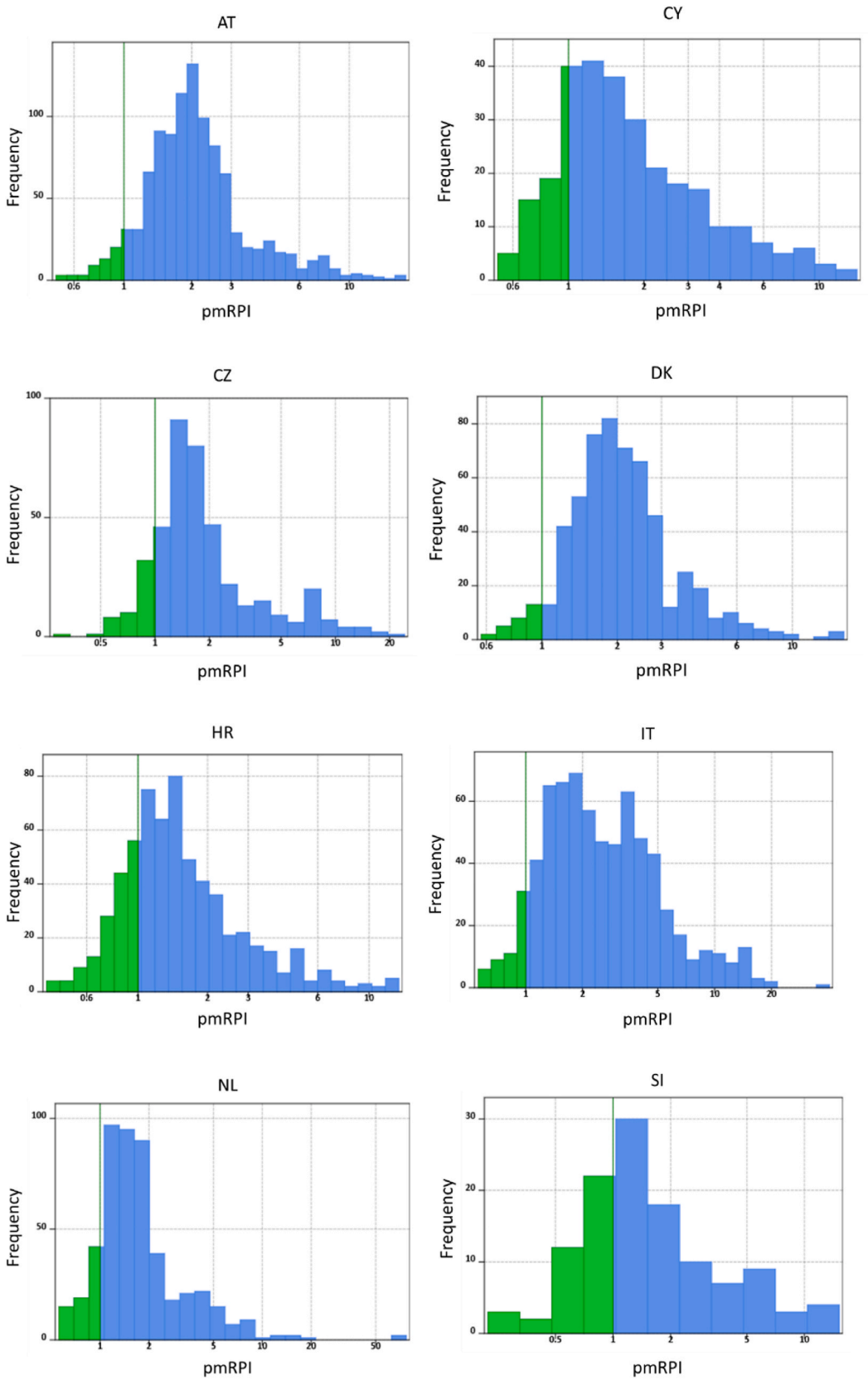
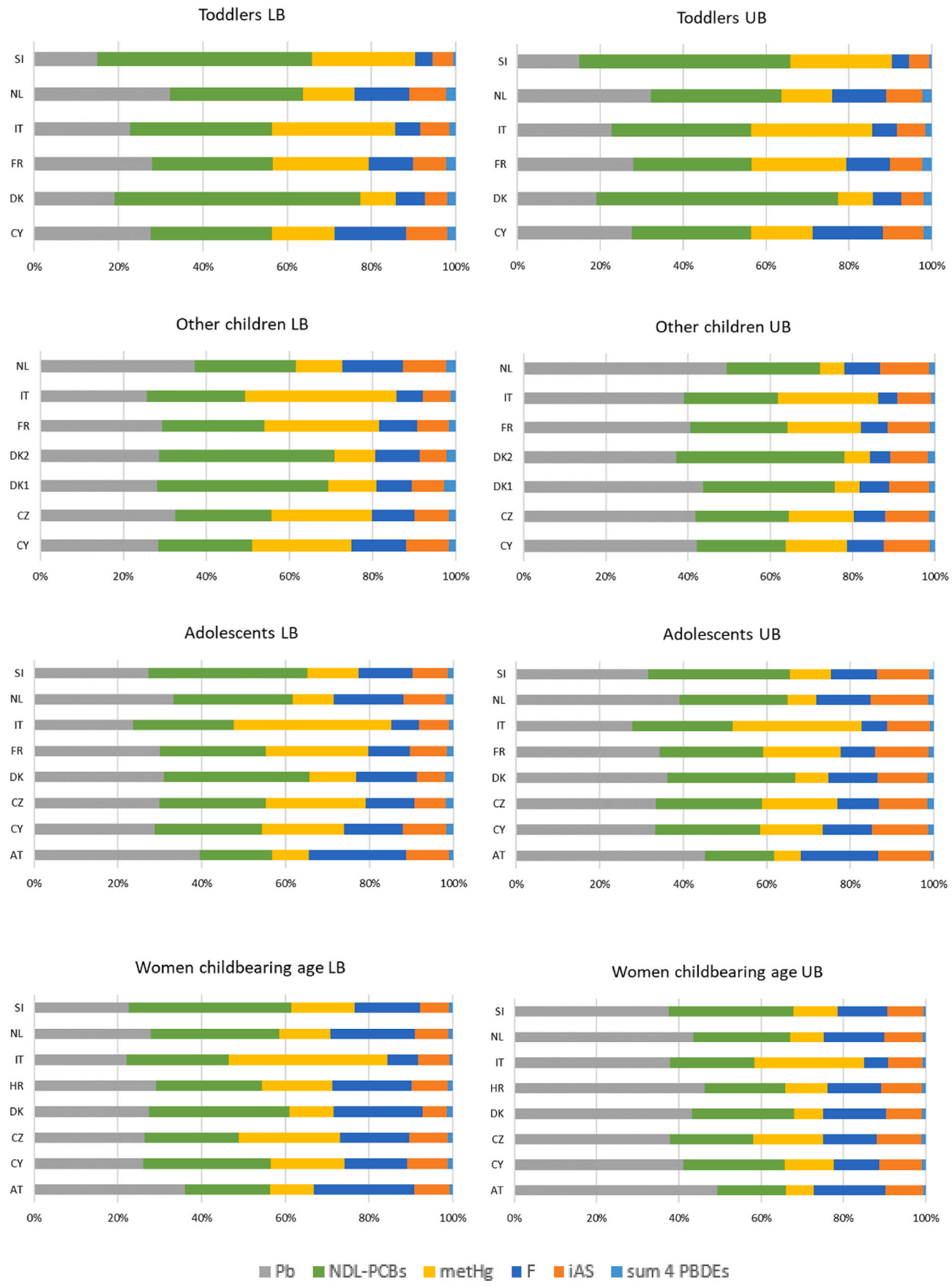


