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Monitoring temporal trends of dioxins, organochlorine pesticides and chlorinated paraffins in pooled serum samples collected from Northern Norwegian women: The MISA cohort study

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ABSTRACT

The ubiquitous presence of legacy and emerging persistent organic pollutants (POPs) in the environmental matrices poses a potential hazard to the humans and creating public health concerns. The present study aimed to evaluate dioxins, dioxin-like polychlorinated biphenyls (PCBs), organochlorine pesticides (OCPs) and chlorinated paraffins (CPs) concentrations in serum of women (postpartum, pregnant and non-pregnant) from Northern Norway to better understand their exposure and contamination status as well as temporal trends across 2007–2009 (MISA 1) to 2019 (MISA 2). Sixty-two blood samples from the MISA 1 cohort and 38 samples from MISA 2 were randomly selected in this study (n = 100). Ninety samples from postpartum (MISA 1) and pregnant women (MISA 2) were randomly combined into 9 pools, with 9–11 individual samples contributing to each pool keeping the groups of pregnant and postpartum women. Remaining 10 samples from non-pregnant women (MISA 2) were allocated into separate group. Geometric mean, minimum and maximum were used to describe the serum concentrations of pooled POPs in MISA cohort. Mann-Whitney *U* test and independent sample *t*-test were applied for trend analysis of blood levels of POPs between MISA 1 and MISA 2. We found the serum concentrations of selected POPs in this study to be at lower range. Serum concentrations of dibenzo-p-dioxins (PCDDs) ($p = 0.010$), polychlorinated dibenzofurans (PCDFs) ($p = 0.002$), dioxins-like PCBs ($p = 0.001$), hexachlorobenzene (HCB) ($p < 0.001$) and p,p'-dichlorodiphenyldichloroethylene (p,p'-DDE) ($p = 0.002$) were decreased between the studied time. In contrast, the serum concentrations of medium chain chlorinated paraffins showed an increasing trend between 2007 and 2009 and 2019 ($p = 0.019$). Our findings report a particular concern of emerging contaminant medium chain chlorinated paraffin exposure to humans. Future observational studies with repeated measurements of chlorinated paraffins in general populations worldwide and large sample size are warranted.

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1. Introduction

Human exposure to persistent organic pollutants (POPs) has been a worldwide concern. POPs include a widely used group of chemicals, such as dioxins, organochlorine pesticides (OCPs), polychlorinated biphenyls (PCBs) and chlorinated paraffins (CPs), which are characterized as being persistent in various environments, have an ability to biomagnify and bioaccumulate and potential for long-range transport (Lallas, 2001; van Mourik et al., 2016). Despite the function of the placental barrier, a growing body of evidence suggests that POPs can transfer from mother to fetus via the placenta and accumulate in fetal tissues or through breastfeeding (Jeong et al., 2018; Müller et al., 2019; Rogan et al., 1986). Due to the immaturity of the developing immune system, the small size, rapid growth and development, the growing fetus and neonates are known particularly to be sensitive to the environmental hazards (Vizcaino et al., 2014).

List of abbreviations

1234678-HpCDD	1,2,3,4,6,7,8-Heptachlorodibenzo-p-dioxin
1234678-HpCDF	1,2,3,4,6,7,8-Heptachlorodibenzofuran
123678-HxCDD	1,2,3,6,7,8-Hexachlorodibenzo-p-dioxin
23478-PeCDF	2,3,4,7,8-Pentachlorodibenzofuran
AMAP	Arctic Monitoring and Assessment Programme
CPs	chlorinated paraffins
DDT	Dichlorodiphenyltrichloroethane
HCB	Hexachlorobenzene
LOD	limit of detection
MCCPs	medium chain chlorinated paraffins
OCDD	octachlorodibenzodioxin
OCPs	organochlorine pesticides
PCBs	polychlorinated biphenyls
PCDDs	polychlorinated dibenzo-p-dioxins
PCDFs	polychlorinated dibenzofurans
p,p'-DDE	p,p'-dichlorodiphenyldichloroethylene
SCCPs	short chain chlorinated paraffins
TEF	Toxic Equivalency Factor
TEQ	toxic equivalence
ww	Wet weight

Dioxins and dioxins-like substances, polychlorinated biphenyls and organochlorine pesticides were among the initial group of twelve POPs under the Stockholm Convention in 2004 (UNEP, 2011). These chemicals are also referred to as the legacy POPs, because their presence in the environment is mainly a legacy of past emissions (AMAP, 2017). Dioxins are a generic term for the polychlorinated dibenzo-p-dioxins (PCDDs), the polychlorinated dibenzofurans (PCDFs) and mono-ortho and non-ortho coplanar polychlorinated biphenyls (dioxin-like PCBs). Dioxins are highly toxic and ubiquitous compounds, but originally, PCDDs and PCDFs did not exist before the industrialization except for very small amounts from the combustion of domestic and chemical waste and geological processes; while PCBs have been produced commercially for several decades (Czuczwa et al., 1984; Ferrario et al., 2000; Safe, 1989; Schecter et al., 2006). Dioxins Toxicity Equivalence Factors (TEFs) have been used to assign the toxicity of PCDDs, PCDFs, and dioxin-like PCBs. The most toxic compound is 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) which has a TEF equal 1 (Safe, 1990). Humans are exposed to dioxins and organochlorine pesticides mainly through dietary pathway (Schuhmacher et al., 1999; Törnkvist et al., 2011), potential health effects are related to the actual body burden, which is determined by the total long term exposure. POPs are highly lipophilic and have the ability to bioaccumulate and biomagnify in the food chain, and therefore these compounds are mainly found in animal fat including meat, fatty fish and dairy products (Chávez-Almazán et al., 2020; Törnkvist et al., 2011). Dioxins and dioxin-like substances, PCBs and pesticides are also known as 'endocrine disrupting chemicals' due to their ability to interfere with hormone signaling or mimic activity of hormones in the human endocrine system (De Coster and van Larebeke, 2012).

