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In-utero and childhood chemical exposome in six European mother-child cohorts

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ABSTRACT

Background: Harmonized data describing simultaneous exposure to a large number of environmental contaminants in-utero and during childhood is currently very limited.
Objectives: To characterize concentrations of a large number of environmental contaminants in pregnant women from Europe and their children, based on chemical analysis of biological samples from mother-child pairs.
Methods: We relied on the Early-Life Exposome project, HELIX, a collaborative project across six established population-based birth cohort studies in Europe. In 1301 subjects, biomarkers of exposure to 45 contaminants (i.e. organochlorine compounds, polybrominated diphenyl ethers, *per-* and polyfluoroalkyl substances, toxic and essential elements, phthalate metabolites, environmental phenols, organophosphate pesticide metabolites and cotinine) were measured in biological samples from children (6–12 years) and their mothers during pregnancy, using highly sensitive biomonitoring methods.
Results: Most of the exposure biomarkers had high detection frequencies in mothers (35 out of 45 biomarkers with > 90% detected) and children (33 out of 45 biomarkers with > 90% detected). Concentrations were significantly different between cohorts for all compounds, and were generally higher in maternal compared to children samples. For most of the persistent compounds the correlations between maternal and child concentrations were moderate to high (Spearman Rho > 0.35), while for most non-persistent compounds correlations were considerably lower (Spearman Rho < 0.15). For mercury, PFOS and PFOA a considerable

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proportion of the samples of both mothers and their children exceeded the HBM I value established by The Human Biomonitoring Commission of the German Federal Environment Agency.

Discussion: Although not based on a representative sample, our study suggests that children across Europe are exposed to a wide range of environmental contaminants in fetal life and childhood including many with potential adverse effects. For values exceeding the HBM I value identification of specific sources of exposure and reducing exposure in an adequate way is recommended. Considerable variability in this "chemical exposome" was seen between cohorts, showing that place of residence is a strong determinant of one's personal exposome. This extensive dataset comprising > 100,000 concentrations of environmental contaminants in mother-child pairs forms a unique possibility for conducting epidemiological studies using an exposome approach.

1. Introduction

A huge increase in industrial and technological development in the 20th century has led to the development of thousands of chemicals every year (CAS Registry, 2017). We are exposed to a wide variety of these chemicals on a daily basis. Many of them, among others a range of environmental contaminants, are suspected to have negative impacts on our health. Both fetuses and children are especially vulnerable to environmental contaminants, and thus it is of particular importance to assess prenatal and early life exposure to such compounds (Barouki et al., 2012). Environmental contaminants have been associated with effects on the nervous system, the immune system, and have also been linked to fetal growth and childhood obesity (Bellinger, 2013; Gascon et al., 2013; La Merrill and Birnbaum, 2011; Vrijheid et al., 2016; Wigle et al., 2008). In the context of simultaneous exposure to several environmental contaminants, some components of the mixture might modify the effect of others, so that the total effect of the mixture may differ from that of the sum of each individual compound (Backhaus et al., 2013). Thus, when assessing exposure - health associations, it may be important to apply a more holistic exposure approach (Backhaus et al., 2013; Robinson and Vrijheid, 2015; Wild, 2012). Up to now, there are plenty of studies available on one-exposure-one-health-outcome, however the data on multiple exposures for the same individuals are scarce (Robinson et al., 2015).

Human exposure to environmental contaminants occurs through several sources and exposure pathways, including consumption of contaminated food and drinking water, air and dust inhalation and ingestion, and dermal absorption after direct contact with consumer products including cosmetics. Furthermore, the fetus is also exposed to chemicals during pregnancy through placental transfer (Dallaire et al., 2014; Mamsen et al., 2017) and the child while being breastfed (van den Berg et al., 2017). For some environmental contaminants, such as *per*- and polyfluoroalkyl substances (PFASs), phthalate and organophosphorus flame retardants, children's exposure might be considerably higher and not necessarily associated with their mother's body burdens (Cequier et al., 2015; Papadopoulou et al., 2016; Sakhi et al., 2017), pointing towards considerable post-natal exposure or differences in toxicokinetics between mothers and children.

Furthermore, for some contaminants, there might be regional differences in the exposure, due to variations for instance in food consumption patterns and lifestyle. Also, the environmental contamination level (e.g. in food, air and dust) might vary between geographical locations (Harrad et al., 2010; Hlouskova et al., 2013). However, comparing levels between studies is usually challenging due to methodological differences, as both the sample collection method and the chemical analysis often differ substantially between studies. To overcome this, there is a need for greater harmonisation in sampling strategies, as shown in the European Union (EU) project DEMOCOPHES (Joas et al., 2012). Further, it is beneficial to minimise the technical uncertainty by relying on a single laboratory for all chemical analyses per compound group in subjects living in different countries, and thus avoid the need for including extensive quality assessment schemes for ensuring comparable data (Schindler et al., 2014).

The aim of this paper is to describe in-utero and childhood (6–12 years) exposure to a wide range of environmental contaminants in a large European population. We further aim to describe differences and correlations in the measured concentrations of environmental contaminants between mothers and their children. We relied on the Human Early Life Exposome (HELIX) project (Vrijheid et al., 2014). The HELIX project is a multilevel study including the entire HELIX cohort of 31,472 women as well as a subcohort of these women for which biological samples from women during pregnancy were withdrawn from existing biobanks and biological samples from their children were collected when the children were between 6 and 12 years of age (Maitre et al., 2018).

2. Methods

2.1. Study population

The participants in this study (n = 1301 mother-child pairs) were recruited from six birth cohorts across Europe as part of the HELIX project (Maitre et al., 2018): BIB (Born in Bradford, UK (n = 205) (Wright et al., 2013), EDEN (Study of determinants of pre- and postnatal developmental, France, n = 198) (Heude et al., 2016), INMA (Environment and Childhood, Spain, n = 223) (Guxens et al., 2012), KANC (Kaunas Cohort, Lithuania n = 204) (Grazuleviciene et al., 2009), MoBa (The Norwegian Mother and Child Cohort Study, Norway (Oslo region) n = 272) (Magnus et al., 2016) and RHEA (Mother–Child Cohort in Crete, Greece n = 199) (Chatzi et al., 2017). The participants were recruited among women included in the entire HELIX cohort (n = 31,472) (Maitre et al., 2018). Approximately 200 mother-child pairs, randomly selected among those fulfilling specific eligibility criteria, were recruited from each of the six birth cohorts. For further information on the cohorts and their inclusion and exclusion criteria see (Maitre et al., 2018) and supplementary information (SI, Tables S1).

All women completed a written consent at recruitment (during pregnancy), while the mother and/or father completed a written consent on behalf of the child at the time of the clinical assessment and collection of biological samples. Ethical permission for conducting the project was obtained from the relevant authorities in the six different countries.

2.2. Environmental contaminants in HELIX

The selected groups of environmental contaminants in HELIX were; organochlorine compounds (OCs) (n = 8), polybrominated diphenyl ethers (PBDEs) (n = 2), *per*- and polyfluoroalkyl substances (PFASs) (n = 5), toxic and essential elements (n = 14), phthalate metabolites (n = 10), environmental phenols (hereafter called phenols, n = 7), organophosphate (OP) pesticide metabolites (n = 6), and cotinine (Table 1). Results for seven essential elements are presented in SI Table S11, while results for the remaining forty-five environmental contaminants are described below.

2.3. Maternal biological samples during pregnancy

For all cohorts, the mothers were recruited (1999–2010) and

Table 1
Environmental contaminants and additional elements asssessed in blood and urine samples from mothers and their children in the HELIX subcohort.