Fig. 1. Distribution of personalised modified reference point indices (pmRPI), which are potency weighted lead-equivalent exposures) for substances relevant to loss of intelligence scores (lead, methyl mercury, inorganic arsenic, fluoride, non-dioxin-like polychlorinated biphenyls and polybrominated diphenyl ethers) relative to the acceptable level of lead exposures (= 1), for women in their childbearing age (18–45 years) in 8 European countries. Results for the lower bound scenario, in which analytical values below the limit of detection or limit of quantification were assumed to equal 0, are shown. AT-Austria, CY-Cyprus, CZ-Czech Republic, DK-Denmark, HR-Croatia, IT-Italy, NL-Netherlands, SI-Slovenia. Values of pm RPI showing acceptable combined exposures (<1) are shaded green, those exceeding the index value of 1 are shown in blue. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)



(caption on next page)

Fig. 2. The percentage contribution of chemicals relevant to IQ loss to the personalised modified reference point index of the total population for toddlers (1–2 years old), other children (3–9 years old), adolescents (10–17 years old) and women in their childbearing ages (18–45 years) of 9 different European countries:Austria-AT, Cyprus-CY, Czech Republic-CZ, Denmark-DK (DK1 and DK 2 denote two different food consumption surveys for the particular subpopulation with DK1 providing the results of 3 years old children and DK2 results of children aged 4–9 years old), France-FR, Croatia-HR, Italy-IT, Netherlands-NL, Slovenia-SI, and for two different scenarios (lower bound-LB and upper bound-UB). For the LB scenario analytical values below the limit of detection or limit of quantification were assumed to equal 0, and for the UB scenario values below the limit of detection or quantification were assumed to equal the value of the particular limit. Pb: lead; NDL-PCBs: Non-dioxin-like PCBs; metHG: methyl mercury; F: fluoride; iAs: inorganic arsenic; PBDE: polybrominated diphenyl ethers.

Van den Brand et al. (2022) in their personalised mRPI distributions for mycotoxins and in the personalised MRA based on the HI approach for deteriorations of semen quality by Kortenkamp et al. (2022).

Another strength of our study is that we used reference values for specific effects, i.e. declines in cognitive ability as measured in terms of IQ loss. This is a rather refined way of performing MRA which avoids the mixing of toxicities as may be the case in low tier assessments based on HBGVs derived for different critical toxicities. Thus, in our case, we could rely on two HBGVs derived for IQ loss (lead, methyl mercury EFSA 2010a; US EPA 2001). In contrast, the HBGV for iAs is based on cancers of the lung, skin and bladder, as well as skin lesions; for NDL-PCBs it is based on liver and thyroid toxicity for NDL-PCBs (EFSA 2009; EFSA 2005). The use of these HBGVs would have biased our assessment. There is currently no HBGV for fluoride. We therefore estimated the corresponding ESRV for IQ loss for iAs, NDL-PCBs and fluoride based on epidemiological data. While there is evidence of associations of PBDE exposures with IQ loss (Eskenazi et al., 2013), there is no information on PBDE congener-specific associations which would have made it difficult to utilize the PBDE congener-specific food occurrence data. We therefore adopted the congener-specific hazard data derived by EFSA (2011a) for developmental neurotoxicity in rodents. Thus, assessments based on reference doses for specific endpoints, as we used in our approach and which shaped the personalised mRPI approach in Vejdovszky et al. (2019), the POD index (EFSA, 2019a), the chemical risk calculator (Boberg et al., 2021) and the normalized total margin of exposure approach (Sprong et al., 2020), provide a more realistic risk assessment.

However, the *de novo* derivation of reference values for specific endpoints can require extensive literature reviews and may be rather resource-intensive, while HBGVs or HBM-GVs are usually more readily available, e.g. in databases such as EFSA's OpenFoodTox database (Kovarich et al. 2016). Approaches based on such values also have merits in that they can provide lower tier MRAs which can be refined if the assessment indicates exceedance of combined acceptable levels (EFSA, 2019a).

4.1.2. Limitations

A major limitation of our study is that non-dietary routes of exposure, such as air, dust and soil, are not considered. Consequently, we very likely underestimated risks from combined exposures. However, for the general population in Europe there is good evidence that non-dietary exposures to lead, iAs, NDL-PCBs and PBDEs are of minor importance compared to dietary exposures. This may not always be the case for children, where uptake via dust and soil can be important routes of exposure to lead, iAs and PBDEs, particularly in highly contaminated areas (EFSA 2010a; EFSA 2011a; EFSA 2012a; EFSA 2005; EFSA 2009).

However, some studies revealed a larger role of non-dietary exposure to PBDE, since ingestion and dermal contact of dust were the major pathways of exposure to PBDE in an American study, accounting for 56–77% of the total exposure in toddlers, children, adolescents and adults, whereas diet only accounted for 20–40% (Johnson-Restepro and Kannan, 2009). In another recent American biomonitoring study, PBDEs exposure was the greatest contributor to IQ loss, followed by lead, organo-phosphates and methyl mercury (Gaylord et al., 2020), while our results show that the contribution of PBDEs to the combined exposure was only limited. This is likely explained by our inability to capture non-dietary exposures to PBDEs in our study; exposure from all routes is accounted for in human biomonitoring studies. Other factors can also explain the observed differences, among them the limited number of analytical data in our study, the differences in PBDE concentrations in dust and food between the US and Europe (Zota et al., 2008; EFSA 2009), the number of PBDEs included, i.e. PBDE- 47, -99, −153, −209 in our study, PBDE-47 in the study of Gaylord et al. (2020) and 20 PBDEs among which the congeners - 47, −99, −153, −209 in the study of Johnson-Restepro and Kannan (2009), and assuming equipotency of all PBDE isomers in other studies.