The term 'chemicals of emerging concern' (CEC) refer to environmental contaminants that are gaining attention, either because they are being newly introduced or because advances in analytical chemistry permit their identification and/or quantification in (environmental) samples with a sufficient degree of reliability (AMAP, 2017). CECs comprise a variety of contaminants, including nanoparticles, pharmaceuticals, and personal care products, flame retardants and some industrial chemicals with potential significant impact on human health and aquatic life. Most of CECs have entered the environment for years, even decades, but their presence has only recently begun to be investigated. Chlorinated paraffins are a group of representative industrial chemicals of the CECs. Chlorinated paraffins (CPs) are polychlorinated n-alkanes mixtures (chemical formula: CnH2n+2-mClm) that are divided into three groups, based on their carbon chain length: short-chain (C10-13, SCCPs), medium-chain (C14-17, MCCPs) and long-chain (C > 17, LCCPs) chlorinated paraffins (Tomy et al., 1998). Ubiquitous in the environment, SCCPs and MCCPs have been widely detected in soil (Gao et al., 2012), sediment (Hüttig and Oehme, 2005) and air (Fridén et al., 2011). Data and evaluation on the LCCPs are relatively scarce, nevertheless, Yuan et al. (2021) recently reported that LCCPs predominated (52% of total CPs) in the muscle of marine mammals from Swedish waters, which is the first study report that LCCPs surpassed those of other CPs in marine mammals (Yuan et al., 2021). However, the studies on human exposure to chlorinated paraffins are very limited (Qiao et al., 2018). CPs are known to be resistant to water, heat and chemicals and therefore widely used in plasticizers in polyvinyl chloride, rubber, surface coatings, adhesives, and sealants (Houghton, 2000). Recently, SCCPs have been classified as POPs by the Stockholm Convention in 2017. Although the persistence, bioaccumulation and potential toxicity of MCCPs have been reported previously (Glüge et al., 2018; Zellmer et al., 2020), MCCPs are still under the evaluation by European Chemicals Agency in REACH regulation (Justin Boucher, 2020). The Norwegian government established national targets for eliminating or substantially reducing releases of priority hazardous substances by 2010 with a view to eliminating them by 2020, and MCCPs are one of the substances on that list (Norwegian Government Security and Service Organization, 2006).

Exposure to POPs has been associated with many adverse health effects, including impaired neurodevelopment, immune and reproductive dysfunction, birth defects, disruption of endocrine function, and cancer (Damstra, 2002; Jones and De Voogt, 1999; Zhang et al., 2016). The concentrations of the POPs in maternal blood during pregnancy give an indication of the potential risk to the developing fetus.Temporal trends of POPs are useful in understanding the human exposure and evaluate the impact of large-scale production and usage on the environment. Substantial decline of blood concentrations of PCBs and pesticides in men and women at reproductive ages has been reported by Nøst et al. (2019) from 1986 to 2007 in Northern Norway. In addition, similar decreasing trends of dioxins and organochlorine compounds in human biomonitoring have been reported in epidemiological studies worldwide (Dallaire et al., 2003; Hardell et al., 2010; Wittsiepe et al., 2000). However, to our knowledge, information regarding to temporal trends in human exposure to chlorinated paraffins is still limited. The current study aims to evaluate the blood serum concentrations of dioxins and dioxins-like compounds, organochlorine pesticides and chlorinated paraffins in women (postpartum, pregnant and non-pregnant) residing in Northern Norway. We further investigated time trends of these POPs between 2007 and 2009 (MISA 1) and 2019 (MISA 2) which will contribute to increase the limited knowledge of human exposure to emerging and legacy contaminants.

2. Methods

2.1. Study population and data collection

The Northern Norway mother-and-child contaminant cohort study, the MISA study, was established in 2007 with the purpose of assessing human exposure and risk factors of persistent toxic substances related to pregnancy and breastfeeding. MISA 1 took place from 2007 until 2009 in different regions of Northern Norway and included 515 women in the second trimester of pregnancy and with repeated blood sampling three days (n = 458) and six weeks postpartum (n = 394). In 2017, we initiated a follow-up, the MISA 2 study, which also included non-pregnant women (nulliparous female university students). For study details, see previous publications by Veyhe et al. (2012).

The studies (#2009/1959 MISA 1; #2017/816 MISA 2) were approved by the Regional Committees for Medical and Health Research Ethics (REC North), as well as by the Norwegian Data Inspectorate. It was conducted in accordance with the Helsinki declaration. Written informed consent was obtained from all participants for any use of data in the study.