Compound group	Compound	Abbreviation	Matrix – child samples	Matrix - maternal, pregnancy samples
Organochlorine compounds (OCs)	2,3′,4,4′,5-Pentachlorobiphenyl	PCB 118	Serum	Plasma (BIB, MoBa)
	2,2′,3,4,4′,5′-Hexachlorobiphenyl	PCB 138		Serum (BIB, EDEN, INMA, RHEA)
	2,2′,4,4′,5,5′-Hexachlorobiphenyl	PCB 153		
	2,2′,3,3′,4,4′,5-Heptachlorobiphenyl	PCB 170		
	2,2′,3,4,4′,5,5′-Heptachlorobiphenyl	PCB 180		
	4,4′dichlorodiphenyltrichloroethane	DDT		
	4,4′dichlorodiphenyldichloroethylene	DDE		
	Hexachlorobenzene	HCB		
Polybrominated diphenylethers (PBDEs)	2,2′,4,4′-Tetrabromodiphenyl Ether	PBDE 47	Serum	Plasma (BIB, MoBa)
	2,2′,4,4′,5,5′-Hexabromodiphenyl ether	PBDE 153		Serum (BIB, EDEN, INMA, RHEA)
Per- and polyfluoroalkyl substances (PFASs)	Perfluorohexane sulfonate	PFHxS	Plasma	Plasma (BIB, INMA, MoBa, RHEA)
	Perfluorooctane sulfonate	PFOS		Serum (BIB, EDEN)
	Perfluorooctanoate	PFOA		Whole blood (KANC)
	Perfluorononanoate	PFNA		
	Perfluoroundecanoate	PFUnDA		
Elements	Arsenic	As	Whole blood	Cord whole blood (INMA)
	Cadmium	Cd		Whole blood (BIB,EDEN, KANC, MoBa, RHEA)
	Cobalt	Co		
	Cesium	Cs		
	Copper	Cu		
	Mercury	Hg		
	Potassium	K		
	Magnesium	Mg		
	Manganese	Mn		
	Molybdenum	Mo		
	Sodium	Na		
	Lead	Pb		
	Thallium	Tl		
	Zinc	Zn		
Phthalate metabolites	Monoethyl phthalate	MEP	Urine: pool of night and morning urine	Urine - 1 spot sample in trimester 1, 2 or 3 (see SI, Table S2)
	Mono-isobutyl phthalate	MiBP		
	Mono-*n*-butyl phthalate	MnBP		
	Mono benzyl phthalate	MBzP		
	Mono-2-ethylhexyl phthalate	MEHP		
	Mono-2-ethyl-5-hydroxyhexyl phthalate	MEHHP		
	Mono-2-ethyl-5-oxohexyl phthalate	MEOHP		
	Mono-2-ethyl 5-carboxypentyl phthalate	MECPP		
	Mono-4-methyl-7-hydroxyoctyl phthalate	oh-MiNP		
	Mono-4-methyl-7-oxooctyl phthalate	oxo-MiNP		
Phenols	Methyl paraben	MEPA	Urine: pool of night and morning urine	Urine - 1 spot sample in trimester 1, 2 or 3 (see SI, Table S2)
	Ethyl paraben	ETPA		
	Propyl paraben	PRPA		
	N-Butyl paraben	BUPA		
	Bisphenol-A	BPA		
	Oxybenzone	OXBE		
	Triclosan	TCS		
Organophosphate (OP) pesticide metabolites	Dimethyl phosphate	DMP	Urine: pool of night and morning urine	Urine - 1 spot sample in trimester 1, 2 or 3 (see SI, Table S2)
	Dimethyl thiophosphate	DMTP		
	Dimethyl dithiophosphate	DMDTP		
	Diethyl phosphate	DEP		
	Diethyl thiophosphate	DETP		
	Diethyl dithiophosphate	DEDTP		
Cotinine	Cotinine	Cotinine	Urine: pool of night and morning urine	Urine - 1 spot sample in trimester 1, 2 or 3 (see SI, Table S2)

biological samples collected during pregnancy, and this study used these biological samples that were stored in the cohort biobanks. More specifically, the year of birth for children in the various cohorts were as follows; BIB (2007–2010); EDEN (2003–2006); INMA (2003–2008); KANC (2007–2008); MoBa (1999–2008); RHEA (2007–2008). The maternal samples from the various cohorts were collected at different time points; INMA, KANC, RHEA recruited during the 1st trimester, EDEN and MoBa recruited during the 1st and 2nd trimesters and BIB recruited during the 2nd and 3rd trimesters. The mean (SD) gestational ages (weeks) at blood sample collection were 26.6 (1.4), 26.1 (1.2), 13.7 (2.0), 39.4 (1.3), 18.7 (0.9) and 14.1 (3.7) for BIB, EDEN, INMA, KANC, MoBa and RHEA, respectively. Further information on matrixes and collection time points can be found in SI, Table S2.

For most of the maternal biological samples, one laboratory performed all measurements for each individual chemical exposure biomarker, to reduce measurement uncertainty (see SI, Table S4). However, for INMA, EDEN and RHEA, some environmental contaminants had been measured previously in all or a considerable part of the samples (see SI, Tables S3–S4). Thus, these results were made available for this study and were used in the statistical analyses. For PFASs, phthalate metabolites and phenols, some but not all biological samples from INMA and EDEN had been analyzed previously, and thus the remaining samples were analyzed at a different laboratory. To ensure comparable results, 10 samples were analyzed in both labs (see SI, Table S6 for further information).

Depending on the contaminant, results are presented for 648 to 1240 maternal samples. There are several reasons for the variety in the number of measurements available. For all cohorts some maternal samples of various matrices were not available in the biobanks. Further, for KANC only whole blood was collected during pregnancy, and thus

neither OCs, PBDEs, phthalate metabolites, phenols nor OP pesticide metabolites could be determined. MEPA and ETPA were not reported in the MoBa samples, as the sample collection containers were contaminated with these compounds. PBDEs had previously been analyzed in the RHEA samples, but these analyses did not include BDE 153 which is thus lacking in this data set. OCs except PCB 170 and DDT had previously been measured in the INMA samples, and no additional serum/plasma was available for assessing these two contaminants as well as PBDEs in this cohort. Further, no whole blood was available for analysis of metals and elements in INMA, but data for Hg was obtained from previous analyses of cord blood.

For OCs, PBDEs, PFASs and Hg, different samples matrices were used for analyses (see SI, Table S4 for further information). For OCs and PBDEs, the concentrations in serum and plasma were assumed to be comparable (1:1 ratio) (Grimvall et al., 1997). For the PFASs, 1:1 ratios were assumed for serum and plasma, while 1:2 ratios were used for whole blood vs serum/plasma (Poothong et al., 2017). Thus, for PFASs all whole blood concentrations were multiplied by two. Finally, cord blood mercury concentrations were divided by 1.7 to be comparable with maternal whole blood concentrations (Stern and Smith, 2003).

2.4. Child biological samples

Children were recruited and biological samples collected between the age of 6 and 12 years (mean: 8.1; IQR: 6.5–8.9). The assessments of children were conducted between December 2013 and February 2016 and included clinical measurements, neurological testing, as well as blood and urine collections (see (Vrijheid et al., 2014) and (Maitre et al., 2018) for further details on the assessments and baseline data of e.g. health outcomes and health determinants). The assessments of all children were performed in a completely harmonized way using the same protocols for sample collection and clinical examination in all the

Table 2
Concentrations of environmental contaminants in blood and urine samples from mothers and children in the HELIX sub cohort.