Some studies also pointed at a larger role for non-dietary sources of NDL-PCBs (Lehmann et al., 2015; Li et al. 2018)), Although banned in the United States and the European Union some decades ago (Lehmann et al., 2015; EFSA 2005), PCBs can be present in the indoor air and dust of many older buildings because of the use of NDL-PCB containing elastic sealants, caulking, paints, and flame retardant coatings (Lehmann et al., 2015). Large contributions of indoor air to the total exposure was shown for all age groups (Lehmann et al., 2015; Li et al. 2018), with contributions observed up to 60.8, 50.5, and 34.6% for children ages 2–3 years and 6–12 years and adults, respectively (Lehmann et al., 2015). Other dietary sources (e.g. tea) and routes of exposure are also relevant for fluoride, such as dental hygiene products, but the information accessible to us was too limited to draw conclusions on their contribution to total fluoride exposures (EFSA 2013). To obtain a more complete picture of the combined exposure to chemicals relevant for IQ loss, other routes of exposure can be included in external exposure assessment. Methodologies to aggregate the exposure from several routes are available (e.g. Husøy et al., 2020: aggregated exposure of di (2-ethylhexyl) phthalate from diet and personal care products) and have been implemented in MCRA (Van der Voet et al., 2020). However, chemical concentration data in consumer products and indoor air was not yet available for the substances included in our case study, and neither were levels in soil and outdoor air (IPCHEM database accessed 22 March 2022).

Another important limitation of our study that leads to an underestimation of the risk is that only certain contaminants were considered. Recently, an endpoint-specific reference value for IQ loss was estimated for cadmium (Chatterjee and Kortenkamp 2022). Cadmium is frequently detected in human biomonitoring samples (Haug et al., 2018; Buekers et al., 2021) at high occurrence rates (e.g. 99.6% and 96.5% quantifiable samples in mothers and child, respectively; Haug et al., 2018). Therefore, cadmium may significantly contribute to the risk of IQ loss.

In addition, human biomonitoring data showed co-exposure to substances from other regulatory domains, such as organophosphate pesticides (Haug et al., 2018), which are also relevant for IQ loss (Grandjean and Landrigan, 2006, 2014). As outlined in the method section, ESRVs of organophosphate pesticides for IQ loss were not readily available. Another issue with adding pesticide exposures to the combined exposure of contaminants is how to integrate different exposure scenarios deemed relevant for the particular regulatory silos. Where the LB and UB scenario is used by EFSA to estimate the risk of contaminants, such as the metals and persistent organic pollutants in our case study, for pesticides other refined scenarios with assumptions for agricultural use based on authorized uses are considered more realistic (EFSA 2020a; and b, EFSA et al., 2022; van Klaveren et al., 2019a and b). Currently, advanced exposure tools calculating exposure distributions are currently unable to deal with different exposure scenarios simultaneously and therefore, combined exposure of substances is often limited to summing percentiles (Sprong et al., 2020). The development of a tool that would be able to aggregate exposures from different regulatory frameworks by allowing simultaneous calculations using different exposure scenarios and

Table 4
Food-substance combinations contributing most to the combined dietary exposure to substances relevant for loss of intelligence presented for toddlers (1–2 years old), other children (3–9 years old), adolescents (10–17 years old) and women in their childbearing ages (18–45 years) of 9 different European countries (Austria-AT, Cyprus-CY, Czech Republic-CZ, Denmark-DK, France-FR, Croatia-HR, Italy-IT, Netherlands-NL, Slovenia-SI) and for two different scenarios (lower bound-LB and upper bound-UB)[a]. Percentages between brackets reflects the fraction of the personalised modified reference point index that can be attributed to the particular food-substance combinations.

Country	Toddlers	Other Children	Adolescents	Women child bearing age
Lower bound				
AT	–	–	F drinking water (23%) Pb grain (products) (11%) MetHg fish & seafood (9%) iAs grain(products) (6%) NDL-PCBs fish & seafood (6%)	F drinking water (24%) MetHg fish & seafood (10%) Pb grain (products) (7%) Pb vegetable (products) (7%) NDL-PCBs fish & seafood (7%)
CY	F drinking water (17%) MetHg fish & seafood (15%) NDL-PCBs fish & seafood (13%) NDL-PCBs dairy (8%) Pb Grain (products) (6%)	MetHg fish & seafood (23%) NDL-PCBs fish & seafood (13%) F drinking water (13%) Pb grain(products) (8%) NDL-PCBs dairy (6%)	MetHg fish & seafood (20%) F drinking water (14%) NDL-PCBs fish & seafood (14%) Pb grains (products) (7%) NDL-PCBs dairy (5%)	MetHg fish & seafood (18%) F drinking water (15%) NDL-PCBs fish & seafood (12%) NDL-PCBs special foods (9%) Pb grain (products) (6%)
CZ	-	MetHg fish & seafood (24%) NDL-PCBs fish & seafood (12%) F drinking water (10%) Pb grain(products) (7%) NDL-PCBs in fats and oils (6%)	MetHg fish & seafood (24%) NDL-PCBs fish & seafood (13%) F drinking water (12%) Pb grain(products) (7%) NDL- PCBs fats and oils (7%)	MetHg fish & seafood (24%) F drinking water (16%) NDL-PCBs fish & seafood (12%) NDL-PCBs fats and oils (5%) Pb grain (products) (5%)
DK	NDL- PCBs fish & seafood (47%) MetHg fish & seafood (8%) NDL-PCBs dairy (7%) F drinking water (7%) Pb grain(products) (6%)	DK1[b] NDL-PCBs fish & seafood (31%) F drinking water (10%) MetHg fish & seafood (9%) Pb grains (products) (8%) NDL-PCBs dairy (7%) DK2[b] NDL-PCbs fish & seafood (41%) MetHg fish & seafood (9%) NDL-PCBs dairy (8%) F drinking water (7%) Pb grains(products) (6%)	NDL-PCBs fish & seafood (22%) F drinking water (15%) MetHg fish & seafood (11%) Pb grain(products) (10%) NDL-PCBs in dairy (7%)	NDL-PCBs fish & seafood (24%) F drinking water (21%) MetHg fish & seafood (11%) Pb grain (products) (6%) Pb vegetable (products) (6%)
FR	MetHg fish & seafood (23%) NDL-PCBs fish & seafood (13%) F drinking water (11%) NDL-PCBs dairy (10%) Pb Grain (products) (7%)	MetHg fish & seafood (27%) NDL-PCBs fish & seafood (15%) Pb grain (products) (10%) F drinking water (9%) NDL-PCBs dairy (6%)	MetHg fish & seafood (24%) NDL-PCBs fish & seafood (14%) Pb grain(products) (11%) F drinking water (10%) iAs grain(products) (5%)	–
HR	-	–	–	F drinking water (19%) MetHg fish & seafood (17%) NDL-PCBs fish & seafood (15%) Pb grain(products) (7%) Pb vegetables (products) (6%)
IT	MetHg fish & seafood (29%) NDL-PCBs fish & seafood (22%) Pb grain (products) products (7%) NDL-PCBs in dairy (6%) F drinking water (6%)	MetHg fish & seafood (35%) NDL-PCBs fish & seafood (15%) Pb grain (products) (7%) F drinking water (6%) NDL-PCBs fats and oils (5%)	MetHg fish & seafood (38%) NDL-PCBs fish & seafood (14%) Pb grain(products) (7%) F drinking water (7%) Pb vegetable (products) (5%)	MetHg fish & seafood (38%) NDL-PCBs fish & seafood (15%) F drinking water (7%) Pb vegetable (products) (6%) Pb grain(products) (5%)
NL	F drinking water (13%) MetHg fish & seafood (12%) NDL-PCBs special foods (9%) NDL- PCBs dairy (9%) Pb grains (products) (8%)	F drinking water (14%) MetHg fish & seafood (10%) Pb grain(products) (9%) NDL-PCBs special foods (8%) NDL- PCBs dairy (8%)	F drinking water (17%) Pb grain (products) (10%) MetHg fish & seafood (10%) NDL-PCBs special foods (9%) iAs grain (products) (6%)	F drinking water (20%) NDL-PCBs special foods (16%) MetHg fish & seafood (12%) Pb vegetable (products) (7%) NDL-PCBs fish & seafood (6%)
SI	NDL- PCBs fish & seafood (13%) F drinking water (13%) MetHg fish & seafood (10%) Pb fruit and fruit products (9%) Pb grain(products) (9%)	–	NDL-PCBs fish & seafood (21%) F drinking water (13%) MetHg in fish & seafood (12%) Pb grain(products) p(8%) NDL-PCBs special foods (7%)	NDL-PCBs fish & seafood (17%) F drinking water (16%) MetHg fish & seafood (15%) NDL-PCBs special foods (15%) Pb grain (products) (5%)

