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Human Biomonitoring of Environmental Contaminants - Examples Offering Tools Towards Safe Food in Sweden

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Authors' contributions

All authors have equally contributed to the review presented here. All authors read and approved the final manuscript.

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ABSTRACT

Introduction: Humans are constantly exposed to a wide variety of environmental contaminants from different sources. The risk assessment of exposure to chemical compounds includes hazard identification, hazard characterization, exposure assessment and risk characterization. Human biomonitoring (HBM), as a method to measure the chemicals or their metabolites in human body fluids and/or tissues, might be used at any stage of risk assessment. However, the most used role of HBM in this process is in the exposure assessment. In order to estimate the body burden of the varied exposure, the Swedish National Food Agency (NFA) applies HBM to complement the traditional calculations based on chemical analyses of the food content and consumers' self-reported food intake, or food purchase statistics.
Aim: To summarize the two main HBM studies performed by the Swedish NFA over the last two decades, i.e. POPUP (Persistent Organic Pollutants in Uppsala Primiparas) and RIKSMATEN (national food survey), and to show how they can give complementary information to improve risk assessment of environmental contaminants.
Results: Levels of a wide range of compounds, including environmental contaminants, have been measured in human samples collected from these studies. These results, collected over a number of years, make it possible to study the general temporal trends for the measured environmental

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contaminants. Additionally, the identification of exposure determinants and exposure pathways has been conducted by aid of collected data on food consumption and life-style factors, and possible associations have been reported.

Conclusion: Overall, the gained results demonstrate how HBM studies provide important information both on the current state and the temporal trends of human exposure to environmental contaminants. Combined with other imperative data collected, HBM is an important complementary tool for risk assessment of environmental contaminants, which in many cases have diet as main source. Consequently, HBM is important in risk management of these contaminants to implement and follow-up risk reducing or preventive actions within the food sector, as well as to provide an early warning on potential threats to public health.

Keywords: Human biomonitoring; exposure assessment; food contaminants; POPUP; RIKSMATEN.

ABBREVIATION

AHTN - 6-acetyl-1,1,2,4,4,7-hexamethyltetraline; As - arsenic; BATE – 2-bromoallyl 2,4,6-tribromophenyl ether; BEH-TEBP – bis(2-ethylhexyl) tetrabromophthalate; BPA - bisphenol A; BTBPE – bis(2,4,6-tribromophenoxy) ethane; Cd - cadmium; DBDPE – decabromodiphenyl ethane; DBE-DBCH - tetrabbromoethylcyclohexane; DBHCTD – hexachlorocyclopentenyl-dibromocyclooctane; DDE – dichlorodiphenyl dichloroethylene;, EH-TBB – 2-ethylhexyl-2,3,4,5-tetrabromobenzoate; HBCD - hexabromocyclododecane; HCB - hexachlorobenzene; HCH - hexachlorocyclohexane; Hg - mercury; HHCB - 1,3,4,7,8-hexahydro-4,6,6,7,8,8,-hexamethyl-cyclopenta[g]-benzopyran; Musk xylene - 5-tert-Butyl-2,4,6-trinitro-meta-xylene; NP - nonylphenol; OBTMBI - octabromotrimethylphenyllindane; Pb - lead; PBB - pentabromobenzene; PBDE - polybrominated diphenylether; PBEB - pentabromoethylbenzene; PBT - pentabromotoluene; PCB - polychlorinated biphenyls; PCDD - polychlorinated dibenzo-p-dioxin; PCDF - polychlorinated dibenzofurans; PCP - pentachlorophenol; PFAA - perfluoroalkyl acid; PFOA - perfluorooctanoic acid; PFOS - perfluorooctane sulfonic acid; Se - selen; U - uranium.

1. INTRODUCTION

Food is often a major source of human exposure to a wide range of hazardous substances, such as industrial chemicals, natural substances and trace elements. To estimate the levels of those substances which consumers are exposed to through the diet, calculations based on the food content and consumers' self-reported food intake are traditionally used. However, this method is not sufficient since it might have low reliability and does not consider factors as for example uptake or metabolism of the contaminant. Therefore, as a complement, the Swedish National Food Agency (NFA) applies human biomonitoring (HBM) to measure the body burden of contaminants, i.e. assessing the internal exposure. HBM is the only tool that integrates exposure from different sources, traces the availability of the food contaminants with potential threats to human health and allows assessment of health- and nutritional status [1]. Moreover, it can demonstrate the temporal trends and population distribution of exposure, identify vulnerable groups and possible emerging risks, as well as be used to following-up risk reducing or preventive actions. Together with other valuable data collected, the results from HBM might therefore form a solid platform for decision making and legislation when it comes to risk- and benefit assessment related to food intake. The European Environment Agency (EEA) concludes that adequate long-term environmental and health monitoring is important to reach a better decision-making and avoid harm to the environment and to humans [*2*].