Due to economic constraints, present chemical analyses of selected compounds were limited to 100 samples. This involved 62 blood samples in the MISA 1 study which were collected three days postpartum between October 2007 and February 2009. Samples which are previously defrosted and volume below 5 ml was excluded. In MISA 2, available samples of ongoing study in the city of Bodø, were included for pregnant women with gestational week between 8 and 20 weeks (n = 28) representing period June until October 2019, and for the latest collection of non-pregnant women (n = 10) from October until November 2019. A total of 90 blood samples of the pregnant and postpartum women was combined into 9 pools with random selection with 9–11 individual blood samples in each pool; among which 6 pools were created from the MISA 1 study and 3 pools were derived from the MISA 2 study samples. The rest 10 samples of non-pregnant women living in Bodø were allocated into separate group (Pool 10). Fig. 1 shows the process of selecting pooled samples in MISA cohort study.

2.2. Blood sample measurements

Blood samples (fasting blood for MISA 1; non fasting blood for MISA 2) were drawn from the antecubital vein with standard equipment into BD Vacutainer (SST II Plus Advance 10/8.5 ml) and were centrifuged at 2000 relative centrifugal force (RCF) for 10 min. Serum was transferred to glass vials pre-rinsed with n-hexane/acetone and stored at minus 20 °C until analysis.

2.3. Chemical analysis of POPs and quality control

The analytical work was conducted at Centre du Toxicologie du Québec (CTQ), Institut National de Santé Publique du Québec (INSPQ), Québec, Canada.

For the analysis of polychlorinated dioxins/furans (PCDD/Fs), dioxin-like PCBs, organochlorine pesticides and chlorinated paraffins listed in Table 1, three different and fully validated methods, according to ISO17025 criteria, have been used to quantify those substances. All three methods were using the same hexane liquid-liquid extraction of carbon 13 analogues spiked serum denaturized with reagent alcohol and saturated ammonium solution.

For organochlorine pesticides, the serum extracts were purified on a florisil column with a mixture of dichloromethane: hexane (25:75) then evaporate, reconstituted in hexane and quantified on a gas-chromatograph coupled to a single quadrupole mass spectrometer operating in electron capture negative chemical ionization (GC-ECNI-MS) with an analytical column DB-XLB 60 m × 0.25 μm x 0.25 μm C13 labeled congeners (6C13-HCB and 12C13-p,p'-DDE) from Cambridge Isotope Laboratories (CIL) were used as internal standard.

For polychlorinated dioxins/furans (PCDD/Fs) and dioxin-like PCBs, the serum extracts were purified and separated on neutral aluminum column with dichloromethane: hexane (50:50). They were then quantified on an atmospheric pressure gas-chromatograph coupled to a tandem mass spectrometer (APGC-MS/MS) on an analytical column DB-XLB 30 m × 0.25 μm x 0.1 μm according to instrumental parameters. Concentrations in pg/L were transformed in pg-TEQ/L according to the Toxic Equivalence Factor (TEF) proposed by WHO in 2005 (Van den Berg et al., 2006). The details regarding internal standards of polychlorinated dioxins/furans and dioxin-like PCBs and their recovery rate for each determination are shown in the supplementary materials Table S1.

For chlorinated paraffins, the serum extracts were purified on two layers (acidified-neutral) silica gel column with dichloromethane: hexane (50:50). Purified extracts, reconstituted in acetonitrile, were analyzed on an ultra-high-pressure liquid chromatograph with UPLC column BEH C18, 50 × 2.1 mm, 1.7 μm and coupled to a time-of-flight high resolution mass spectrometer (QToF) where chlorine enhanced atmospheric negative chemical ionization was performed with dichloromethane. The mass spectrometer resolution was set to achieve

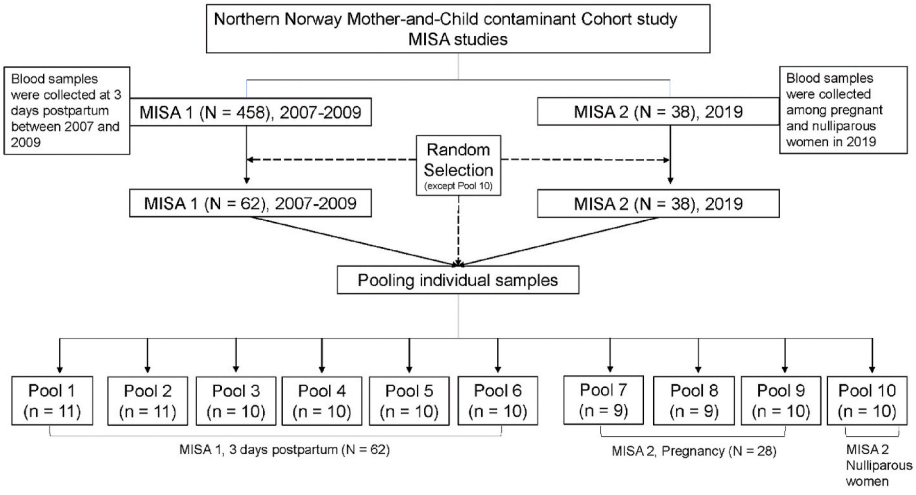

Fig. 1. The process of selecting individual sample into pooled sample. The number of individual samples indicated with 'N', and the number of individual samples in each pool indicated as 'n'. Random selection was used to select samples from pregnant women and postpartum women in MISA 1 and MISA 2 (pool 1 to pool 9); and non-pregnant from MISA 2 were allocated into one group.