		Maternal samples						Child samples					
Compound		P25	P50	P75	Max	n analyzed	% quantifiable samples	P25	P50	P75	Max	n analyzed	% quantifiable samples
PCB 118	ng/g lipid	1.57	2.64	4.82	39.0	829	79.1	1.51	1.98	2.94	134	1279	99.8
PCB 138	ng/g lipid	5.54	9.10	16.1	132	1048	96.5	3.36	5.37	8.70	215	1279	99.8
PCB 153	ng/g lipid	10.4	17.6	30.5	214	1048	99.6	7.28	11.6	18.6	217	1279	100
PCB 170	ng/g lipid	1.84	3.69	7.06	84.5	826	99.5	0.56	1.26	2.75	27.5	1279	90.7
PCB 180	ng/g lipid	5.78	10.4	18.6	201	1048	97.6	1.62	3.68	8.02	62.5	1279	99.2
DDT	ng/g lipid	0.82	1.33	3.06	94.1	826	65.6	0.28	0.71	1.65	198	1279	79.8
DDE	ng/g lipid	25.9	52.3	111	1903	1048	99.9	11.6	21.8	45.6	2158	1279	100
HCB	ng/g lipid	5.59	8.16	13.0	164	1048	99.1	6.27	8.19	11.4	88.1	1279	99.9
PBDE 47	ng/g lipid	0.27	0.43	0.75	34.74	684	80.8	0.15	0.23	0.37	41.7	1279	90.8
PBDE 153	ng/g lipid	0.03	0.45	0.66	198	648	72.9	0.03	0.16	0.42	16.5	1279	54.4
PFOA	μg/L	1.38	2.30	3.34	31.6	1240	99.7	1.19	1.55	1.97	6.66	1301	100
PFNA	μg/L	0.43	0.69	1.08	5.92	1240	97.9	0.30	0.47	0.72	11.5	1301	99.5
PFUnDA	μg/L	0.10	0.19	0.29	2.80	1032	95.4	0.02	0.03	0.09	1.51	1301	68.6
PFHxS	μg/L	0.31	0.55	0.91	21.0	1240	97.5	0.19	0.36	0.61	28.5	1301	99.7
PFOS	μg/L	4.12	6.41	9.63	48.0	1240	100	1.26	2.03	3.22	33.8	1301	99.8
As	μg/L	0.28	1.19	2.27	90.1	833	58.5	0.28	1.37	2.34	63.6	1298	67.1
Cd	μg/L	0.15	0.22	0.33	27.9	833	99.6	0.04	0.07	0.09	1.79	1298	86.5
Cs	μg/L	1.19	1.56	2.15	10.9	833	100	1.04	1.38	1.77	8.37	1298	100
Hg	μg/L	0.98	1.90	3.45	43.5	1020	98.9	0.42	0.86	1.75	20.1	1298	97.7
Pb	μg/L	7.14	9.66	13.20	187	833	100	6.39	8.53	11.1	213	1298	100
Tl	μg/L					833	1.1					1298	7.2
MEP	μg/g creat.	72.0	179	469	17,733	1080	99.0	16.4	33.5	76.4	3197	1301	100
MiBP	μg/g creat.	23.3	38.7	60.7	705	1088	99.9	25.9	41.8	73.3	861	1301	100
MnBP	μg/g creat.	18.3	29.6	47.3	6445	1089	100	15.3	23.9	38.3	488	1301	100
MBzP	μg/g creat.	3.63	7.33	15.3	775.1	1088	99.7	3.00	5.00	8.51	351	1300	99.9
MEHP	μg/g creat.	4.42	8.73	15.3	417	1085	99.5	1.70	2.88	5.10	282	1260	96.8
MEHHP	μg/g creat.	10.5	18.2	31.2	967	1089	100	12.2	20.1	33.2	2241	1298	99.8
MEOHP	μg/g creat.	8.29	14.1	23.7	783	1089	100	7.66	12.5	20.8	1289	1300	99.9
MECPP	μg/g creat.	22.4	33.6	52.3	1361	913	99.9	21.5	35.1	59.5	3681	1300	99.9
oh-MiNP	μg/g creat.	0.61	0.91	1.47	66.5	914	92.6	3.38	5.36	9.26	548	1301	100
oxo-MiNP	μg/g creat.	0.62	1.03	1.75	75.1	914	95.7	1.86	2.83	4.87	680	1301	100
MEPA	μg/g creat.	39.5	167	389	39,241	815	99.8	3.28	6.50	26.4	23,963	1299	99.7
ETPA	μg/g creat.	1.14	6.26	26.72	6774	817	97.4	0.43	0.67	1.22	2033	1298	99.3
PRPA	μg/g creat.	8.87	44.2	134	12,463	1083	97.3	0.02	0.22	1.68	1758	1284	67.3
BUPA	μg/g creat.	0.36	3.37	14.4	371	1083	97.0	0.04	0.08	0.16	96.8	1296	96.6
BPA	μg/g creat.	1.55	2.82	6.60	107	1084	99.4	2.42	4.06	7.17	362	1289	98.3
OXBE	μg/g creat.	1.46	4.90	27.5	12,837	1085	99.3	0.86	2.16	6.96	7985	1301	99.9
TCS	μg/g creat.	1.50	6.28	79.9	1653	1085	98.5	0.32	0.61	1.50	702	1301	100
DMP	μg/g creat.	4.13	8.37	16.4	321	1080	90.8	0.29	0.78	4.70	83.3	1295	49.3
DMTP	μg/g creat.	2.05	4.96	12.4	220	1084	88.9	1.27	2.99	6.50	405	1300	90.4
DMDTP	μg/g creat.	0.05	0.19	1.54	134	969	41.6					1300	18.2
DEP	μg/g creat.	1.86	3.33	6.44	198	1082	97.8	0.47	1.83	4.52	665	1299	80.9
DETP	μg/g creat.	0.12	0.58	2.56	44.3	1037	50	0.10	0.18	1.72	78.5	1280	43.5
DEDTP	μg/g creat.					1084	1.7					1301	1.5
Cotinine	μg/g creat.	1.49	5.25	23.7	15,410	1093	43.7					1301	17.4

n analyzed: samples with biomarker measurements and fat/creatinine measurements.
P25: 25th percentile.
P50: 50th percentile.
P75: 75th percentile.
% quantifiable samples: % of the biomarker measurements with concentrations reported.
For compounds with < 20% detection frequency no statistical calculations were performed.

six cohorts. There was a thorough training of the fieldworkers, and supervision through visits during the establishment of the subcohort by the subcohort coordinator. The urine sample analyzed was a pool of equal amounts of two spot urine samples collected at bed time the day before and in the morning the day of the clinical examination. The blood sample was drawn the same day as all clinical measurements and neurological testing were performed.

To reduce measurement uncertainty and obtain as comparable results as possible, one laboratory performed all measurements for each individual chemical exposure biomarker. The samples were randomized into batches before chemical analyses, aiming at a minimum of three cohorts to be included in each batch.

2.5. Chemical analysis

A list of the environmental contaminants determined in urine and blood of maternal and child samples is given in Table 1. Creatinine concentrations were determined in all urine samples to facilitate adjustments for variation in urinary dilution. Similarly, plasma/serum lipids were determined to be able to report concentrations of the lipophilic compounds (PCBs, PBDEs, DDT, DDE and HCB) per gram of lipid.

Analyses of all environmental contaminants determined as part of the HELIX project were performed at the Department of Environmental Exposure and Epidemiology at the Norwegian Institute of Public Health (NIPH), in Norway or in collaboration with their contract laboratories (elements, creatinine, cotinine and lipids). In addition, already available data for some cohorts were included for specific groups of compounds. Further details, references to the chemical analyses methods and limit of quantification (LOQ)/limit of detection (LOD) are described in SI, Tables A2–A5.

Concentrations of triglycerides, phospholipids and total cholesterol were determined enzymatically, and calculated according to the method described by (Grimvall et al., 1997).

Procedure blanks were prepared in the same way as real samples and were analyzed along with each batch of samples. For almost all compounds the procedure blanks were below or equal to the LOD. Low concentrations of PCB 153 and HCB, were detected, but no blank subtraction was performed as no trends in the blank levels were observed during the 18 months analysis period. In some few sample preparation batches, the DEP concentrations in the procedure blanks were considerable, and thus the mean blank level was subtracted from the sample concentrations for the samples included in these batches.

For all methods, internal quality control (QC) samples were analyzed along with each batch of samples to ensure high quality of the

Table 3

Median concentrations of environmental contaminants in blood and urine samples from mothers and children in the six cohorts included in the HELIX sub cohort study.