At present, substances of human health concern related to food intake include the regulated compounds (e.g. the persistent organic pollutants [POPs] under the Stockholm Convention), a wide range of high production volume chemicals (e.g. nonylphenol [NP] and phthalates), perfluoroalkyl acids (PFAA), natural compounds (e.g. toxins and metals), etc. While POPs are persistent in the biotic and abiotic environment, some of the less persistent compounds of current concern (e.g. phthalates and parabens) have shorter half-lives in the human body and therefore make HBM more challenging. Due to differences in nature and toxicokinetics of the individual chemical, HBM is a complex procedure which requires certain methodological procedures and qualified analytical methods. To consequently use HBM in the dietary risk assessment, it is important to have high quality data on both: a) the internal exposure to the compound of interest determined by analysis of human samples; b) identification of the exposure determinants by using dietary survey, food frequency questionnaire, and registration of other factors which could affect the exposure (e.g. environmental data, age, region, occupation, etc.).

Below we describe the two most important series of HBM studies on environmental contaminants performed by the Swedish NFA over the last decades. The studies supply information about the internal exposure and identification of exposure determinants. This review summarizes the results regarding environmental contaminants monitored in different population groups in Sweden and their correlation to dietary habits in order to demonstrate the feasibility of HBM in dietary risk assessment.

2. HUMAN BIOMONITORING STUDIES AT THE SWEDISH NFA

In general, HBM programs are designed to answer certain predetermined questions. Therefore, a number of factors such as the sampling matrix, frequency of sampling and storage conditions employed in the program should be carefully selected. It is common that the usage of an initiated program might change over time, which makes the initial planning more challenging. Therefore, the HBM studies initiated by the Swedish NFA have different design based on the research questions asked. An overview of the sampling roster for the two of HBM studies reviewed here, named POPUP and RIKSMATEN, is given in Table 1. In addition to the peer-reviewed published material, several publications from these two studies have been produced within the Health-Related Environmental Program conducted by the Swedish Environmental Protection Agency [3-12]. As this is a review of published analytical studies, no method description is given. Instead, we refer to the publications in the reference list for more details.

2.1 POPUP

To protect Swedish consumers from high exposure to PCBs and PCDD/Fs, the NFA has issued consumption advisories since the 1980s concerning certain fish species from the Baltic Sea known to contain high levels of these chemicals (e.g. wild-caught salmon, herring and arctic char). The levels of PCDD/Fs and PCBs in these fish species often exceed the maximum limits set by the European Union (EU), but Sweden has negotiated a derogation regarding the maximum limits, which means that the fish may be sold on the domestic market. An important prerequisite for the EU derogation is that the fish consumption advice regarding contaminated fish is known by the important risk groups, thus protecting the Swedish population from high PCDD/F exposure from contaminated fish. In 1996, the scientific basis of dietary guidelines regarding consumption of contaminated fish was revised. The Swedish NFA concluded that data on POP exposure of pregnant and nursing women in Sweden were scarce. To improve basic data for future dietary risk assessments of POPs, a cohort describing POP exposure in first-time mothers (primiparas) giving birth at the Uppsala County, called POPUP (Persistent Organic Pollutants in Uppsala Primiparas) was started, and is still ongoing. The women in the cohort were initially (1996-1999) recruited at the antenatal care clinics as controls, i.e. giving normal birth, in a case-control study of risk factors for early miscarriages [41]. To increase the number of participants from the coastal regions, a complementary recruitment was conducted in Östhammar, located at the coast of the Baltic Sea [26]. The POPUP cohort was restricted to first-time mothers because nursing is an important elimination route for both endogenous and exogenous substances and the body burden of POPs in women differs depending on number of childbirths. From January 1996 to May 1999, a total of 376 primiparas where asked to participate in the study from which 325 women donated blood serum at week 32-34 of pregnancy, and 211 women donated breast milk at 3 weeks after delivery [26]. Furthermore, blood samples were collected from some of the infants at 3-weeks and 3-months age. Some women also provided hair and cord blood samples at birth [13], while some of the participants were included into an in depth study regarding the maternal serum transfer of PCBs during pregnancy [15]. The dietary survey was collected by in-person interviews and self-administered food frequency questionnaires, and life-style information was gathered through a certain questionnaire.