Table 1
Overview of POPs compounds assessed in pooled serum samples of women in MISA 1 and 2 studies during period 2007-2009 and 2019, respectively.

Compound group	Compound	Abbreviation or congener	Detection frequency		Unit
			MISA 1	MISA 2	
Polychlorinated dibenzodioxins (PCDDs)	2,3,7,8-Tetrachlorodibenzo-P-dioxin	2378-TCDD	0	0	pg-TEQ/L
	1,2,3,7,8-Pentachlorodibenzo-P-dioxin	12378-PeCDD	50%	0	
	1,2,3,4,7,8-Hexachlorodibenzo-P-dioxin	123478-HxCDD	0	0	
	1,2,3,6,7,8-Hexachlorodibenzo-p-dioxin	123678-HxCDD	100%	75%	
	1,2,3,7,8,9-Hexachlorodibenzo-P-dioxin	123789-HxCDD	33%	0	
	1,2,3,4,6,7,8-Heptachlorodibenzo-P-dioxin	1234678-HpCDD	100%	100%	
	Octachlorodibenzodioxin	OCDD	100%	100%	
Polychlorinated dibenzofurans (PCDFs)	2,3,7,8-Tetrachlorodibenzofuran	2378-TCDF	0	0	pg-TEQ/L
	1,2,3,7,8-Pentachlorodibenzofuran	12378-PeCDF	0	0	
	2,3,4,7,8-Pentachlorodibenzofuran	23478-PeCDF	100%	75%	
	1,2,3,4,7,8-Hexachlorodibenzofurans	123478-HxCDF	0	0	
	1,2,3,6,7,8-Hexachlorodibenzofuran	123678-HxCDF	0	25%	
	2,3,4,6,7,8-Hexachlorodibenzofuran	234678-HxCDF	0	0	
	1,2,3,7,8,9- Hexachlorodibenzofuran	123789-HxCDF	0	0	
	1,2,3,4,6,7,8-Heptachlorodibenzofuran	1234678-HpCDF	100%	75%	
	1,2,3,4,7,8,9-Heptachlorodibenzofuran	1234789-HpCDF	0	0	
	Octachlorodibenzofuran	OCDF	0	0	
Dioxins-like polychlorinated biphenyls (PCBs)	3,3′,4,4′-Tetrachlorobiphenyl	PCB 77	0	0	pg-TEQ/L
	3,4,4′,5-Tetrachlorobiphenyl	PCB 81	0	0	
	3,3′,4,4′,5-Pentachlorobiphenyl	PCB 126	100%	100%	
	3,3′,4,4′,5,5′-Hexachlorobiphenyl	PCB 169	100%	100%	
Organochlorine pesticides (OCPs)	Aldrin	-	0	0	μg/L wet weight
	Alpha-Endosulfan	-	0	0	
	Beta-Endosulfan	-	0	0	
	Dieldrin	-	0	0	
	Endrin	-	0	0	
	Hexachlorobenzene	HCB	100%	100%	
	p,p′-dichlorodiphenyldichloroethylene	p,p′-DDE	100%	100%	
	Toxaphene Parlar-No. 26	-	83%	0	
	Toxaphene Parlar-No. 50	-	100%	0	
Chlorinated paraffins	Short chain chlorinated paraffins (SCCPs)	C10H17Cl5	0	50%	μg/L wet weight
		C10H16Cl6	0	50%	
		C10H15Cl7	0	0	
		C10H14Cl8	0	0	
		C10H13Cl9	0	0	
		C10H12Cl10	0	0	
		C11H19Cl5	33%	75%	
		C11H18Cl6	83%	75%	
		C11H17Cl7	33%	25%	
		C11H16Cl8	N.A.	N.A.	
		C11H15Cl9	0	0	
		C11H14Cl10	0	0	
		C12H21Cl5	0	0	
		C12H20Cl6	0	50%	
		C12H19Cl7	0	50%	
		C12H18Cl8	0	25%	
Chlorinated paraffins (CPs)	Short chain chlorinated paraffins (SCCPs)	C12H17Cl9	0	0	μg/L wet weight
		C12H16Cl10	0	0	
		C13H23Cl5	0	0	
		C13H22Cl6	0	0	
		C13H21Cl7	0	25%	
		C13H20Cl8	0	25%	
		C13H19Cl9	0	0	
		C13H18Cl10	0	0	
Chlorinated paraffins (CPs)	Medium chain chlorinated paraffins (MCCPs)	C14H25Cl5	0	0	μg/L wet weight
		C14H24Cl6	0	50%	
		C14H23Cl7	50%	100%	
		C14H22Cl8	67%	100%	
		C14H21Cl9	0	50%	
		C14H20Cl10	0	0	
		C15H27Cl5	17%	25%	
		C15H26Cl6	17%	50%	
		C15H25Cl7	50%	75%	
		C15H24Cl8	17%	50%	
		C15H23Cl9	0	0	
		C15H22Cl10	0	0	
		C16H29Cl5	0	25%	
		C16H28Cl6	17%	0	
		C16H27Cl7	0	0	
		C16H26Cl8	0	0	
		C16H25Cl9	0	0	
		C16H24Cl10	0	0	
		C17H31Cl5	0	0	

(*continued on next page*)

Table 1 (*continued*)