		Maternal samples						Child samples					
Compound		BIB	EDEN	INMA	KANC	MoBa	RHEA	BIB	EDEN	INMA	KANC	MoBa	RHEA
PCB 118	ng/g lipid	1.54	6.60			3.63	1.56	1.45	2.37	1.79	3.93	2.23	1.59
PCB 138	ng/g lipid	3.41	22.8	10.9		10.2	6.05	2.73	5.34	5.28	8.39	8.31	3.73
PCB 153	ng/g lipid	7.39	45.7	19.6		21.2	11.5	6.04	11.1	12.3	15.3	18.6	7.84
PCB 170	ng/g lipid	1.12	13.4			4.03	3.37	0.42	1.23	1.66	1.31	3.26	0.61
PCB 180	ng/g lipid	3.55	35.4	13.6		11.5	6.40	1.14	3.59	5.35	3.68	9.22	1.79
DDT	ng/g lipid	1.00	2.55			0.96	1.39	0.31	0.61	0.44	2.23	0.46	1.74
DDE	ng/g lipid	24.9	64.1	62.8		26.6	168	11.1	12.9	17.3	47.1	17.9	60.1
HCB	ng/g lipid	4.69	9.24	23.0		7.44	7.58	6.71	6.24	7.68	20.6	9.77	7.50
PBDE 47	ng/g lipid	0.39	0.39			0.43	1.92	0.27	0.27	0.20	0.23	0.24	0.18
PBDE 153	ng/g lipid	0.60	0.31			0.41		0.34	0.03	0.03	0.10	0.30	0.03
PFOA	μg/L	1.99	3.49	2.77	1.02	2.14	2.39	1.88	1.46	1.44	1.30	1.76	1.32
PFNA	μg/L	0.34	0.93	0.79	0.65	0.50	1.40	0.26	0.51	0.44	0.43	0.80	0.45
PFUnDA	μg/L	0.03	0.16	0.30	0.20	0.25	0.28	0.02	0.05	0.03	0.02	0.08	0.03
PFHxS	μg/L	0.46	1.01	0.79	0.35	0.64	0.27	0.33	0.64	0.32	0.15	0.62	0.13
PFOS	μg/L	3.88	13.4	6.15	4.34	9.21	5.33	1.52	3.01	1.43	1.24	3.21	2.16
As	μg/L	1.02	1.43		0.28	2.01	1.46	1.41	1.55	1.78	0.28	1.49	1.31
Cd	μg/L	0.23	0.19		0.19	0.18	0.32	0.07	0.07	0.05	0.06	0.08	0.06
Cs	μg/L	1.21	1.91		1.19	2.23	1.49	1.13	2.02	1.54	0.87	1.64	1.23
Hg	μg/L	1.10	3.01	3.94	0.68	1.94	2.84	0.77	1.78	1.93	0.27	0.82	0.69
Pb	μg/L	8.68	12.2		11.00	8.44	10.10	8.82	9.58	8.89	9.47	6.27	8.57
MEP	μg/g creat.	182	132	355		153	140	46.4	42.8	84.8	27.6	13.8	33.4
MiBP	μg/g creat.	37.2	56.7	31.9		30.5	41.4	63.8	37.3	29.6	76.7	25.0	48.7
MnBP	μg/g creat.	22.7	46.6	27.8		31.6	20.9	25.6	18.1	15.4	44.6	24.7	24.9
MBzP	μg/g creat.	3.50	20.3	9.56		5.85	5.10	2.71	6.01	4.98	6.43	4.19	6.58
MEHP	μg/g creat.	3.65	9.67	8.29		12.4	6.84	3.12	1.89	3.44	3.41	1.92	5.32
MEHHP	μg/g creat.	9.19	29.2	19.5		17.8	18.5	22.7	11.0	21.2	27.6	12.1	36.7
MEOHP	μg/g creat.	8.38	22.3	15.8		13.2	12.6	12.8	6.98	13.0	17.9	8.05	23.1
MECPP	μg/g creat.	25.6	43.9	30.7		34.5	31.2	39.2	17.7	36.1	51.8	22.7	67.1
oh-MiNP	μg/g creat.	0.74	0.75	1.34		1.37	0.89	7.71	3.69	5.42	4.92	4.98	5.79
oxo-MiNP	μg/g creat.	0.88	0.85	1.25		1.29	1.03	3.23	1.99	3.16	2.61	2.53	4.13
MEPA	μg/g creat.	180	102	240			149	11.9	4.47	15.0	7.50	4.11	5.77
ETPA	μg/g creat.	2.12	3.92	15.3			5.13	0.71	0.58	0.73	0.72	0.63	0.68
PRPA	μg/g creat.	62.9	12.5	54.9		70.4	26.5	0.74	0.07	1.29	0.11	0.04	0.08
BUPA	μg/g creat.	0.50	1.27	4.23		10.9	0.99	0.07	0.04	0.11	0.11	0.08	0.09
BPA	μg/g creat.	1.59	2.50	2.68		9.54	1.98	4.84	2.35	3.99	3.73	4.66	4.79
OXBE	μg/g creat.	7.66	1.70	3.63		15.0	3.45	3.78	0.62	2.13	2.50	3.23	1.74
TCS	μg/g creat.	3.52	25.3	33.8		3.15	2.53	1.33	0.60	1.03	0.84	0.25	0.50
DMP	μg/g creat.	3.81	11.6	10.41		9.34	8.25	0.50	0.77	0.54	0.48	2.16	2.28
DMTP	μg/g creat.	1.87	7.26	5.45		5.59	5.44	2.34	3.37	3.60	2.68	2.66	3.80
DMDTP	μg/g creat.	0.07	0.89	0.14		0.13	0.89						
DEP	μg/g creat.	2.99	3.82	3.55		3.68	2.83	3.38	1.63	1.64	0.81	2.43	2.18
DETP	μg/g creat.	0.66	0.90	0.26		0.81	0.37	0.17	0.15	0.25	0.14	0.17	0.83
Cotinine	μg/g creat.	5.16	2.93	4.99		3.47	22						

determinations throughout the project. To monitor possible batch differences during the project, the results of all internal control samples were plotted in quality control charts per contaminant. This was of particular importance for the maternal samples where randomisation of samples from several cohorts in each batch of samples was not feasible. The results were found satisfactory and no batch correction was applied. Furthermore, Certified Reference Materials or samples from previous interlaboratory comparisons were available for OCs, PBDEs, PFASs, phthalate metabolites and phenols, as well as for toxic and essential elements, which were analyzed at regular intervals and minimum once per 200 samples. For OCs, PBDEs, PFASs and selected phenols, the laboratory at NIPH also participated in at least one interlaboratory comparison during the period when HELIX samples were analyzed. For further information see SI, Table S12.

2.6. Statistical analyses

For all determinations conducted at the NIPH or their contract laboratories, concentrations were also reported below LOQ whenever a signal was observable on the instrument. These results were used in the statistical calculations. For samples where no concentrations had been generated (concentrations below LOD), singly imputed values were obtained using a quantile regression approach for the imputation of left-censored missing data implemented in the *imputeLOD* function available in the *rexposome* package in the R software (The R Project (Computing TRPfS, 2016)).

Concentrations of OCs and PBDEs are presented in ng/g lipid, while the results for phthalate metabolites, phenols and OP pesticide metabolites are given as µg/g creatinine. Crude blood and urine concentrations in maternal and child samples were summarized by descriptive statistics (Table 2). In the descriptive statistics, we have presented data for compounds that were quantified in > 20% of the samples. The concentration distributions were tested for normality using Shapiro-Wilk test, and as expected, none of the distributions were normally distributed. Thus, non-parametric tests were used in the statistical analyses. These analyses were limited to compounds for which