Since year 2000, first-time mothers with a normal delivery have been randomly recruited at Uppsala University Hospital. Approximately 30 mothers have been donating breast milk and blood samples 3 weeks after delivery every 1-2 years. Women born in non-Nordic countries have been excluded to avoid the introduction of additional exposure determinants. Overall, more than 400 mothers and 100 infants participated in POPUP since 1996. The cohort has been expanded with sampling of blood serum taken at the age of 4, 8 and 12 years and reported health status of the child. Also, in 2009-2010 blood was sampled from paired mother-toddlers (11-15 months of age) [23]. In 2008 the POPUP cohort was used to recruit primiparas to participate in a dust sampling to match to breast milk samples [42]. The collected samples were analyzed and thereafter stored for future research.

2.2 RIKSMATEN

The nationwide diet survey RIKSMATEN was conducted on adults (18-80 years of age) between May 2010 and July 2011 at four occasions in Sweden. The selection of participants was performed by Statistics Sweden, and the population was divided into seven regions according to affiliation to Swedish Occupational and Environmental Medicine Centers (OEMCs). Each region included the region capitals and 2 additional counties that were randomly selected [39]. In total, 1008 individuals were randomly invited to participate in both, diet survey and sample collection. Out of these, 300 individuals (30%) chose to donate the blood and urine samples used for subsequent chemical analyses of environmental contaminants. A four-day diet registration and a self-administered questionnaire including lifestyle and living conditions were also collected.

3. REVIEW OF RESULTS

3.1 Exposure Levels of Monitored Contaminants

An overview of the matrix and chemicals analyzed is presented in Table 1.

<u>3.1.1 POPUP cohort</u>

3.1.1.1 Blood samples

Blood samples in the POPUP cohort were used to determine the internal exposure of PCB including OH-PCB, pentachlorophenol (PCP), DDE, HCB, HCH, Chlordane, PFAA, bisphenol A (BPA) and NP (Table 1). PCB-153 levels in serum from primiparas women in 1996-1999 (sampled week 32-34) were in the range of 10-180 ng/g lw (lipid weight), DDE 20-600 ng/g lw, HCB 10-160 ng/g lw, HCH 3-60 ng/g lw, and chlordanes 1-20 ng/g lw [16-18]. Serum from mothers sampled between 1996 and 2010 were pooled for each year and analyzed for PBDE and HBCD [22]. BDE-153 (0.5-1.8 ng/g lw) and BDE-209 (0.5-4.0 ng/g lw) dominated the serum levels. In 24 matched serum samples from mothers and toddlers sampled in 2009-2010, BDE-153 was the predominant congener in the mothers while in toddlers, BDE-209 was found in the highest concentrations [23]. HBCD concentrations above limit of quantification (LOQ) were found in only 11% of the pooled serum samples from 1996-2010 and the mean was 0.31 ng/g lw [22].

PFAAs were determined in composite samples of blood serum from 1996-2010 and levels of PFOS and PFOA ranged from 5 to 28 ng/g and from 1.4 to 3.1 ng/g, respectively [14]. About 40% of the sampled women had detectable levels of NP in blood serum [19]. In the same study about 20% of the women had detectable BPA levels [19,20], however it was later demonstrated that those levels most likely came from an identified BPA contamination of the equipment, illustrating the importance of accurate sampling and handling procedures [20]. The conclusion of the study was that serum levels of unconjugated BPA are below 0.2 ng/ml in Swedish nursing women taking contamination into account [20].

3.1.1.2 Breast milk

Breast milk can reflect the exposure for the mother, fetus, and infant. Samples of breast milk from the POPUP cohort have been analyzed for PCB, PCDD/Fs, chlorinated pesticides, PBDE, HBCD, PFAA, musk compounds and metals (ref e.g. [21,22,26-28,31]). In Table 2, the post-natal exposure (point estimate of the daily intake, PEDI) has been calculated based on the POP levels analyzed in breast milk by assuming an average breast milk intake of 600 mL per day and a lipid content of 4% in milk [21]. The tolerable daily intake (TDI) levels have been set for the exposure to only a limited number of compounds by the European Food Safety Authority (EFSA), based on exposure concentrations and toxicological effects of concern. Assuming a body weight of an average infant at 6 months of age of 7 kg, a comparison of the post-natal exposure to the TDI levels is presented in Table 2. The daily intake of PCBs (non-DL) and TEQ (toxic equivalent) from PCDD/Fs and dioxin-like PCBs (DL-PCBs) via breast milk within the POPUP study was estimated to 151 ng/kg bw and 0.019 ng WHO-TEQ/kg bw (recalculated to 600 mL of daily intake of milk) [25]. These levels exceed the established TDI of 20 ng/kg bw and and 0.002 ng WHO-TEQ/kg bw for the non-DL PCBs and the PCDD/Fs and dioxin-like PCBs, respectively [43,44]. Although, the TDIs are set for an average lifelong exposure and any comparison should be done with caution. An earlier study from Patandin and coworkers (1999) showed that the cumulative intake of total-TEQ after 6 months of breastfeeding contributed to 12-14% of the total cumulative TEQ-intake at 25 years of age, demonstrating the breastfeeding as a main exposure route [45].