Compound group	Compound	Abbreviation or congener	Detection frequency		Unit
			MISA 1	MISA 2	
		C17H30Cl6	33%	0	
		C17H29Cl7	0	0	
		C17H28Cl8	0	0	
		C17H27Cl9	0	0	
		C17H26Cl10	0	0	

N.A. Not Available.

better than 20 000 FWHM. Calibration and quantification were made by homologue congeners groups, based on characterized commercial SCCP and MCCP mixtures according to Yuan et al. (2017a) approaches, using a calibrant solution, made by mixing equal concentrations of the following commercial standards, SCCP C10–C13 51.5%Cl, SCCP C10–C13 55.5% Cl, SCCPC10–C13 63% Cl, MCCP C14–C17 42% Cl, MCCP C14–C17 52% Cl, and MCCP C14–C17 57% Cl from Dr. Ehrenstorfer supplier. Single C13 labeled congeners (1,5.5.6.6.10-C10Cl6, 1,1,1,3,10,12,12, 12-C12Cl8) from Cambridge Isotope Laboratories (CIL) were used as internal standard. Single unlabeled SCCP-MCCP congeners from Chiron were used as additional internal standards and the recovery of these congeners are presented in supplementary materials Table S2. All the chlorine adducts m/z masses used for quantifying the 48 homologue groups are listed in Table 1.

For all methods, limit of detection (LOD) was based on 3 times the standard deviation from ten replicate analysis of uncontaminated matrices spiked at levels around 3 to 8 times the LOD levels. Multiple procedural blanks were done for each analytical sequence in order to assess proper contamination subtraction when occurring. For PCDD/Fs and coplanar PCBs only OCDD and PCB 77, PCB 126 required minor subtraction. For SCCP-MCCP contamination correction were required for congeners of C10, C11, C12, C14, C15 chain length containing 5, 6 and 7 atoms of chlorine. The highest results of SCCP and MCCP were confirmed with replicated analysis in order to validate the absence of accidental contamination.

Centre du Toxicologie du Québec (CTQ), Institut National de Santé Publique du Québec (INSPQ), Québec, Canada has successfully participated in the Arctic Monitoring and Assessment Programme (AMAP) ring test external quality assessment scheme covering method performance for organochlorine pesticides and dioxin-like PCBs. Method accuracy was also thoroughly calculated with the analysis of NIST certified reference material SRM 1958 (NIST, 2018). Unfortunately, no external quality assessment scheme or reference materials are available to date for evaluation of method performance for chlorinated paraffins (SCCPs, MCCPs).

2.4. Summary of POPs compounds in this study

The results of this paper are restricted to POPs with detection rate over 30% of the pooled samples in both MISA 1 and 2 studies. Table 1 shows the list of POPs analyzed in our study. Details on the concentrations of compounds involved in this study are presented in the Supplementary Material Tables S3 and S4 and S5.

2.5. Statistical analyses

Statistical analyses were conducted using IBM SPSS for Windows statistical package version 26. Geometric mean (GM), minimum and maximum were used to describe the serum pooled POPs concentration in MISA 1 and MISA 2. Concentrations of selected chemicals below the LOD were replaced by LOD/2. The distributions of pooled POPs concentrations were normally distributed according to the Shapiro-Wilk test and Q-Q plot, with the exception of PCDDs and MCCPs. We therefore performed Mann-Whitney *U* test to examine temporal trends of PCDDs and MCCPs. The differences of other POPs between MISA 1 and MISA 2 were analyzed using independent sample *t*-test. In order to eliminate potential influence of serum POPs levels of non-pregnant women on the temporal trends, sensitivity analyses were conducted by excluding pool 10 (non-pregnant women). A significance level of $p < 0.05$ (two tailed) was set for all analyses.

3. Results and discussion

The overall age range of the participating women was between 19 and 41 years. Pool 3 and 4 (both MISA 1) had the similar and highest average age compared with the other pools which are around 33 years. In contrast, the average age of the pool 10 (MISA 2, nulliparous women) was the lowest with average age of 21 years old.

3.1. PCDD/Fs and dioxin-like PCBs concentrations and congeners patterns

The serum concentrations for pooled samples of PCDDs, PCDFs, dioxin-like PCBs and Σdioxins were expressed in pg-TEQ/L (Table 2). The selected Σ(PCDD/Fs + coplanar PCBs) in serum concentration ranges from 4.5 to 32.9 pg-TEQ/L among pooled samples, with geometric means of 24.6 and 6.2 pg-TEQ/L in MISA 1 and 2, respectively. Pool 2 (MISA 1) had the highest concentrations of all the selected Σ(PCDD/Fs + coplanar PCB) while Pool 9 (MISA 2, pregnant women) was the lowest. For PCDD/Fs, the total TEQ concentration ranges from 1.65 (pool 9) to 12.6 (pool 3, MISA 1) pg-TEQ/L, with a geometric mean of 5.4 pg-TEQ/L. 23478-PeCDF (68.0%) was the predominant PCDD/Fs congener profile, followed by 123678-HxCDD (20.9%) and 1234678-HpCDD (6.2%). In MISA 1 and 2, the serum concentrations of dioxin-like PCB 126 and PCB 169 range from 2.3 (pool 10) to 17.6 (pool 2) pg-TEQ/L and 0.8 (pool 10) to 4.6 (pool 3) pg-TEQ/L, with geometric means of 6.7 and 2.3 pg-TEQ/L, respectively. Our results show the highest contribution to the total TEQs in the serum was from the coplanar PCBs (62.9%), followed by PCDFs (26.1%) and the PCDDs (10.9%). In addition, declining trends were observed for PCDDs ($p = 0.010$), PCDFs ($p = 0.002$) and coplanar PCBs ($p = 0.001$) (Fig. 2).