(*continued on next page*)

Table 4 (*continued*)

Country	Toddlers	Other Children	Adolescents	Women child bearing age
Upper bound				
AT	-	-	F drinking water (16%)	F drinking water (17%)
			Pb grain (products) (12%)	Pb vegetable (products) (12%)
			Pb vegetable (products) (9%)	Pb grain (products) (8%)
			Pb fruit (products) (6%)	MetHg fish & seafood (7%)
			MetHg fish & seafood (6%)	Pb drinking water (6%)
CY	F drinking water (11%)	MetHg fish & seafood (15%)	MetHg fish & seafood (13%)	Pb vegetable (products) (12%)
	NDL-PCBs in dairy (9%)	F drinking water (9%)	F drinking water (10%)	MetHg fish & seafood (12%)
	MetHg fish & seafood (9%)	Pb vegetables (products) (9%)	NDL-PCBs fish & seafood (9%)	F drinking water (11%)
	NDL-PCBs fish & seafood (8%)	Pb grain (products) (9%)	Pb vegetable (products) (8%)	NDL- PCBs fish & seafood (8%)
	Pb vegetables (products) ((7%)	NDL-PCBs fish & seafood (8%)	Pb grain (products) (8%)	Pb grain (products) (6%)
CZ	-	MetHg fish & seafood (16%)	MetHg fish & seafood (16%)	MetHg fish & seafood (17%)
		NDL-PCBs fish & seafood (8%)	F drinking water (9%)	F drinking water (13%)
		F drinking water (8%)	NDL-PCBs fish & seafood (9%)	NDL-PCBs fish & seafood (9%)
		Pb grains (products) (8%)	Pb grain (products) (8%)	Pb vegetable (products) (7%)
		Pb vegetable (products) (6%)	Pb vegetable (products) (6%)	Pb grain (products) (6%)
DK	NDL-PCBs fish & seafood (31%)	DK1	NDL-PCBs fish & seafood (13%)	NDL-PCBs fish & seafood (15%)
	NDL-PCBs dairy (9%)	NDL-PCBs fish & seafood (19%)	F drinking water (10%)	F drinking water (15%)
	Pb dairy (7%)	Pb vegetables (products) (10%)	Pb grain (products) (9%)	Pb vegetable (products) (10%)
	Pb grain (products) (6%)	Pb grain (products) (8%)	Pb vegetable (products) (9%)	MetHg fish & seafood (7%)
	MetHg fish & seafood (6%)	NDL-PCBs dairy (8%)	NDL-PCBs dairy (7%)	Pb grain (products) (6%)
		F drinking water (7%)		
		DK2		
		NDL-PCBs fish & seafood (27%)		
		NDL-PCBs dairy (9%)		
		Pb grain (products) (7%)		
		Pb vegetables (products) (7%)		
		Pb dairy (6%)		
FR	MetHg fish & seafood (14%)	MetHg fish & seafood (18%)	MetHg fish & seafood (16%)	-
	NDL-PCBs in dairy (11%)	NDL-PCBs fish & seafood (10%)	Pb grain (products) (12%)	
	Pb foods for infants and small children (9%)	Pb grain (products) (10%)	NDL-PCBs fish & seafood (9%)	
	NDL-PCBs fish & seafood (8%)	Pb vegetable (products) (8%)	Pb vegetable (products) (8%)	
	F drinking water (7%)	NDL-PCBs dairy (7%)	F drinking water (7%)	
HR	-	-	-	F drinking water (13%)
				Pb vegetable (products) ((13%)
				MetHg fish & seafood (10%)
				NDL-PCBs fish & seafood (9%)
				Pb grain (products) (8%)
IT	MetHg fish & seafood (20%)	MetHg fish & seafood (24%)	MetHg fish & seafood (26%)	MetHg fish & seafood (27%)
	NDL- PCBs fish & seafood (15%)	NDL-PCBs fish & seafood (11%)	NDL-PCBs fish & seafood (10%)	Pb vegetable (products) (13%)
	Pb grains (products) (8%)	Pb vegetable (products) (9%)	Pb vegetable (products) (10%)	NDL-PCBs fish & seafood (11%)
	NDL-PCBs dairy (7%)	Pb grain (products) (9%)	Pb grains (products) (9%)	Pb grain (products) (7%)
	Pb vegetables (products) (6%)	Pb fruit (products) (5%)	F drinking water (5%)	F drinking water (6%)
NL	Pb fruit (products) (10%)	Pb grain (products) (9%)	F drinking water (11%)	F drinking water (15%)
	NDL-PCBs dairy (9%)	F drinking water (9%)	Pb grain (products) (10%)	Pb vegetable (products) (11%)
	F drinking water (8%)	Pb vegetable (products) (8%)	Pb vegetable (products) (8%)	NDL-PCBs special foods (10%)
	Pb grain (products) (8%)	Pb fruit (products) (8%)	MetHg fish & seafood (6%)	MetHg in fish & seafood (8%)
	Pb dairy (7%)	NDL-PCBs dairy (8%)	iAs grain (products) (6%)	Pb grain (products) (6%)
SI	Pb fruit (products) (12%)	-	NDL-PCBs fish & seafood (14%)	F drinking water (12%)
	Pb grain (products) (9%)		Pb grain (products) (10%)	NDL-PCBs fish & seafood (12%)
	F drinking water (8%)		F drinking water (10%)	MetHg fish &seafood (11%)
	NDL-PCBs fish & seafood (7%)		MetHg fish & seafood (8%)	Pb vegetable (products) (10%)
	Pb vegetable (products) (7%)		Pb vegetable (products) (7%)	NDL-PCBs special foods (10%)

Pb: lead; NDL-PCBs: Non-dioxin-like PCBs; metHG: methyl mercury; F: fluoride; iAs: inorganic arsenic

[a] For the LB scenario analytical values below the limit of detection or limit of quantification were assumed to equal 0, and for the UB scenario values below the limit of detection or quantification were assumed to equal the value of the particular limit.