The major PFAA isomer measured in breast milk samples was PFOS. Its daily post-natal exposure was 10 times lower than the established TDI for adults of 150 ng PFOS/kg. Also, a number of metals and trace elements (n=32) were measured in breast milk [31]. The EDI of Cd was below the TDI by a factor of ca 50 and of U by a factor of ca 25 (Table 2). The daily intake of musk compounds were well below the provisional TDI for HHCB, AHTN and musk xylene (Table 2) [27,46].

3.1.1.3 Temporal trends

In general, POP levels in the environment have decreased the last decades due to e.g. preventive actions taken within the Stockholm convention [52]. The temporal trends of several target compounds (e.g. PCBs, PCDDs, PBDEs, DDE) in the POPUP cohort have been published spanning over several time periods up to 2010 [5,8,17,28], and recently the last 30 samples collected in 2012 were added to the whole period of 1996 to 2012 [36]. As an example, results show that PCB levels have decreased in breast milk with about 7% annually [8,28,36]. Regarding PCDD/Fs, PCDD levels in breast milk are decreasing more rapidly than PCDF, on a TEQ basis (8% and 5% respectively) [36].

Levels of chlorinated pesticides (DDT/DDE, HCB, β-HCH, oxychlordane, *trans*-nonachlor) in breast milk decreased with 6-11% annually over the whole time period 1996-2012 [36]. For DDT/DDE and HCB, the decline seemed to be faster in 1996-2003 than in 2004-2012 [36].

General temporal trends for PBDEs in breast milk did not follow any consistent pattern during the period 1996-2006 [28]. More specifically, the concentrations of BDE-47 and BDE-99 decreased, while concentration of BDE-153 increased. No change in BDE-100 concentration was observed. Similar results were reported in the POPUP-cohort between 1996 and 2012, where BDE-47, BDE-99 and BDE-100 decreased by 5-10% per year and BDE-153 increased by 1.5% [8,36]. If dividing the whole period into 1996-2004 and 2004-2012, the increase for BDE-153 was 6.2% for the first period while the levels decreased by 3.3% by the end of the second period. These trends probably reflect a voluntary phase-out of the PBDEs and finally the inclusion PBDEs in the Restrictions of Hazardous Substances (RoHS) directive for electronic equipment [53]. The sum of PBDE concentrations of the congeners analyzed (BDE-47, -99, -100, -153 and -154) peaked around 1998 in breast milk samples from the period 1996-2001 [30]. To establish the time trend for BDE-209, three pooled blood serum samples per year (1996-2010), representing 5-25 individuals from the POPUP cohort were analyzed [22]. BDE-209 could be quantified in all samples, showing the abundance and bioavailability of this compound. No significant time trend could be observed for the BDE-209 levels and concentrations in the pooled blood serum samples ranged from 0.5 ng/g lw to 4.0 ng/g lw.

In most breast milk samples analyzed between 1996-2006, HBCD levels were below limit of quantification (LOQ <0.2 ng/g lipid) [28]. As the analytical method has improved, HBCD levels above LOQ were reported in most samples collected during 2002-2012 [8,36]. A non-significant decreasing trend for HBCD levels of 2.5% per year was reported during the period 2002-2012 [8,36].

No temporal trends could be detected for PFAAs determined in pooled breast milk samples during the time period 1996-2004 [21]. However, in blood serum a decreasing trend was reported for the sum of PFAA between 1996 and 2010 [14]. On a congener basis, it was revealed that the PFOA, PFOS and PFDS were decreasing, whereas PFNA, PFDA, PFBS and PFHxS were increasing in the blood serum samples [14,21]. The total decrease is probably explained by the decrease of the two most dominant congeners PFOS and PFOA. The third dominant congener (PFHxS) increased two-fold between 1996 and 2010. Further investigation revealed that drinking water in some regions in Uppsala county was contaminated with PFAA, mainly PFHxS, which most likely origin from an airport training facility where fire-fighting foam has been excessively used [54]. As a result, a contaminated water supplier in that region was closed [55].