Previous epidemiological studies on dioxins primarily focused on 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), which is an indicator substance for all dioxin congeners as it is an unavoidable by-product of different organochlorine chemicals, and for the toxicity equivalents as well (Pereira, 2004; Wittsiepe et al., 2000). However, TCDD was under the limit of detection in all the pooled samples in our study. Congener patterns play an important role in identifying the source and incident related dioxin exposure. 23478-PeCDF was the major congener for PCDD/Fs detected in our study, followed by 123678-HxCDD and 1234678-HpCDD. Different congeners patterns were reported in earlier studies (Wittsiepe et al., 2000; Yu et al., 2019), which might imply global PCDD/Fs sources to be different compared to our study. More than 90% of human dioxin exposure is through the consumption of various food groups (WHO, 2016). Previous epidemiological studies in Taiwan and Spain suggested that the frequency of fish and seafood consumption might be the most significant contributor to human blood PCDD/F levels (Chen et al., 2003; Schuhmacher et al., 1999). The varying concentration of serum dioxins may therefore reflect dissimilarities in dietary intake. Our observations were consistent with a few

Table 2
Summary of pooled serum concentrations (pg-TEQ/L) of PCDD/Fs and coplanar PCBs of women in MISA 1 and MISA 2 study during period 2007–2009 and 2019, respectively.

MISA studies	Pool #	N	Average age (years)	Age (Min-Max)	PCDDs			PCDFs		Coplanar PCBs		Σdioxins
					123678-HxCDD	1234678-HpCDD	OCDD	23478-PeCDF	1234678-HpCDF	PCB 126	PCB 169	
Limit of detection					0.4	0.1	0.003	1.7	0.1	0.8	0.4	
Toxicity Equivalence Factors (TEFs)					0.1	0.01	0.0003	0.3	0.01	0.1	0.03	
MISA 1	1[a]	11	29.9	19–37	1.9	0.4	0.2	6.9	0.3	13.1	4.1	27.0
	2[a]	11	29.7	22–39	2.1	0.6	0.2	8.4	0.2	17.6	3.8	32.9
	3[a]	10	33.1	25–40	2.1	0.8	0.2	9.2	0.3	14	4.6	31.2
	4[a]	10	33.0	29–40	1.9	0.6	0.2	4.2	0.1	9.9	3.1	20.1
	5[a]	10	29.2	22–34	1.7	0.3	0.2	4.2	0.2	6.6	2.7	15.9
	6[a]	10	33.4	28–41	2.5	0.5	0.2	5.4	0.1	12.2	4.2	25.2
MISA 2	7[b,*]	9	31.9	25–40	0.5	0.2	0.1	2.1	0.05	3.5	1.4	7.6
	8[b,*]	9	28.9	23–38	0.2	0.4	0.1	2.0	0.2	3.6	1.2	7.5
	9[b,*]	10	28.3	20–32	0.4	0.2	0.1	0.85	0.1	2.6	1.0	4.5
	10[b, †]	10	21.2	19–24	0.5	0.1	0.1	1.7	0.1	2.3	0.8	5.6
MISA 1 Total concentration					16.6 (PCDDs)			39.5 (PCDFs)		95.9 (Co-PCBs)		152.0
MISA 2 Total concentration					2.9 (PCDDs)			7.1 (PCDFs)		16.4 (Co-PCBs)		26.4
MISA 1 Geometric mean					2.7 (PCDDs)			6.3 (PCDFs)		15.4 (Co-PCBs)		24.6
MISA 2 Geometric mean					0.7 (PCDDs)			1.7 (PCDFs)		4.0 (Co-PCBs)		6.5

n is the number of individual samples in each pool. For abbreviations of the compounds, see the abbreviations list. [a] MISA 1, 3 days postpartum; [b] MISA 2; * Pregnancy, [†]Non-pregnant women.

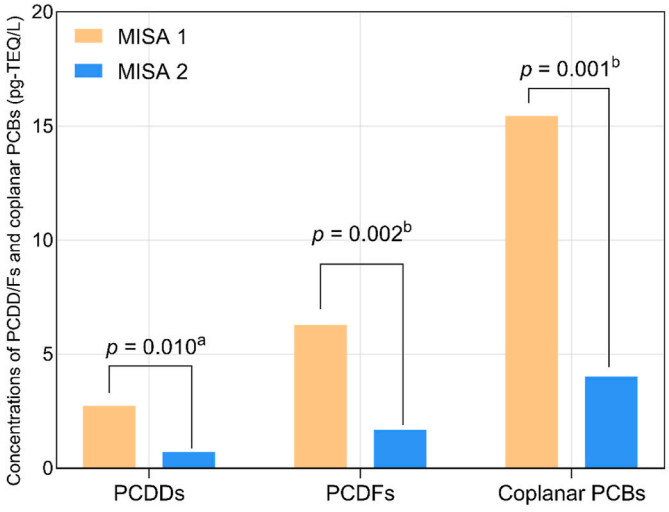

Fig. 2. Comparisons of geometric mean serum concentrations (pg-TEQ/L) of the PCDD/Fs and coplanar PCBs in the pooled samples of women from the MISA 1 and MISA 2 study during period 2007–2009 and 2019, respectively. [a] Mann Whitney *U* test was used to compare the serum PCDDs levels between MISA 1 and MISA 2. [b] Independent sample *t*-test was used for trend analysis of PCDFs and coplanar PCBs. For abbreviations of the compounds, see the abbreviations list.