[b] Two Danish food consumption sources were available. DK1 reflects the results obtained for the DANSDA 2005–08 food consumption survey (children aged 4–9 years old) and DK2 those of IAT 2006–07 food consumption survey (children aged 3-years old).

results in the generation of exposure distribution would allow for more realistic exposure assessments (Sprong et al., 2020). For the purpose of this case study, only different classes of contaminants were considered.

In our study we summed the indicator NDL-PCBs in food. To obtain the total exposure to NDL-PCBs we multiplied the resulting values by 2 (EFSA, 2005). In doing so, information on the risk driving congener(s) is lost. If such information is needed, additional calculations for NDL-PCBs and PBDEs using the individual congeners could be performed.

In our study, we focussed on MRA of dietary chemicals. However, non-chemical stressors may also affect cognitive development of children. A cumulative impact assessment includes such non-chemical stressors. A recent meta-analysis showed that alongside toxic chemicals, several non-chemical stressors such as maternal health, the mother's ability to access information relevant to a healthy pregnancy, dietary nutrients and quality of social interaction, had a significant impact on the child's cognitive development (Nilsen et al., 2020). It was beyond the scope of our case study to include those non-chemical stressors.

4.1.3. Uncertainties

In common with all risk assessments, the assessment performed in our case study is affected by uncertainties. Their identification is needed to assess whether the assessment represents an over- or an underestimation of risks. This is challenging in the case of a MRA, as the uncertainties behind every single chemical assessment may multiply leading to rather complex patterns of under- or over-estimations of combined risks. For a meaningful interpretation of the risks, an integration of those uncertainties into a final conclusion of the magnitude of over- or underestimation is needed. For pesticide MRAs, EFSA used a probabilistic approach for the integration of uncertainties into an overall conclusion (EFSA 2020a; and b, 2022). They identified 31, 34 and 41 sources of uncertainty (in food consumption, concentration data, hazard data and MRA methodology) for combined exposures to pesticides relevant for chronic effects on the thyroid and for pesticides relevant for acute effects on the nervous system, and craniofacial malformation respectively (EFSA 2020a; and b, 2022). Uncertainties were quantified at the high level of exposures using expert knowledge elicitation following principles of the EFSA guidance (EFSA 2014). This methodology resulted in a factor 3–5 lower combined risks to pesticides relevant for acute effects on the nervous system and a factor 2–4 lower for chronic effects on the thyroid (EFSA, 2020a and b). It was not the purpose of our study to perform such a sophisticated uncertainty analysis as this is resource intensive, and requires several experts with different backgrounds. Instead, we identified the major uncertainties, which future in-depth uncertainty analysis could build upon. Those are described below. Where possible, the direction of the uncertainty (over- or underestimation was given).

4.1.4. Endpoint IQ loss

We selected the loss of 1 IQ point as a measure of cognitive deficits in the developing child, since this degree of cognitive decline at the population level can have an economic impact on societies (Gould, 2009; Grandjean et al., 2012; Bellanger et al., 2013; Trasande and Liu, 2011; Pichery et al., 2011; Gaylord et al., 2020). IQ tests usually consists of several subtests, each measuring a different aspect of cognitive development, such as memory, verbal and spatial reasoning, planning, learning and the comprehension and use of language. Developmental neurotoxicants could affect a certain aspect of cognitive functioning rather than all aspects (EFSA 2010a). The PODs in our study were obtained from heterogenous endpoints, varying from general cognitive indexes (methyl mercury and fluoride), full scale IQ scores (lead, NDL-PCBs) or raw verbal IQ scores (iAs; Table 1). The use of such heterogenous endpoints in a combined assessment could result in uncertainty. This is probably limited for the general cognitive index, which showed concurrent validity with intelligence tests, including the Stanford–Binet IQ (r0.81) and full-scale IQ score (r0.71) from the Wechsler Preschool and Primary Scale of Intelligence (WPPSI) (Grandjean et al., 2022; Kaplan and Sacuzzo, 2010). The uncertainty caused by only including a particular subset (e.g. only verbal IQ or performance IQ) could be larger as exemplified for iAs. Here, the endpoint was based on raw verbal IQ scores. While iAs also affected full scale IQ score, the association between iAs intake and adverse effect in children was by a factor of 3 lower compared with verbal IQ scores as performance and processing speed were not affected (Tsuji et al., 2015). Thus, the use of heterogenous endpoints (full IQ scores or particular IQ scores) may have biased our calculation of personalised mRPI. One could therefore question whether a MRA should be performed based on mixing ESRV for full IQ scores and more specific cognitive functions.

The chemicals in our cumulative assessment group showed sex-specific sensitivities on cognitive development. For example, the ESRV of iAs was based on IQ loss observed in girls, which showed larger IQ losses than boys. In contrast, for fluoride larger effects on IQ loss were observed in boys. Yet, both boys and girls were included for the derivation of the ESRV. As generally the ESRV is based on the most sensitive gender, inclusion of both boys and girls in the derivation of the ESRV would have led to an underestimation of the personalised mRPI.

4.1.5. Model assumptions

Implicit in our adding up of lead-equivalent risk quotients in the personalised mRPI is the assumption of dose addition. The possibility of synergisms or (partial) antagonisms was not considered and this is a potential source of under- or overestimations of risks. However, a recent systematic review of the frequency of synergisms has shown that dose addition provides a good approximation of expected mixture effects (Martin et al., 2022).

4.1.6. Likelihood of co-exposure

In our case study, the likelihood of co-exposure to several pollutants was addressed by reviewing human biomonitoring detection rates (i.e. percentage of measurements above the LOD or LOQ, whatever applicable). For example, in the study described by Haug et al. (2018) occurrence rates varied from 54% for PBDE-153 in children aged 6–12 years to 100% for lead in maternal and children's blood. Occurrence rates of 90% of higher were observed for several PCBs, PBDE-47, mercury and lead, which indicates a high chance of co-occurrence. Besides PBDE-153, a lower occurrence rate was observed for arsenic (59% in maternal blood and 67% in children aged 6–12 years). Hence the chance of co-exposure to PBDE-153 and iAs is smaller, but still present. Assuming 100% co-exposure as we did in our study may have overestimated the personalised mRPI. More sophisticated methods to assess co-exposure patterns based on biomonitoring data are available, such as network analysis (Ottenbros et al., 2021), or external exposures such as the Sparse non-negative matrix under-approximation which has been applied to mothers' milk (EFSA 2021a; Crépet et al., 2022). Application of these methodologies may refine our analysis.