Table 1. Overview of samples from the two biomonitoring studies, POPUP and RIKSMATEN, that has been analysed for food contaminants and used in publications. The numbers of individual samples are given for each year and matrix (n=total number of samples)

Cohort	Sample matrix	Sampling period	1996-1999	2000-2012	References	Chemicals analysed
POPUP	Maternal hair	Week 32-34	123		[13]	Hg
	Maternal serum during pregnancy	Week 6-11	19		[14]	PFAA
		Week 9-36 [a]	50		[15]	PCB (incl. OH-PCB), PCP
		Week 32-34	325		[14,16-18]	PCB, DDE, HCB, HCH, chlordane, PFAA
	Maternal serum after delivery	Week 3	172	273	[14,19-22]	PFAA, NP, BPA
		Month 3	19		[14]	PFAA
		Month 11-15		24	[23]	PBDE
	Cord blood	Week 0	123		[13,14]	PFAA, Hg, Se
	Infant blood	Month 11-15		24	[23]	PBDE
	Infant faeces	Month 11-15		22	[24]	PBDE, DBDPE, HBCD, BTBPE, BEH-TEBP, DBE-DBCH, BATE, PBB, PBT, PBEB, DBHCTD, OBTMBI
	Breast milk	Week 3	195	244	[8,9,12,16,18,21, 22,25-36]	PCB, PCDD/F, DDE, PBDE, HBCD, PFAS, Musk, metals and trace elements (n=32)
RIKSMATEN	Adult blood			273	[4,37-39]	PCB, HCB, HCH, chlordane, DDE, PBDE, PFAA, Pb, Hg, Cd
	Adult urine			300	[4,37,40]	Phthalates, BPA, Cd

[a] *Samples were collected from 10 women on 5-7 occasions during pregnancy*

Table 2. The post-natal exposure expressed as point estimate of the daily intake (PEDI) is calculated from breast milk concentrations reported in the POPUP cohort and compared to the Tolerable Daily Intake (TDI) as found in literature. The margin-of-safety is calculated as the ratio between the EDI and the TDI and a value >1 implies an exposure at risk

Compound group	Compound	Breast milk concentration	EDI (ng/kg bw/day)[a]	TDI (ng/kg bw/day)	Ratio EDI/TDI	Reference
POP	Non-DL PCBs [b]	44 ng/g lw[c]	151	20[d]	7.6	[36]
	PCDD/F (TEQ)[e]	5.5 pg/g lw[c]	0.019	0.002[f]	9.5	[36]
	DDE	34 ng/g lw[c]	117	10000[g]	0.01	[36]
	PBDE[h]	1.3 ng/g lw[c]	4.5	N.E.[i]	--	[36]
	PFOS	0.17 ng/mL[j]	15	150[k]	0.1	[21]
Metals	Pb	1.2 ng/mL[l]	103	N.E.[m]	--	[31]
	Cd	0.075 ng/mL[l]	6.4	360[n]	0.02	[31]
	U	0.3 ng/mL[l]	26	600[n]	0.04	[31]
Musk	HHCB	64 ng/g lw[o]	220	500000[p]	<0.001	[27]
	AHTN	10 ng/g lw[o]	34	50000[p]	<0.001	[27]
	Musk xylene	9.5 ng/g lw[o]	33	7000[p]	0.005	[27]

N.E. = Not Established [a] Assuming intake of 600 mL breast milk per day of 4% lipid content and 100% uptake, and an average weight of 7 kg at 6 months of age for the EDI calculation [21]. [b] Sum of PCB 28, 138, 153, 180. [c] Median level in 30 samples collected in 2012. [d] Based on a Aroclor 1254 mixture and averaged over the whole life [43]. [e] PCDD/F and DL-PCBs. [f] The Scientific Committee for Food (SCF) fixed a tolerable weekly intake ('TWI') for dioxins and dioxin-like PCBs of 14 pg WHO-TEQ/kg body weight [44]. [g] The Joint FAO/WHO meeting on Pesticide Residues derived a provisional TDI for DDT of 0.01 mg/kg b.w [47]. [h] Sum of BDE-47, 99, 100 and 153. [i] [48]. [j] Median level in 12 breast milk samples from 2004. [k] [49]. [l] Median level in 60 breast milk samples from 2002-2009. [m] [50]. [n] [51]. [o] Median level in 101 breast milk samples from 1996-2003. [p] [46]

Concentrations of the musk compounds AHTN and musk xylene in breast milk declined significantly between 1996 and 2003 (11% and 17% per year, respectively) [27], suggesting a decline in the industrial use of these compounds in consumer products, or alterations in the consumer use patterns of perfumed products. No temporal trend in HHCB concentrations in breast milk was seen [*27*].