previous epidemiological studies which reported PCB 126 as a major contributor to TEQs in human exposure to dioxin-like PCBs (Lampa et al., 2018; Park et al., 2014), it has the strongest toxic equivalency factor among the dioxin-like PCBs (Van den Berg et al., 2006). The dominant contributor to TEQs in the present study was dioxin-like PCBs, similar to the observation reported in the Inuit mothers from the Arctic Canada (Van Oostdam et al., 2005). In contrast, Rawn et al. (2012) reported that the contribution of dioxin-like PCBs to TEQ concentrations was small relative to PCDD/Fs in the Canadian population study. Similar to our observations, multiple studies reported a declining trend in blood levels of dioxins in pregnant women and the general population as the national and international regulations were undertaken worldwide (Muzembo et al., 2019; Nadal et al., 2008; Wittsiepe et al., 2000).

3.2. Organochlorine pesticides (OCPs)

Most of the selected OCPs compounds were not detectable in the pooled samples with the exception of hexachlorobenzene (HCB) and p,p'-Dichlorodiphenyldichloroethylene (p,p'-DDE) which were detected in all the pooled samples. The concentrations of HCB and p,p'-DDE range from 0.05 to 0.1 μg/L wet weight (ww) (GM = 0.07 μg/L ww) and 0.06–0.38 μg/L ww (GM = 0.17 μg/L ww), respectively (Table 3). Pool 2 and Pool 3, representing MISA 1, had relatively high total

Table 3
Summary of pooled serum concentration (μg/L wet weight) of organochlorine pesticides of women in the MISA 1 and MISA 2 study during period 2007–2009 and 2019, respectively.

MISA studies	Pool #	n	Average age (years)	Age (Min-Max)	HCB	p,p'-DDE	ΣOCPs
LOD					0.02	0.02	
MISA 1	1[a]	11	29.9	19–37	0.1	0.27	0.37
	2[a]	11	29.7	22–39	0.1	0.38	0.48
	3[a]	10	33.1	25–40	0.09	0.29	0.38
	4[a]	10	33.0	29–40	0.08	0.24	0.32
	5[a]	10	29.2	22–34	0.07	0.15	0.22
	6[a]	10	33.4	28–41	0.08	0.28	0.36
MISA 2	7[b,*]	9	31.9	25–40	0.05	0.11	0.16
	8[b,*]	9	28.9	23–38	0.05	0.11	0.16
	9[b,*]	10	28.30	20–32	0.05	0.08	0.13
	10[b, †]	10	21.2	19–24	0.05	0.06	0.11
MISA 1 Total concentration					0.52	1.61	2.13
MISA 2 Total concentration					0.20	0.36	0.56
MISA 1 Geometric mean					0.09	0.26	0.35
MISA 2 Geometric mean					0.05	0.09	0.14

n is the number of individual samples in each pool. For abbreviations of the compounds, see the abbreviations list. [a] MISA 1, 3 days postpartum; [b] MISA 2; * Pregnancy, [†]Non-pregnant women.

concentrations of HCB and p,p'-DDE with 0.48 μg/L and 0.38 μg/L ww, respectively. The samples from non-pregnant women in MISA 2 (Pool 10) had the lowest concentration of OCPs, with a sum of HCB and p,p'-DDE of 0.11 μg/L. We also observed decreasing trends in the concentrations of HCB ($p < 0.001$) and p,p'-DDE ($p = 0.002$) across MISA 1 (2007–2009) and MISA 2 (2019). (Fig. 3).

The most abundant OCP was p,p'-DDE, which is in agreement with previous epidemiological study from Norway (Furberg et al., 2002) and other regions worldwide (Bush et al., 1984; Hansen et al., 2009). p, p′-DDE is the main metabolite of pesticide dichlorodiphenyltrichloroethane (DDT) and a marker of past exposure to this organochlorine pesticide (Arrebola et al., 2013). The use of DDT in Norway was banned in 1970 (Kveseth et al., 1979). Humans are exposed to DDT primarily through dietary intake, and major dietary exposure of DDE are fish, seafood, meat, and dairy products (Chávez-Almazán et al., 2020). DDT residues in food have declined since it was banned, but because of the extreme persistence of DDT and DDE, it is expected that low levels of residues exposure will be present in food products for decades (Cheremisinoff and Rosenfeld, 2011). Although HCB has not been used as a pesticide in Norway, it is produced as a by-product during thermal processes. For example, two known large point sources of HCB in Norway are a magnesium factory in Telemark, in the southeast, and a nickel smelter on the south coast; however, these releases decreased enormously as a result of extensive measures taken by the Norwegian government (AMAP, 1998). The serum concentrations of HCB and p,p'-DDE observed in our study were lower compared to those reported globally (Supplementary Material Table S6) (Bravo et al., 2019; Cao et al., 2011; Hansen et al., 2009; Reid et al., 2013). Following national and international regulations on organochlorine pesticide, declining concentrations of blood HCB and p,p'-DDE were reported in a number of studies (Abass et al., 2018; Hardell et al., 2010; Koureas et al., 2019; Thomas et al., 2017), and these findings are consistent with our results.