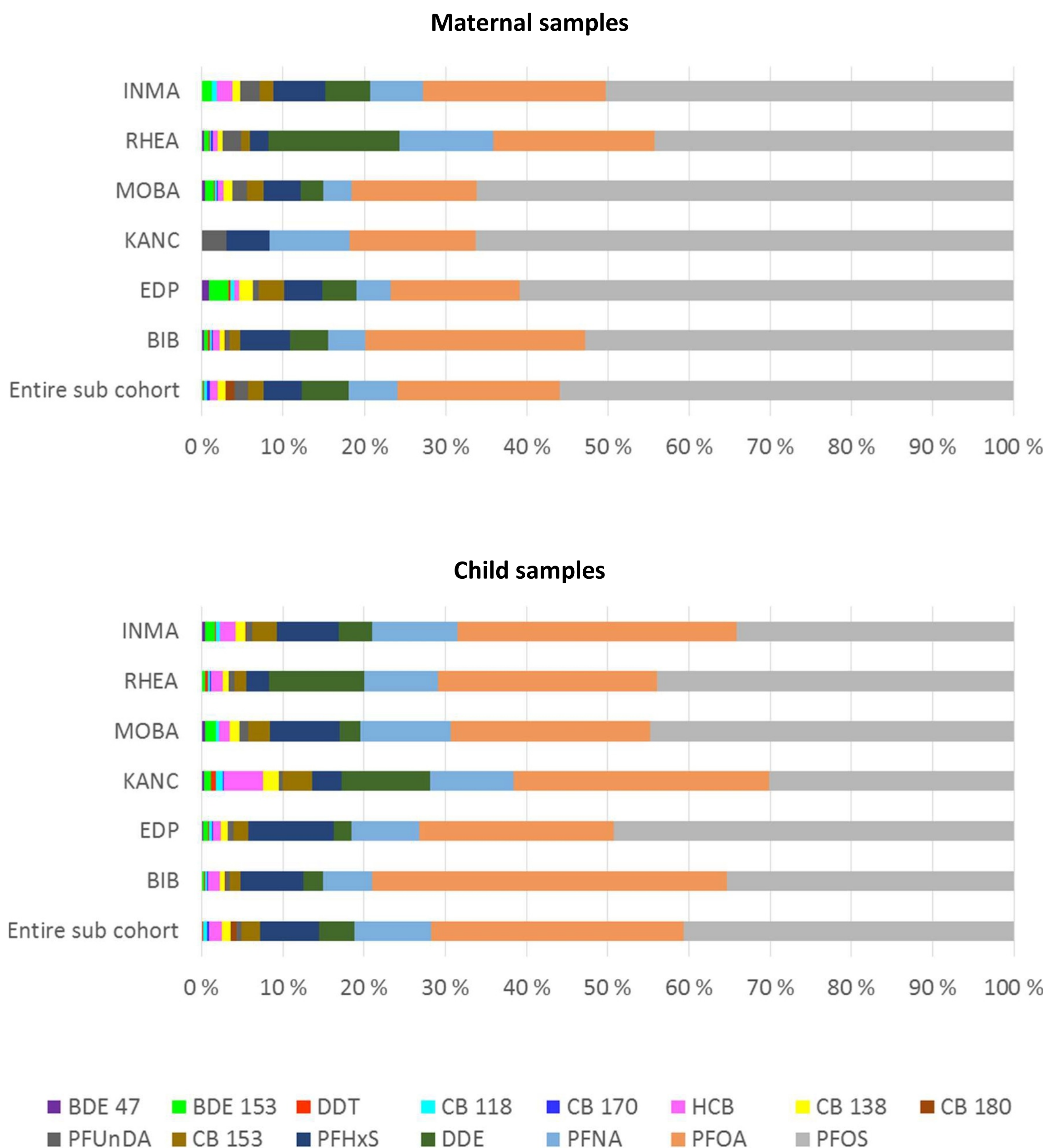

Fig. 1. Relative distribution of OCs, PBDEs and PFASs in plasma/serum from mothers and their children.

the proportion of quantifiable samples was above 50%.Wilcoxon Rank Sum test was used to assess pairwise differences between maternal and child samples. Differences between cohorts were explored using Kruskal-Wallis test for mothers and children, and correlations between mothers and children were evaluated using Spearman Rank Correlation coefficients (rho). Differences between cohorts were also assessed for the child samples after adjustment for child age, as the age of the children at sample collection varied systematically and considerably between cohorts (Maitre et al., 2018). *P*-values < 0.05 were considered statistically significant in all statistical tests. All statistical analyses were performed using the SPSS Version 23 (Chicago, IL, USA).

Relative contributions of OCs, PBDEs and PFASs in serum/plasma for maternal and child samples were calculated based on unadjusted concentrations for OCs, PBDEs (ng/g) and assuming that 1 g plasma/serum equals to 1 mL of plasma/serum. For evaluation of the relative contributions of the non-persistent compounds in urine, one phthalate metabolite was chosen per parent compound (i.e. MEHHP and oh-MINP were chosen as representatives of diethylhexyl phthalate (DEHP) and diisononyl phthalate (DINP), respectively).

3. Results

Basic characteristics for the entire subcohort as well as separately for all six cohorts have been described in (Maitre et al., 2018). Approximately 45% of the subcohort children were females and 90% were Caucasian. The mean (interquartile range (IQR)) child age at sample collection for the entire subcohort was 8.1 (6.5–8.9) years, and differed between cohorts being 6.6 (6.5–6.8) years for BIB, 10.9 (10.4–11.2) years for EDEN, 8.8 (8.4–9.2) years for INMA, 6.4 (6.1–6.8) years for KANC, 8.5 (8.2–8.8) years for MoBa and 6.5 (6.4–6.6) years for RHEA (Maitre et al., 2018). Similarly, the means (interquartile range (IQR)) of the maternal ages at sample collection were 28.6 (25.0–33.0) years for BIB, 30.5 (27.5–34.0) years for EDEN, 32.0 (29.5–34.8) years for INMA, 29.2 (25.7–32.3) years for KANC, 32.7 (30.0–35.0) years for MoBa and 30.8 (27.3–34.0) years for RHEA.

3.1. Maternal concentrations during pregnancy

For 35 of the 45 compounds considered, the proportion of

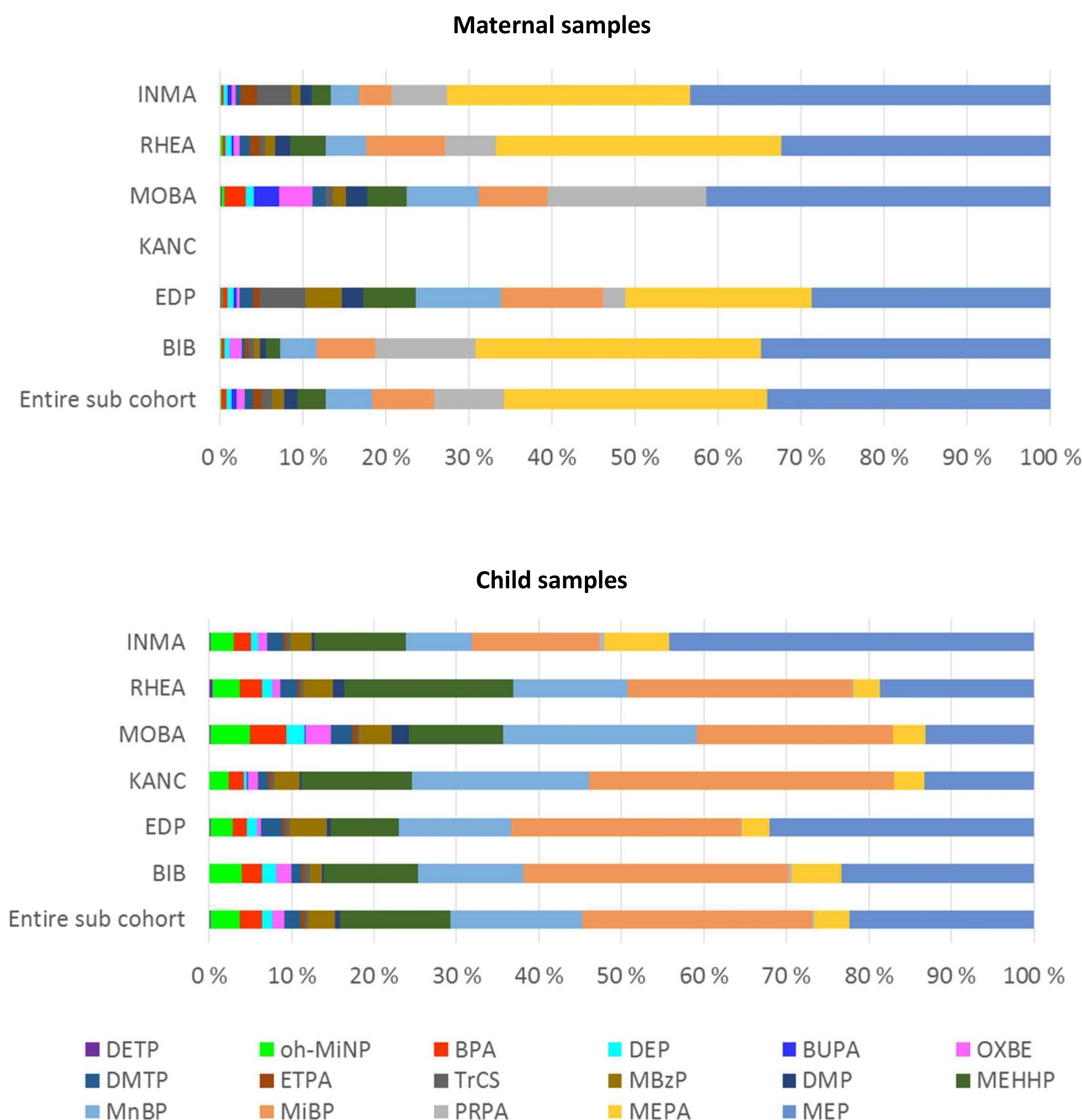

Fig. 2. Relative distribution of non-persistent compounds in urine samples from mothers and their children.