3.1.2 RIKSMATEN

Samples collected form adults in RIKSMATEN showed that men had higher PCB, HCB, HCH, PFAA and metal (Pb, Hg) levels in blood than women [39,56,57]. PFAA levels were around 17 ng/mL, with PFOS being the dominant congener in the population [56]. The daily intake of PFOS and PFOA were estimated from the serum concentrations measured by NFA using a one-compartment, first-order, pharmacokinetic model. Using the maximum concentrations determined in serum the corresponding daily intake was calculated to be 4 ng PFOS/kg bw and 1 ng PFOA/kg bw [56]. This is well below established TDIs set by EFSA in 2008 [49]. Phthalates including their metabolites and BPA were measured in urine, and the highest median level reported was of the phthalate metabolite mono-ethyl phthalate (49 ng/mL), followed by mono-n-butyl phthalate (43 ng/mL), and the BPA median concentration was 1.3 ng/mL [4]. In a food basket study conducted by Swedish NFA the estimated mean intake per person of BPA and NP were 2.5 µg/day and 15.5 µg/day, respectively [19,58]. These results indicate that food is a relevant exposure route for these compounds [19].

Pb, Hg and Cd were determined in whole blood and Cd additionally in urine (Table 1). The average levels in whole blood were 13 µg/L for Pb, 1.1 µg/L for Hg and 0.19 µg/L for Cd [57]. Hg and Cd levels were generally below health based reference values. Among fertile women, 30% had Pb levels above a reference level of 12 µg/L for developmental effects in children established by EFSA [57].

3.2 Associations with Food Intake

In POPUP and RIKSMATEN, positive associations have been found between levels of POPs in serum and breast milk and intake of fish [17,39,56,59]. Furthermore, it was observed that women who were breastfed during infancy and grew up on the Baltic coast of Sweden where availability of contaminated fish from the Baltic Sea is rather high, had higher levels of PCBs and PCDD/Fs in breast milk [33]. This finding indicates that exposure early in life via breastfeeding and consumption of contaminated fish still affect body burden later in life including pregnancy period. The observed strong association of age with the levels of POPs in human serum and breast milk could be due to a change of fish intake pattern over time, exposure time increasing with age, or due to the fact that elderly individuals might be exposed to higher doses of environmental contaminants earlier in life compared to younger individuals as a result of the declining environmental levels [39]. Most of the PCBs in plasma were positively correlated to the proportion of very long-chain n–3 fatty acids which typically originate from fish [39]. It further strengthens a relationship between fish intake and POP concentrations. Interestingly, a less persistent PCB (CB-28) was instead associated with the age of the residential building indicating indoor exposure as an alternative exposure route, e.g. PCB containing building material [33,39]. HCB concentrations, on the other hand, have been associated with higher intake of fat from dairy products [39,60]. No significant correlation was found between breast milk concentration of PBDEs and dietary intake [33]. Mono-ethyl phthalate levels were associated to food consumption out of a tube, and mono-butylbenzyl phthalate to soft drinks [4].

Both measured maternal total Hg in hair samples and methyl-Hg in cord blood from the POPUP cohort increased significantly with increasing total consumption of seafood [13]. Correlation to chicken consumption was also observed and it was suggested that the Hg in chicken originated from fishmeal used as a source of protein in animal feed.

Blood levels of Hg in blood samples from RIKSMATEN were significantly correlated to fish intake while Pb to intake of game and alcohol. Cd levels correlated to low iron levels in plasma as well as low meat consumption [57].

3.3 Non-food Exposure Determinants

The exposure pathways can vary due to passive and active choices in our daily life. Therefore, in order to draw consistent conclusions from HBM data, other non-food related exposure determinants were taken into consideration, e.g. life-style determinants and place of residence, in these studies. Age is a major determinant of e.g. PCBs and metals as their concentrations increase with age, mainly due to bioaccumulation [17,26,33,39,56,57]. Also, elderly individuals might have higher levels compared to younger population due to higher exposure at earlier life time. This confounding factor is important to include in the analysis of temporal trends as an increased exposure during the monitoring time span can counteract the actual decreasing trend in the study material [28].

Other determinants known to influence the data interpretation are:

- Short-term changes in body constitution, e.g. before and after pregnancy [17,33,39]
- The choices of household products which can influence the internal levels of e.g. perfume [27]
- The household dust composition of e.g. the flame retardants [32,61]
- High physical activity [33]
- Education level [27,39,56]
- Smoking [30,57]
- The location and material of the residents house [4]

As a complement to the actual POPUP-study, first-time mothers from other geographically well-spread regions of Sweden were recruited to study regional differences in exposure to POPs. It was concluded that the exposure pattern was similar in the studied group, although food consumption habits differed significantly between regions [62]. On the contrary, samples analyzed within the nationwide RIKSMATEN reported differences in POP concentrations between regions [39,56]. This is probably due to a more diverse population sampled in RIKSMATEN and that the participants were randomly selected nationwide. No regional differences were found in levels of metals analysed [37].