Human biomonitoring studies usually only analyse total mercury and arsenic (e.g. Haug et al., 2018; Julvez et al., 2021). As only methyl mercury and iAs are relevant for IQ loss, establishing co-exposures based on inspecting occurrence rates of total mercury and arsenic may introduce an element of uncertainty regarding co-exposures to methyl mercury and iAs. Measuring different forms of the metals may improve determination of co-exposures. Inclusion based on occurrence rates of total mercury and arsenic may have resulted in overestimations of exposure in the assessment, since occurrence rates of methylmercury and iAs may differ.

We also included fluoride in our case group, because fluoridation of drinking water is common practice in some European regions. Fluoride is not always considered in human biomonitoring studies. As fluoride may be obtained from other (dietary) sources (see 4.2.1 limitations) inclusion of fluoride in biomonitoring programs would be helpful to establish real-life mixtures.

4.1.7. Assessment group membership

With respect to the grouping of substances based on an effect on IQ loss, it should be noted that adverse effects of iAs and fluoride on IQ loss are still under debate. Based on the available evidence, the overall association between low-dose iAs exposure and IQ loss was considered as weak and therefore Tsuji et al. (2015) included only the study of Hamadani et al. (2011), a well-controlled study from the Bangladesh cohort with the most pronounced effect of iAs on IQ loss for the establishment of an ESRV. Some may question whether a substance can be considered as a member of the assessment group for IQ loss, based on overall weak associations with cognitive declines. According to the EFSA guidance on grouping, a higher degree of certainty in grouping efforts can be achieved when knowledge of an adverse outcome pathway (AOP) or the mode of actions is available (EFSA 2021a). Comprehensive AOPs for IQ loss have not yet been constructed and there is limited information on the mode of actions for IQ loss for the substances in our assessment group. Only the metals play a role in the AOP for deficits in learning and cognition (Von Stackelberg et al., 2015), but for the other substances included in our study the available information is limited. A putative AOP for developmental neurotoxicity as part of an integrated approach to testing and assessment was proposed recently by the EFSA PPR panel (EFSA 2021c). The use of AOPs in the classification of substances that have an effect on IQ loss can be evaluated in future studies. As iAs was included in the AOP of von Stackelberg et al. (2015), we included iAs in the assessment group IQ loss.

The detrimental effect of fluoride on cognitive function at low dose exposures in community fluoridation areas has been doubted by Guth et al. (2020, 2021). According to those authors, effects are predominantly observed in highly contaminated areas and from studies with shortcomings in design, such as small sample size and no adjustment for important cofounders, such as maternal IQ and co-exposure to other neurotoxicants. Some well-designed prospective studies from community water fluoridation areas which allowed for controlling well-known confounding factors showed contradictory results.

With respect to PBDE, two recent systematic reviews showed an adverse association between PBDE exposure and cognitive development in children (Lam et al., 2017; Gibson et al., 2018). Lam et al. (2017) concluded that sufficient evidence existed to support and association between developmental PBDE exposure in humans and IQ loss in children, Gibson et al. (2018) were more precautious in their conclusion because several uncontrolled confounders, such as co-exposure to known neurotoxicants, lack of statistical power due to small sample sizes and no statistical correction for multiple comparison, might have affected the outcome and impaired comparison across studies. Therefore, Gibson et al. (2018) advocated standardization of outcome assessment in future work.

4.1.8. ESRVs

Benchmark dose modelling is the preferred approach to establish ESRVs, since it makes a more extended use of dose-response data and it allows for quantification of the uncertainties in the dose-response data, in contrast to more simple approaches such as the NOAEL (EFSA 2017). To take the uncertainty of the benchmark dose into account, the lower bound of the confidence interval BMDL around the bench mark dose is used to derive the POD. In our case study, ESRVs based on BMDLs were obtained for lead, methyl mercury, fluoride, NDL-PCBs (Table 1 main text; all based on epidemiological data) and PBDEs (animal data). For iAs, only a LOAEL was available, which indicates that the ESRV of iAs is less robust.

In our study, we predominantly used ESRVs that were already published. As the aim of our case study was a proof of principle rather than a comprehensive risk assessment, we did not update established ESRVs as this was beyond the scope of our case study. Future research could update and/or refine ESRVs by using data from well-equipped mother/child cohorts addressing cognitive development, such as the HOME cohort; Kalloo et al., 2020, Braun et al., 2017 or the HELIX cohorts (Maitre et al., 2018). In our paper, we describe the uncertainties and indicate, where possible, whether this led to an under- or overestimation of the risk and the subsequent identification of the risk drivers. Table 5 summarizes those uncertainties, together with the direction of the effect on the risk. A detailed explanation on the uncertainties around the ESRVs is provided in Supplemental material E. A general uncertainty was the extrapolation of ESRVs derived for a certain age group to another age group, as was done for several substances (Tables 1 and 5). When extrapolating a reference point in urine or blood into an external dose, differences in kinetics between children and adults should be taken into account. Frequently noted uncertainties leading to overestimations of the personalised mRPI were: uncontrolled confounding (lead and iAs), cumulation of conservative assumptions for kinetic modelling (lead, iAs and PBDEs), and the choice of UFs (methyl mercury and PBDEs). An underestimation of the personalised mRPI was considered due to extrapolation of BMDLs (lead: extrapolation of the BMDL of women in their child-bearing age to toddlers and other children), assumptions for kinetic modelling (for fluoride), uncontrolled confounding for positive effects of fish consumption (methylmercury), inclusion of all dioxin-like PCBs in the ESRV of NDL-PCBS, and ignoring other relevant PBDE congeners.

4.1.9. Exposure data

Uncertainties in exposure data are related to food consumption data, occurrence data and matching food consumption data to concentration data. Sampling uncertainty in food and consumption data due to limited sampling size was quantified by bootstrapping (Efron 1979; Efron and Tibshirani 1993). This yielded the boundaries of the uncertainty interval around the personalised mRPI listed in Table 3, which indicate what the personalised mRPI could have been if other samples from the population and foods were used, assuming that representative sampling was applied. Generally, the upper boundary was about a factor 1.2 higher than the lower boundary at median personalised mRPI estimates, for the P95 the upper boundary was about a factor 1.5 higher. Only for some subpopulations was the ratio between the upper and lower boundary larger. This was predominantly applicable for subpopulations with a smaller size of less than 200 (Table 2). Exposure percentiles obtained for small subpopulations are statistically less robust. EFSA indicated that percentiles calculated over a number of subjects/days lower than 60 for the 95th percentile requires a cautious interpretation of the results since they may not be statistically robust (EFSA 2011b). As none of the lower boundaries of the uncertainty interval around the personalised mRPI is smaller than 1, the impact of sampling uncertainty on MRA is small.

Uncertainty around samples below the LOQ was addressed by the lower and upper bound scenario where those samples were substituted by zero or the value of the LOQ, respectively. Those scenarios were selected as they are frequently performed in risk assessment of contaminants. Other more realistic scenarios are available, such as the median bound (in which samples below the LOQ are assumed to equal half the value of the LOQ) and more sophisticated scenarios considering the distribution of samples below and above the LOQ.