quantifiable samples was above 90% (Table 2). The highest median concentrations within each group of contaminants were observed for DDE (52.3 ng/g lipid), PFOS (6.41 ng/mL), Pb (9.66 µg/L), MEP (179 µg/g creatinine), MEPA (167 µg/g creatinine) and DMP (8.37 µg/g creatinine). The compounds with the highest median concentrations were the same when exploring the data cohort by cohort as for the entire subcohort (see Table 3 and SI, Table S7). Statistically significant differences in the concentrations were found between cohorts for all contaminants, and for many compounds relatively large between-cohort differences were observed. Within the different groups of compounds, the cohort with the highest median concentration varied between compounds. For instance, for OCs, BIB, EDEN, INMA and RHEA had at least one compound for which they had the highest median concentration. The largest relative differences between cohorts were observed for PCB 170, PCB180, PFUnDA, BUPA, TCS and DMDTP, where the median concentrations were at least ten times higher in the cohorts with the highest median concentration compared to the ones with the lowest.

3.2. Child concentrations

For 33 of 45 contaminants, > 90% of the samples were quantifiable, and only nine contaminants were quantifiable in < 70% of the samples (Table 2). The most abundant contaminants within each contaminant group were the same as for the maternal samples, except that for phthalates the highest median concentration in the child samples was observed for MiBP and that, among OP pesticide metabolites, DMTP had the highest median concentration.

When exploring the data by individual cohorts (Table 3, SI, Table S8), the picture was more complex. Statistically significant differences between two or more cohorts were seen for all contaminants, and this was also the case when adjusting for age of the child at sample collection (data not shown). Among OCs and PBDEs, the highest median concentration was found for DDE in all cohorts except for MoBa where PCB 153 was the most abundant compound. For PFASs, PFOS was the most abundant contaminant in the samples from EDEN, MoBa and RHEA, while for BIB and KANC, PFOA was found in the highest median concentration. For INMA the median concentrations of PFOS and PFOA were similar. Also for phthalates the most abundant contaminant varied by cohort, being MEP for EDEN, MECPP for RHEA and MiBP for the four remaining cohorts. For phenols, MEPA was the most abundant contaminant in all cohorts except MoBa, where the highest median concentration was observed for BPA.

3.3. Relative contributions of environmental contaminants

The median relative contributions of the POPs and PFASs in serum/plasma from maternal and child samples are presented in Fig. 1, both for the entire subcohort and also by cohort. Similarly, in Fig. 2 the median relative contributions of the three groups of non-persistent

Table 4
Correlations and differences between measured concentrations of environmental contaminants in blood and urine samples from mothers and children in the HELIX sub cohort.

Compound	Median difference between child and maternal samples		Median % difference between child and maternal samples	Spearman correlation, rho	n pairs
PCB 118	−0.77**	ng/g lipid	−29.4	0.51**	817
PCB 138	−4.06**	ng/g lipid	−44.7	0.49**	1032
PCB 153	−6.72**	ng/g lipid	−38.3	0.49**	1032
PCB 170	−2.56**	ng/g lipid	−69.9	0.47**	814
PCB 180	−6.55**	ng/g lipid	−63.8	0.52**	1032
DDT	−0.75**	ng/g lipid	−56.6	0.39**	814
DDE	−34.1**	ng/g lipid	−64.8	0.57**	1032
HCB	−0.66**	ng/g lipid	−8.1	0.14**	1032
PBDE 47	−0.17**	ng/g lipid	−39.4	0.20**	674
PBDE 153	−0.18**	ng/g lipid	−39.6	0.28**	638
PFOA	−0.74**	µg/L	−32.2	0.19**	1240
PFNA	−0.21**	µg/L	−31.2	0.19**	1240
PFUnDA	−0.16**	µg/L	−82.3	0.27**	1032
PFHxS	−0.18**	µg/L	−32.7	0.51**	1240
PFOS	−4.41**	µg/L	−68.7	0.50**	1240
As	0.07	µg/L	5.9	0.21**	831
Cd	−0.15**	µg/L	−68.7	0.023	831
Cs	−0.30**	µg/L	−19.2	0.60**	831
Hg	−1.14**	µg/L	−59.8	0.50**	1018
Pb	−1.30**	µg/L	−13.4	0.37**	831
MEP	−142**	µg/g creat.	−79.6	0.17**	1080
MiBP	−0.97	µg/g creat.	−2.5	0.13**	1088
MnBP	−8.21**	µg/g creat.	−27.7	0.11**	1089
MBzP	−2.63**	µg/g creat.	−35.8	0.21**	1087
MEHP	−5.81**	µg/g creat.	−68.0	−0.034	1049
MEHHP	−0.28	µg/g creat.	−1.5	−0.073*	1086
MEOHP	−2.82**	µg/g creat.	−20.0	−0.070*	1088
MECPP	−4.06	µg/g creat.	−12.1	−0.088**	912
oh-MiNP	4.65**	µg/g creat.	513.9	0.021	914
oxo-MiNP	1.82**	µg/g creat.	176.5	0.014	914
MEPA	−159**	µg/g creat.	−95.3	0.064	815
ETPA	−5.49**	µg/g creat.	−89.2	0.13**	815
PRPA	−43.6**	µg/g creat.	−99.5	0.091**	1068
BUPA	−3.29**	µg/g creat.	−97.7	0.089**	1078
BPA	1.28**	µg/g creat.	45.5	0.088**	1074
OXBE	−2.84**	µg/g creat.	−58.0	0.26**	1085
TCS	−5.71**	µg/g creat.	−91.0	0.18**	1085
DMTP	−1.94**	µg/g creat.	−39.2	0.046	1084
DEP	−1.25**	µg/g creat.	−37.4	0.041	1080

** Significant at the 0.01 level (2-tailed).
* Significant at the 0.05 level (2-tailed).

compounds, phthalate metabolites, phenols and OP pesticide metabolites, can be seen.

PFASs were the most prominent persistent compounds in blood, contributing to > 75% of the total concentrations of these two compound groups for all cohorts, both in the maternal and child samples. Among the non-persistent compounds in the maternal samples, MEP, MEPA and PRPA were the most prominent compounds, both when looking at the entire subcohort and for the separate cohorts. In contrast, in the child samples MEPA and PRPA were not among the major relative contributors, while MiBP and MnBP contributed considerably.

For single compounds, there were large variations in the relative contributions between cohorts and between maternal and child samples. For example, the PFOS contribution was 66% in maternal samples from MoBa, but only 44% in maternal samples from RHEA. In child samples from MoBa and EDEN, PFOS contributed only with 24% (median) to the total amount of POPs and PFASs in serum/plasma, while it was as high as 44% in BIB. Among the individual non-persistent compounds, the variations in the relative contribution between cohorts were also considerable. For example, the relative contribution of MEP in child urine varied between 13% (MoBa and KANC) and 44% (INMA), while for PRPA in maternal urine it varied between 3% in EDEN and 19% in MoBa.