3.4 Mother-child Transfer

The transfer of contaminants from mother to infant_has been studied in POPUP. Excretion of POPs via lactation makes breastfeeding one of the major pathways of infant exposure to these contaminants [39]. It was observed that the number of months the mothers were breastfed during infancy was positively associated to pregnancy serum concentrations of PCBs and DDE [17] as well as PCBs and PCDD/Fs in breast milk [33]. This clearly demonstrates the significant influence of exposure to POPs at early lifetime.

In the POPUP study, between 1996 and 1999, ten primiparas women participated in an in-depth study regarding change in serum concentrations of PCB and their hydroxylated metabolites (OH-PCB) during pregnancy [15]. No change of PCB levels was observed, on a fresh weight basis, although a decrease in PCB levels on lipid weight basis was reported, due to increased blood lipid levels during pregnancy. OH-PCB levels were within the same range as the precursor PCBs on a fresh weight basis. The study material was too small to draw any further conclusions. In another study performed by Meijer and coworkers, the PCB and OH-PCB levels were determined in paired samples of mother serum and cord blood of newborn [63]. They reported a transfer over the placenta of 60-80% for the PCB and OH-PCB demonstrating a relevant exposure pathway for the fetus.

The correlation between serum and breast milk levels of PBDE in paired samples was found to be strong [9,22]. It was therefore concluded that breast milk is a representative matrix to estimate maternal exposure and can therefore be used as indicator of body burden. Blood serum levels were in general higher than breast milk levels and the quotient increased with molecular weight. PBDE and 21 other brominated flame retardants were determined in matched serum samples from 24 mothers and their toddlers in the POPUP cohort [*23*]. Several PBDE, especially the high molecular weight congener levels were significantly higher in toddlers than in their mothers. Lack of correlations between the matched serum samples indicated different exposure routes in mothers versus toddlers; in toddler's exposure from dust was suggested to be more pronounced.

The serum levels of PFAA have been reported lower among women than men comparing measurements in both POPUP and RIKSMATEN [21,56]. It was proposed that elimination among women via breastfeeding could probably contribute to this observation. A strong correlation of PFAA levels in cord blood and maternal serum has been reported in POPUP, especially just before or after delivery, demonstrating the transfer over the placenta to the fetus [14]. It has been indicated that ca 1% of the PFOS and 2% of PFHxS is transferred from maternal blood to breast milk [21].

Some women within POPUP were also asked to give hair samples and cord blood at birth of their infant to see if hair was a suitable and representative matrix for early-life exposure to the newborn. MeHg in cord blood was significantly associated to total Hg levels in maternal hair [13]. Significantly lower Hg concentrations were found in hair corresponding to late pregnancy compared to early pregnancy. The transport of MeHg to the growing fetus may contribute to lower maternal hair Hg concentrations in late pregnancy, but a reported lower fish consumption during pregnancy is also a probable cause [13].

3.5 Health Outcomes

Some possible health outcomes have been investigated for its link to chemical exposure within the POPUP cohort. Birth weight showed a weak but significant positive association to background prenatal exposure to di-*ortho* PCBs [34] which might be non-beneficial since a positive association between birth weight and risk of obesity later in life was shown by others [64]. In contrast to PCBs, an inverse association to birth weight was seen for PBDE exposure. [34].

Data from studies within POPUP cohort also indicates that background exposure to PCBs and DDE early in life may modulate the immune system development, although the mechanism is congener based and not yet understood [16]. There is an emerging concern regarding the effect of environmental contaminants on the endocrine system as was highlighted by the World Health Organization [65]. Thyroid hormones (TH) play a crucial role in the normal development during early life stages. Hence, fetal and neonatal levels of POPs which could affect the homeostasis of TH are of special interest. Therefore, the effect of PCB, PCDD/F and DDE exposure on maternal and fetal TH levels in mother-child pairs within POPUP cohort was studied [18]. The results showed weak and in most cases non-significant associations between analyzed POPs and TH levels in infants. In mothers, a significant inverse association was observed between total T3 in blood serum and PCDD/F levels in breast milk.