Several other sources of uncertainties could not be quantified in our assessment. Those are listed in Table 6. A detailed description of the uncertainties is provided in Supplemental material F. Uncertainties included the use of the food coding system and assumptions made to handle data gaps. Table 6 also indicates the direction of the uncertainty: over- or underestimation of the personalised mRPI. In many cases, the direction of uncertainty was indeterminate. An exception was the use of conversion factors for methylmercury which resulted in an overestimation of the personalised mRPI and the contribution of methylmercury to the personalised mRPI. In addition, aggregation of foods in higher hierarchical FoodEx groups if less than 50 measurements per food group resulted in an overestimation of the iAs exposure and thus the personalised mRPI. Due to aggregating of foods (e.g. pasta, which could consist of rice-based pasta, such as rice noodles, and wheat-based pasta) and the oversampling of rice-based products compared with products

Table 5
Summary of sources of uncertainty around the endpoint-specific references values for IQ loss for lead, methyl mercury, inorganic arsenic (iAs), fluoride, non-dioxin-like perchlorinated biphenyls (NDL-PCBs) and polybrominated diphenyl ethers (PBDEs) and their effect on the personalised modified reference point index (personalised mRPI).

Substance	Type of uncertainty	Description	Direction effect on personalised mRPI	Reference
Lead	Uncontrolled confounding	Uncontrolled confounding, measurement error and other potential causal factors as common weaknesses were identified in the study of Lanphear, particularly for lead concentrations in blood below 50 or 100 μg/L. Whether this also affected piecewise linear function with breakpoint at 100 μg/L used by EFSA for the derivation of the $BMDL_{01}$ is not known to us.	+/−	Wilson and Wilson (2016), Van Landingham et al. (2021)
	Kinetic modelling	Conservative assumptions used for modelling dietary exposure out of blood concentrations.	+	EFSA 2010a
	Extrapolation $BMDL_{01}$ women childbearing age to other age groups	EFSA derived two $BMDL_{01}$s for IQ loss, one of 0.5 μg/kg bw per day for children aged 0–7 years and another one of 0.54 μg/kg bw/day for women in their child bearing age. Only 0.54 μg/kg bw/day was used in our study.	- (toddlers, other children)	EFSA 2010a
	Choice of UF	EFSA was in their opinion on the risk of lead not very clear which margin of exposure would be adequate, it could be interpreted as both 1 or 10. We used an UF of 1, while 10 could have been more appropriate.	–	EFSA 2010a
Methyl mercury	Point of departure	Considerable study uncertainty in the quantification of IQ loss upon prenatal methyl mercury exposure, with regression coefficients varying from 0 (no effect) to 1.5 (i.e. increase in the maternal hair concentration with 1 μg/g resulted in a loss of 1.5 IQ point). Differences could be explained by distinct exposure patterns, population genetic variability and nutrition (e.g. n-3 fatty acid intake).	+/−	Cohen et al. (2005)
	Uncontrolled confounding	While Rice et al. (2003) investigated the confounding effect of PCBs, they did not consider confounding beneficial effects of n-3 fatty acids in fish. When those were taken into account the ESRV was close to 0.1 μg/kg bw. Appropriate UFs were not provided.	- (if an UF is to be taken into account)	Groth (2017)
	Linear extrapolation $BMDL_{05}$ to $BMDL_{01}$	Not clear whether the UF of 10 covers the uncertainty caused by linear extrapolation of a $BMDL_{05}$ to a $BMDL_{01}$ as we did in our study	+/−	
	Choice of UF	Choice of UF varied from 10 in studies for IQ loss to 6.4 for other DNT effects derived from the same population(s). Difference is based on whether inter-species differences in toxicodynamics would require an additional UF. Rice et al., adapted the UF of US EPA (10), which based their study on 1 population. Rice et al. showed that the ESRV would not change when other (more sensitive) populations were included. EFSA and JECFA concluded that an UF for inter-species differences in toxicodynamics was not needed as a sensitive population was included. It should be noted that JECFA concluded that the UF could be further refined and reduced.	+	Rice et al. (2003) US EPA (2001) JECFA (2004) EFSA (2012)
iAs	Point of departure	Study uncertainty in the quantification of IQ loss due to large variability in studies caused by different study designs. The LOAEL was based on one well-designed study in a possible sensitive population due to malnutrition. Other well-designed studies were performed after the study of Hamadani. BMD modelling from all eligible studies would reduce uncertainty.	+/−	Tsuji et al. (2015)
	Uncontrolled confounding	Hamadani incompletely assessed maternal IQ, which is well-known confounder. Adjustment for study IQ in another study attenuated the association between iAs exposure and IQ loss. Studies performed after the study of Hamadani showed modest declines of IQ scores, with effects being more pronounced in girls than in boys. Residual confounding, such as exposure to other neurotoxicants could not be excluded.	+	Wasserman et al. (2011) Vahter et al. (2020)
	Kinetic model	Choice of parameter values and assumptions: Conservative assumption urinary excretion rates	+	Tsuji et al. (2011)
		Fraction of oral dose excreted in urine based on monkeys	+/−	
Fluoride	Point of departure	Boys more sensitive to the effect than girls. BMCL for pooled data (boys and girls used).	–	Grandjean et al. (2022)
	Kinetic model	The fractional retention of fluoride is only constant (i.e. 36% for adults) at a daily dietary intake of 2 mg/kg or higher (Villa et al., 2010). Below a total daily intake of 0.8 mg/day, fluoride excretion exceeds the intake, resulting in a negative fluoride balance. This means that at a daily urinary excretion of 0.3 mg, the consequent intake would be smaller than 0.3 mg/day instead of 0.6 mg/kg. Taken together, a urinary excretion of 0.3 mg/day leading to 1 IQ point loss is highly uncertain.	–	Rugg-Gunn et al. (2011), Villa et al. (2010)
		Extrapolation of maternal kinetics to children. Kinetics differ for different age groups	–	
		Use of upper boundary of interval around intake levels (highest intake), selection of midpoint would have led to a lower ESRV	–	
NDL-PCBs	Point of departure	ESRV based on total PCBs, which included dioxin-like PCBs, which are not associated with developmental neurotoxicity.	–	Jacobson et al. (2002), JECFA 2016 EFSA 2018

(*continued on next page*)

Table 5 (*continued*)