3.4. Differences in concentrations between maternal and child samples

Further statistical analyses were performed for the 40 contaminants detected in > 50% of the samples (Table 3). The number of mother-child pairs included in the evaluations varied between 638 and 1240, depending on the contaminant. With the exception of four contaminants (As, MiBP, MEHHP and MECPP), statistically significant differences between maternal and child median concentrations were observed (Table 4). The median percent difference between maternal and child samples (child-maternal) varied from −99.5 to +513.9%, among all contaminants with statistically significant differences. Higher median concentrations were observed for maternal pregnancy samples compared to child samples for all OCs, PBDEs, PFASs, toxic elements and OP pesticide metabolites, as well as for phthalate metabolites and phenols except for oh-MiNP, oxo-MiNP and BPA (for which the median concentration was 4.1 μg/g creatinine in children and 2.8 in their mothers). The mean relative differences for OCs, PBDEs, PFASs, toxic elements, phthalate metabolites, phenols and OP pesticide metabolites were −47%, −40% -49%, −32%, +44%, −69% and −38%, respectively, but there were large variations within the compound groups. For example, among phthalates there were metabolites where no significant difference between maternal and child samples were seen (e.g. MiBP, MEHHP, MECPP), metabolites with higher concentrations in children compared to mothers during pregnancy (e.g. oh-MiNP, oxo-MiNP) and metabolites with lower concentrations in children compared to mothers during pregnancy (e.g. MEP, MnBP, MBzP, MEHP, MEOHP).

Also, when looking at each cohort separately, statistically significant differences between maternal and child samples were observed for most contaminants (SI, Table S9). Further, for some of these contaminants there were specific patterns for the various cohorts. For HCB, statistically significantly lower median concentrations for mothers compared to children were found for BIB and MoBa, while the opposite was observed for EDEN and INMA. For PFNA, all cohorts showed statistically significantly higher median concentrations in mothers during pregnancy than in children, except in MoBa where the median % difference between children and mothers was +64.9%. As opposed to the rest of the cohorts, the As and BPA concentrations in MoBa were statistically significantly higher in mothers during pregnancy than in their children. For phthalates, six of ten phthalates metabolites had different patterns for the various cohorts, and most frequently maternal concentrations were higher than child concentrations in BIB and RHEA, while the opposite was the case for EDEN, MoBa and INMA. In all cohorts except BIB, mothers had statistically significantly higher concentrations of DEP during pregnancy compared to their children.

3.5. Correlations between concentrations of maternal and child samples

Statistically significant correlations between paired maternal and child samples were observed for all OCs, PBDEs, PFASs and toxic elements except Cd (Table 4). The highest Spearman correlation coefficient was found for Cs (rho = 0.60, $p < 0.01$). Correlation coefficients above 0.4 were also observed for all PCBs, DDE, PFHxS, PFOS and Hg. Also for the non-persistent compounds statistically significant correlations between maternal and child samples were observed for as many as two thirds of the compounds, but the correlation coefficients were considerably lower (< 0.21). Interestingly, for the DEHP metabolites (MEHP, MEHHP, MEOHP and MECPP) the correlations between maternal and child samples were weak and negative.

Spearman correlation coefficients between maternal and child samples varied greatly between cohorts (SI, Table S10). For the toxic elements Cd, Pb and Cs the highest mother-child correlations were observed in the samples from BIB, while for PFOS, PFOA and PFNA, KANC was the cohort where the highest correlation coefficients were observed. For BDE 47 a Spearman rho of 0.48 was observed for the samples from RHEA, while for the other cohorts the maximum was 0.25. For all PCBs and DDE the highest mother-child correlations were obtained in the samples from MoBa, but BIB showed a particularly high correlation coefficient for DDE.

4. Discussion

A wide range of persistent and non-persistent environmental contaminants were determined in paired maternal and child samples from six birth cohorts across Europe. To our knowledge, this is the first study in Europe which includes harmonized collection of biological samples and clinical examinations for children from several countries. Most of the compounds were detected in almost all individuals, demonstrating that both mothers and children are exposed to a complex mixture of environmental contaminants.

4.1. Maternal and child concentrations

PFASs contributed most to the sum of persistent compounds (including OCs, PBDEs and PFASs) in both maternal and child blood samples. One might think that this reflects higher exposure to PFASs compared to the other POPs, but it is more likely that the higher contribution of PFASs is attributed to differences in the distribution of these contaminants in the body, as PCBs are mainly distributed in lipids (Jensen, 1987), while PFASs are bound to serum/plasma proteins (Han et al., 2003; Jones et al., 2003). Due to this, the total body burden of OCs and PBDEs is expected to be higher than for PFASs. However, it is not clear whether the adverse health effects primarily are caused by the burden of a specific organ, the proportion of the environmental contaminants circulating in the blood stream or if the entire body burden of a specific chemical is more relevant.

The highest median blood concentration of DDE, a metabolite of DDT, was observed in the RHEA cohort for both mothers and children, while the highest median concentrations of DDT were found in KANC (children) and EDEN (mothers). This indicates that recent exposure to DDT is not the main reason for the relatively high concentrations of DDE in the RHEA cohort, but rather historical exposure and exposure to DDE from diet (Bjermo et al., 2013).

MEP, MEPA and PRPA were the dominating compounds in maternal urine samples, while in the child samples MEP along with MiNP and MnBP had the highest relative contribution among the non-persistent compounds. This could be explained by personal care products and other cosmetics being the major exposure source of MEPA and PRPA (Guo and Kannan, 2013; Guo et al., 2014), while the main exposure pathway to DEP, DiBP and DnBP (parent compounds of MEP, MiBP and

MnBP, respectively) is inhalation of indoor air (Giovanoulis et al., 2018). It should be mentioned, that a comparison among the non-persistent compounds is challenging, as the biomarkers analyzed for these compound groups are either metabolites (phthalates and OP pesticides) or representing only a fraction of the parent compounds (parabens) (Moos et al., 2017). Another challenge when comparing concentrations of non-persistent compounds is that these compounds have short half-lives and thus the measured concentrations reflects only recent exposure (Meeker et al., 2009; Robinson and Vrijheid, 2015). The temporal variability of exposure to these non-persistent compounds has been investigated in the HELIX in-depth panel studies for children and pregnant women, where multiple urine samples have been collected (Casas et al., 2018).

Statistically significant differences in the blood and urine concentrations between cohorts were observed for all compounds, both for mothers and children, reflecting differences in exposure. Differences in concentrations between mothers and children varied greatly between cohorts, probably due to differences in food consumption patterns, food contamination levels, difference in use of consumer products and personal care products, as well as the level of contamination of the indoor environment. The ages of the mothers and children at sample collection could potentially have an impact on the measured concentrations, in particular for persistent compounds which usually bioaccumulate. The ages of the children at sample collection were different between cohorts (Maitre et al., 2018). Thus, differences between cohorts were also explored after adjustment for age, but all significant differences remained. The maternal ages at sample collection were similar between cohorts, and have thus likely not had an influence on the observed differences between cohorts.

Another complicating factor when looking into differences between cohorts is that the various cohorts recruited pregnant women at different time points. For instance, EDEN completed their recruitment between 2003 and 2006, while the samples in BIB were collected between 2007 and 2010 (see Maitre et al., 2018 for details). Consequently, temporal variations resulting in alternations in levels both in the environment and in the diet may have had an influence on the observed differences between cohorts for the maternal samples. Indeed, we see, for example, that median maternal PCB levels are lower in the younger cohorts RHEA and BiB than in the older cohort EDEN, whereas such differences are not apparent in the child samples (collected in the same calendar years in all cohorts) (Table 3). However, further analysis of this would require a different study design; in our sample, the variables calendar year and cohort are not sufficiently separate to be analyzed independently.

For some compounds, national bans may have had an impact. For example, BPA was banned from all food contact materials in 2015 in France. We observed lower concentration of BPA in children from the EDEN cohort compared to the other cohorts (Table 3 and Mann Whitney Test, $p < 0.01$, results not shown), even though the ban is supposed to have been enforced after the time when most study participants in this study had been enrolled. The maternal samples from EDEN were similar to the median concentrations in several other cohorts.