4. HUMAN BIOMONITORING – BENEFITS AND CHALLENGES

The POPUP cohort has become central for HBM conducted by the Swedish NFA, monitoring contaminants in breast milk and hence exposure within a sensitive population group, i.e. pregnant women, fetuses and small children at developing stages. Results from the POPUP study are an important part of the scientific basis for the fish consumption advice regarding PCDD/F and DL-PCB-contaminated fish from the Baltic Sea [66]. The consumption data from RIKSMATEN was, for example, used for scenario calculations of PCDD/F and DL-PCB intake from Baltic Sea herring [67]. Consumption of fatty Baltic Sea fish increases the risk of children and young women to exceed the TDI for PCDD/Fs. Despite this potential risk, the result from a risk-benefit assessment demonstrated the health benefits of consuming fish [68]. Altogether, the gained knowledge was applied to form a dietary advice on fish consumption [68].

Another advantage of HBM is the potential as an early warning system for support in policy making to prevent and/or minimize health risks. As mentioned above, as a result of collected HBM data, drinking water contaminated with aqueous film-forming foams has been suggested as and proved to be a factor behind increasing exposure to PFHxS in Uppsala residents [55].

To improve risk assessment, the Swedish NFA has conducted several targeted HBM where exposure to certain substances has been investigated. As an example, in a study on Swedish hunters´ families, it was observed that consumption of game meat and the number of discharges might result in moderately elevated blood Pb levels in adults, but not in children [69]. The obtained results were part of the basis for the revised advice to hunters and their families, and those who often consume game meat [70]. The Swedish NFA has also applied HBM to evaluate nutrition status [71] and exposure to natural toxins, i.e. the mycotoxins, which are naturally occurring secondary metabolites of fungi commonly found to contaminate large volumes of staple food [40].

Experimental studies have produced strong evidence that mixtures of chemicals might induce combined effects. Therefore, it is now generally accepted that the chemical-by-chemical approach may be not sufficient for a safe and effective risk assessment [72]. Using the HBM approach, combined effects can be accounted for when evaluating health effects induced by chemical exposure including the presence of unknown substances. By using pooled samples, a large range of chemicals can be analyzed and the combined effects evaluated. Obviously, the risk-benefit approach adds a new comprehensive dimension to the assessment of the exposure to mixtures [73].

For dietary risk assessment, HBM data needs interpretation. A topic frequently discussed by EFSAs Panel on Contaminants in the Food Chain (CONTAM) is that it is of vital importance to cover different diets, age classes, gender and routes of exposure, including contamination through packaging, processing, cookware, etc. [74,75]. It is challenging to address such a broad spectra of questions in HBM while aiming to achieve high participation rate, representativity and the statistical power of the study. Despite uncertainty of the data based on interviews and questionnaires, a well-planned HBM must take into consideration different confounders that can alter the outcome of dietary exposure. To secure the data, certain biomarkers can be applied, e.g. measurement of cotinine in urine samples can be used as a marker of smoking [76] or analysis of fatty acid compositions by very long-chain n-3 fatty acids in plasma phospholipids to assess fish intake [39].

A strong correlation between different chemical groups can make it difficult to identify the most important contributor to the effect studied [16]. Another pitfall is that the confounders can be associated to other determinants not analyzed in the material. As an example, the observed positive association between blood levels of Hg and intake of vegetables may be due to the fact that individuals with high intake of vegetables adhere to an overall healthy diet which includes higher consumption of Hg-contaminated fish [57].

In general, there is a demand for more high quality HBM data considering e.g. geographical coverage and data comparability [77,78]. Harmonized protocols to conduct HBM are developed within e.g. Global Monitoring Program (GMP) under the United Nations Environment Programme (UNEP), Environment and Health Information System (ENHIS) under WHO, and European projects such as COPHES and DEMOCOPHES [76]. Recently, an international workshop dedicated to HBM was organized by the Swedish NFA [78]. Based on the presented data and collected knowledge, it was agreed that well-planned HBM provides a powerful tool in policy making towards consumer safety.

5. CONCLUSIONS

Here we have summarized the two main HBM studies on environmental contaminants performed by the Swedish NFA over the last two decades, i.e. the POPUP and the RIKSMATEN. We believe that these studies represent a step forward in the process to bring a risk-benefit assessment to more advanced level. The results demonstrate the feasibility of HBM to provide data both on the current state and the temporal trends of human exposure to environmental contaminants. Moreover, HBM studies, as conducted by NFA, generate storage of samples and relevant data used for future needs. Altogether, HBM generates an important tool in risk assessment, in prioritizing and following-up risk reducing or preventive actions as well as in early warning system. Hence, it is strongly recommended to conduct well-designed HBM studies to secure consumer safety ahead.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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