Substance	Type of uncertainty	Description	Direction effect on personalised mRPI	Reference
	Congener specific toxicity	Toxic potency could also differ between congeners. Preliminary neurotoxicity equivalency factors have been proposed, but not included in our study. The use of well-established neurotoxicity equivalency factors would result in a more precise estimation of the contribution of (individual) NDL-PCB to the combined exposure.	+/−	Simon et al. (2007), Rayne & Forest (2010), Pradeep et al., 2019).
	Kinetic model	Use of half-life of 10 years for all NDL-PCBs. NDL-PCB half-lives differ from 2.6 years for PCB 52 to 14.1 years for PCB 153	+/−	Ritter et al. (2011)
	Choice of UF	UF of 2 was applied for the extrapolation $BMDL_{05}$ to $BMDL_{01}$	+/−	
PBDEs	Point of departure	$BMDL_{10}$ for developmental neurotoxicity in animals rather than humans. It is not clear how the findings in the developmental neurotoxicity study in animals actually relate to IQ loss in children. Ideally data from epidemiological studies should be used. A recent meta-analysis of four prospective cohort studies pointed at a dose-dependent relationship between PBDE exposure and IQ loss. However, it was not possible to derive ESRVs for the different congeners. More human data on individual congeners are needed.	+/−	Lam et al. (2017), EFSA 2011a
		EFSA summarized the uncertainties in the animal studies affecting the ESRVs for developmental neurotoxicity, which included use of technological mixtures instead of pure congeners for toxicity studies, unknown levels of impurities, single dose administration during the pre- and postnatal period, no stratification of litter mates.	+	EFSA 2011a
	Congeners not considered	8 congeners, i.e. −28, −47, −99, −100, −153, −154, −183 and 209 were considered of primary importance by EFSA because of the composition of the technical PBDE mixtures and concentration in the environment and in food. Only PBDE -47, −99, −153, and −209 were included in the case study, because only ESRV were available for those congeners.	–	EFSA 2011a
	Kinetic model	Limited data on half-lives are available for PBDEs in human, and available data pointed at large variability. The largest half-lives of the individual congeners was used.	+	EFSA (2011a)
	Choice of UF	UF of 100 for PBDE-209, based on the study of Martin et al. According to EFSA, the animal $BMDL_{10}$ of 1.7 mg/kw bw expressed as an external dose can be compared with the estimated human dietary exposure, and EFSA related the exposure of PBDE-209 to the minimal margin of exposure of 2.5.	+	Martin et al. (2017) EFSA (2011a)

based on other grains, the personalised mRPI was overestimated. Exclusion of data for which no occurrence data were available (e.g. methylmercury in foods other than fish and seafood, NDL-PCBS in vegetable foods) resulted in an underestimation of the personalised mRPI.

The issue of limited concentration data used for certain substances can be addressed by including the entire EFSA data set which comprises 27 countries, rather than the 4–13 countries included in our study. However, this would not resolve the issue for NDL-PCBs and PBDEs congeners. For NDL-PCBs, concentration data for congeners other than the 6 indicator congeners were very limited. As those 6 indicator NDL-PCBs comprise approximately 50% of the total PCBs (EFSA 2005, 2012b; JECFA 2016), we calculated the exposure by multiplying the sum of the 6 congeners of NDL-PCB with a factor two. Particular if congeners would differ in potency, as described under uncertainties in ESRVs, the sum of 6 indicator congeners multiplied by two could have led to an under- or overestimation of the exposure. Once better information on potencies of the different congeners is available, the NDL-PCB congeners to be analysed in food can be reconsidered. Regarding PBDEs, concentration data (life stock meat, cow milk and eggs) for the four other congeners deemed relevant for dietary exposure by EFSA (2011a) were available in the concentration database.

5. Conclusions

Our case study shows that specific and targeted MRA using a component-based personalised mRPI approach can be performed for mixtures of dietary chemicals. The mixtures were selected in 1) having a high co-occurrence rate in human biomonitoring studies and 2) sharing a common adverse effect. By using this approach to estimate external dietary exposure, we performed MRA for the deleterious effect of combined exposure of lead, methyl mercury, iAs, fluoride, NDL-PCBs and PNDEs on cognitive development, determined by IQ loss.

All included populations exceeded the acceptable level of combined exposure. NDL-PCBs in fish, other seafood and dairy, lead in grains and fruits, methylmercury in fish and other seafoods, and fluoride in water contributed most to exposure and the subsequent risk. PBDEs hardly contributed to the combined exposure.

Uncertainties were identified for the likelihood of co-exposure, assessment group membership, values of ESRVs based on epidemiological (lead, methylmercury, iAS, fluoride and NDL-PCBs) and animal data (PBDE), and exposure data. Those uncertainties lead to a complex pattern of under- and overestimations, which would require probabilistic modelling based on expert knowledge elicitation for integration of the identified uncertainties into an overall uncertainty estimate. In addition, the listed uncertainties could be used to refine future MRA for cognitive decline.

CRediT author statement

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Table 6
Non-quantified uncertainties in exposure data.

Input data	Source	Description	Direction	Comment
Food consumption data	Food coding	Recoding FoodEx2 into FoodEx1	+/−	Not all food consumptions surveys were available in FoodEx1, the food coding used to match food consumption data to occurrence data. FoodEx2 is more refined, but currently the Dutch recipes database is not available in FoodEx2
		Food coding not always discriminate different food products (e.g. crackers which could be rice-based or wheat based).	+/−	FoodEx2 is more refined and could have prevented this issue
	Representativeness	Under sampling of specific consumption patterns	+/−	E.g. vegetarians, vegans
		Infrequently consumed foods	+/−	E.g. fish consumption in the Netherlands
	Number of reporting days	Extrapolation of few days of consumption to long-term exposure	+/−	Higher number of consumption days included (e.g. 7 days for Denmark) resulted in less uncertainty.
	Reporting foods	Underreporting of non-healthy foods and overreporting of health foods, frequency of consumption	+/−	
Occurrence data	Reported concentrations	Errors in reported concentrations or units	+/−	
	Measurement uncertainty	Analytical method not provided, measurement error	+/−	
	Limited data	Use of conversion factors:		Not applicable for other substances
		- iAs, mean of large range ratio iAs to total As (see Annex G)	+/−	
		- Methyl mercury (see Annex C)	+	
		- NDL-PCBs (Sum 6 indicator congeners times 2)	+/−	
		Aggregation of foods if less than 50 measurements were available:		
		- iAs	+	iAs in rice vs lower concentrations in other grains
		- Other substances	+/−	
		Exclusion of foods for which no data was obtained and for which above mentioned assumptions could not be used	-	
	Concentration data expressed per fat weight	Inaccurate description of the percentage fat weight in a sample. Assuming mean fat content of Dutch food composition database (NEVO)	+/−	Accounts only for NDL-PCBs and PBDEs
	Regional variability	Concentration in food and drinking water may vary between regions	+/−	Particularly for lead, iAs and fluoride in drinking water. Sensitivity analysis showed up to 14% lower pmRPIs when Dutch drinking water concentrations were used
	Measurements below LOQ	Assumed to be 0	–	Particularly when non-sensitive analytical methods (high LOQ) are used.
		Assumed to be value of LOQ	+	
	Processed foods	Processing (e.g. washing, cooking) may affect the concentration in food. Concentrations are often provided in raw agricultural commodities (e.g. wheat) or ingredients (wheat flour) but not in processed foods (e.g. wheat bread).	+/−	Processing factors were not used.
Matching food consumption data to occurrence data	Regional variability	Use of (mean of) Dutch food recipes data may not be representative to other countries	+/−	

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Appendix A. Supplementary data

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