Further, for the women, varying breast-feeding practices among the countries, which is known to have an impact on the blood concentrations of persistent compounds, is likely also a reason for the observed differences (Brantsaeter et al., 2013; Gascon et al., 2015). Similarly, for children their concentrations of persistent compounds are likely affected by how long they have been breastfed (Papadopoulou et al., 2016). In a former study on maternal BPA in the MoBa cohort, it was speculated that the collected urine samples were contaminated with BPA from equipment used in the sample collection process (Longnecker et al., 2013). Unfortunately, such equipment was not available for any of the cohorts and the potential influence of contamination during sample collection could thus not be assessed. Thus, it is important to keep in mind that for the maternal samples the differences by cohorts could also potentially be influenced by such issues.

Differences in the relative contributions of various persistent compounds between cohorts, were observed (Fig. 1). This is advantageous when assessing exposure - health relationships, as the fact that different cohorts have different correlations between compounds can provide insights to disentangle which compounds are likely to have a causal exposure - health relationship.

It is difficult to compare the concentrations from the present study with other Nationwide biomonitoring programs, among others due to the wide range of compounds and relatively large differences in concentrations between cohorts in the present study, and also because sampling time point and age may have large impacts on the concentrations. However, we found that the concentrations are in the same range as data from the multinational European study called DEMOCOPHES for phthalate metabolites and BPA in both maternal and child samples (Cerna et al., 2015; Covaci et al., 2015; Cullen et al., 2017; Cutanda et al., 2015; Den Hond et al., 2015; Exley et al., 2015; Schwedler et al., 2017). Further, the levels were with some exceptions (BDE 47, BDE 153, MiBP and MEHP for maternal samples, and MiBP for child samples) similar to concentrations reported in the National Health and Nutrition Examination Survey (NHANES) conducted in the US (CDC, 2018).

4.2. Comparison with human biomonitoring values

As an indication of how the levels in the present study are compared to established human biomonitoring values, a comparison with two sets of human biomonitoring (HBM) values developed by The Human Biomonitoring Commission of the German Federal Environment Agency (UBA) was performed (The Human Biomonitoring Commission, Germany, 2017). This commission states that the HBM I value represents a value where concentrations below this threshold are considered to pose no risk for adverse health effects. For values above the HBM II value, there is an increased risk for adverse health effects and, consequently, an acute need for exposure reduction measures. For compounds measured in HELIX where HBM II values exists (mercury, selected PCBs), a maximum of 1% of the samples exceeded the set thresholds (1% of mothers for mercury and PCBs, and 0.1% of children for mercury and PCBs). In contrast, 66% and 58% of the mothers had concentrations above the HBM I value for PFOS and PFOA, respectively. The corresponding numbers for children were 8.6 and 23%. For phthalates, BPA and TCS, $< 2\%$ of the mothers and children exceeded the HBM I value, while for mercury 12% and 4.4% of the mothers and children, respectively, had concentrations in their whole blood above the HBM I value. The consequence of an exceedance of the HBM I value is, according to Human Biomonitoring Commission, a need for identifying specific sources of exposure and reducing exposure in an adequate way.

4.3. Differences and correlations between maternal and child samples

Statistically significant differences between maternal and child samples were observed for most compounds. This is not surprising, in particular for the non-persistent chemicals, when taking into account the six to twelve years between the sample collections for mothers and their children. Among the compounds with significant differences, higher concentrations were observed in maternal samples compared to child samples for all compounds except BPA and the metabolites of DINP. For compounds with long elimination half-lives, bioaccumulation resulting in increasing concentrations with increasing age, would lead to higher concentrations in mothers compared to children. The observed differences may also be due to changes in exposure over time, but for non-persistent compounds also differences in the use of consumer products between mothers and children e.g. personal care products would have an impact. Some former studies assessing phthalates in paired maternal and child samples collected at the same time point

have found higher concentrations in child urine compared to their mothers urine (Kasper-Sonnenberg et al., 2012). However, as the maternal and child samples in this project were collected 6–12 years apart, the present study is not directly comparable. The higher concentrations of DINP metabolites in children compared to mothers in the present study may be explained by an increasing use of DINP, a major replacement for DEHP, in recent years (Koch et al., 2017; Sakhi et al., 2017). The higher BPA concentrations in children compared to mothers is in contrast to findings in the DEMOCOPHES study, where similar concentrations of BPA were observed in urine samples collected at the same time point for both mothers and children (5–12 years). One might speculate that as children in this age group are eating more relative to their body weight than their mothers (Sakhi et al., 2018), child exposure is higher and thus the concentrations in urine will be higher. Further, as the urine samples were collected 6–12 years apart, the levels in food and other exposure sources have likely also changed.

As expected, statistically significant correlations between maternal and child samples were observed for most of the persistent compounds. Correlation coefficients above 0.4, which can be considered moderate to high bearing in mind the 6–12 years between sample collections for mothers and children, were observed for all PCBs, DDE, PFHxS, PFOS and Hg. Exposure in utero and from breastfeeding are likely contributing to this. This is supported by the fact that the women in MoBa reported the most extensive breastfeeding (data not shown), and for all PCBs, DDE and HCB the highest correlations between maternal and child samples were observed in MoBa. Further, for many of the persistent compounds the major exposure occur through the diet, and concentrations in the diet may not change so rapidly, particularly not for foods of animal origin. For several compounds, stronger significant correlations were observed for the entire subcohort compared to the individual cohorts. This is likely due to large differences between the cohorts, explaining part of the maternal-child correlation when combining all the cohorts.

Due to the long period between sample collections for mothers and their children, significant maternal-child sample correlations were not expected for the non-persistent compounds. This was confirmed, even though weak but significant positive or negative correlations were observed for more than half of the compounds.

4.4. Strengths and limitations

The major strengths of this study are the large sample size ($n = 1301$ mother-child pairs), the harmonized sample collections of all children from the six cohorts, and, with few exceptions, the analysis of all samples of a compound group in one laboratory. In HELIX, harmonized data on molecular omics signatures, outdoor exposures, clinical measurements, neurological testing, and questionnaires variables, are also available for the assessment of exposome - health associations (Maitre et al., 2018). Furthermore, this unique dataset forms basis for characterization of the early-life exposome (Tamayo, (in review)). Additional non-targeted methods are desirable for obtaining an even broader picture of the early-life chemical exposome (Dennis et al., 2017). However, at present the non-targeted methods available do not have sufficient sensitivity and accuracy to replace targeted methods similar to those applied in the present study for the majority of the substances.

Two of the limitations of this study are that the urine and blood collections of the maternal pregnancy samples were not performed in a harmonized way and that the equipment used for collection of maternal pregnancy samples were no longer available for assessment of blank contamination, both because pregnancy samples were collected many years before the start of the collaborative HELIX project. Until analysis, the maternal samples had been stored in their respective biobanks according to well-defined procedures. However, as the samples had been stored for many years before chemical analyses, the sample integrity may potentially have been affected to some, but likely to a limited extent (Baird et al., 2010; Kato et al., 2011). For some contaminants, the analyses of the maternal samples have been carried out in more than one lab. This may have resulted in small differences between cohorts due to analytical uncertainties, for these contaminants. However, for most of these compounds an interlab comparison was carried out, demonstrating high correlations between the results obtained in the different labs (SI, Table S6). New, standardized sample collections and analyses, such as conducted in the HELIX children, is an important implementation to reduce such challenges.

In summary, this unique study comprising comparable concentrations of a wide range of environmental contaminants in a large sample of mothers and their children from six European birth cohorts, confirms that both children and women around Europe are exposed to numerous potentially harmful chemicals. Significant differences between cohorts, and between mothers and children were observed for all environmental contaminants, demonstrating that the in-utero and childhood chemical exposome differs substantially between age groups and countries. For PFOS and PFOA in particular, many individuals exceeded the threshold (HBM I value) which suggests there is a need for assessing sources of exposure and reducing the exposure. It is of concern that for most compounds where HBM values has been established, at least some few individuals had an internal exposure exceeding the HBM I value. The present study demonstrates that through extensive planning it is possible to conduct harmonized sample collection and analysis of multiple compound groups in human samples from large multi-national projects. This extensive dataset comprising > 100,000 concentrations of 45 environmental contaminants in mother child pairs from six European birth cohorts forms a unique possibility for conducting epidemiological studies using an exposome approach.

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Declaration of interests

None

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2018.09.056.

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