3.3. Chlorinated paraffins (CPs)

Short and medium chain chlorinated paraffins were also analyzed in our study. Most of the chlorinated paraffins congeners were below the detection limit in our samples. In addition, the detected samples were at a very low concentration of CPs exposure. Table 4 shows the concentrations of CP congeners with detection frequency above 30% of the samples. In Pool 3 most of the congeners were < LOD, except congener of C14H22Cl8; and similarly, all the selected MCCPs were < LOD in Pool 5. In contrast, most of the congeners were detected in the pooled samples from MISA 2, except in Pool 9. The serum concentration of ΣCPs ranges from 0.03 to 0.26 μg/L ww (GM = 0.07 μg/L ww). Non-pregnant women (MISA 2, pool 10) had the highest levels of CPs compared to other pools, with a ∑CPs concentration of 0.26 μg/L ww. Serum level of MCCPs was found increasing from MISA 1 to MISA 2 ($p = 0.019$) (Fig. 4). The geometric mean concentration of serum SCCPs was found moderately higher in MISA 2 than in the MISA 1 ($p = 0.628$) (Fig. 4). MCCPs were the most abundant CPs in about two-thirds of the total serum CP concentrations. The mean ΣMCCPs/ΣSCCPs (0.51/0.32) level ratio was 1.60 for all samples.

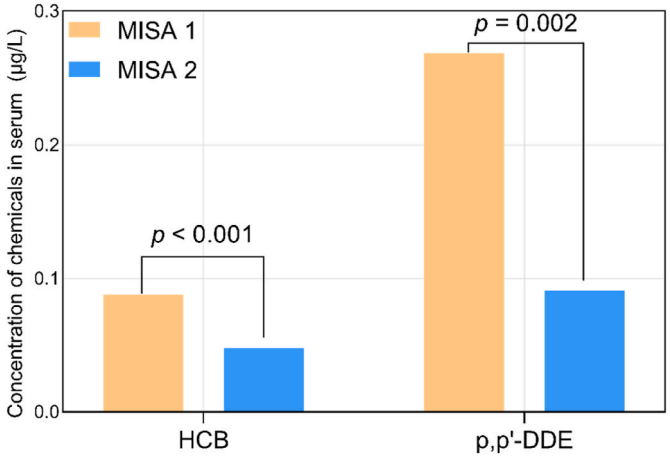

Fig. 3. Comparisons of geometric mean serum concentrations (μg/L) of pesticides in the pooled samples of women in the MISA 1 (year 2007–2009) and MISA 2 study (year 2019). Independent sample *t*-test was used for trend analysis of HCB and p,p'-DDE between MISA 1 and MISA 2. For abbreviations of the compounds, see the abbreviations list.

The patterns of carbon and chlorine groups in our study were compared with the previous investigations. C11-CPs and C14-CPs were the most abundant components of SCCPs and MCCPs in this study, which is in line with earlier studies on maternal and cord serum (Aamir et al., 2019; Qiao et al., 2018). The total serum concentrations of SCCPs and MCCPs in our study were 0.32 and 0.51 μg/L ww, respectively. Aamir et al. (2019) reported the maternal sera concentrations of ΣSCCP and ΣMCCP ranged from 15.9 to 584 and 29.3–1006 μg/L, respectively in the Chinese population. Compared with the concentrations in China, SCCPs and MCCPs in the current study were at very low level, this is likely because China is the largest producer of chlorinated paraffins (Shen et al., 2016). Serum MCCPs concentrations increase over time in our study was supported by a similar time trend analysis in men from Australia between 2004 and 2015 (van Mourik et al., 2020) and in environmental matrices (Chen et al., 2011). Our study indicates a growing concern of the MCCPs, which were in agreement with previous studies (Glüge et al., 2018; van Mourik et al., 2016). The restriction on SCCPs was implemented globally and as a result MCCPs are being used as alternatives of SCCPs for many applications, causing an increased production of MCCPs over time (Yuan et al., 2017b). In our study, MCCP levels in serum were higher than that of SCCP, with a mean ΣMCCPs/ΣSCCPs level ratio of 1.60 for all studied samples. The observed ΣMCCPs/ΣSCCPs ratio in our study was comparable with the study from Australia analyzed between 2004 and 2015 (ratio = 2.6) (van Mourik et al., 2020), and from Wuhan, China collected between 2015 and 2016 (ratio = 2.0) (Aamir et al., 2019). On the contrary, Li et al. (2017) reported ΣMCCPs/ΣSCCPs ratio of 0.2 among 50 adults sampled during 2012 in Shenzhen, China. This may be due to differences in regional exposure to CPs in Chinese general population. In addition, Thomas et al. (2006) found that the SCCPs were predominant compounds, with the ΣMCCPs/ΣSCCPs ratio of 0.1 from the human milk samples collected in UK between 2001 and 2002. However, our samples for MISA 1 were collected 5 years later to the UK study and MISA 2 includes recent collection in 2019. This may explain the differences in ΣMCCPs/ΣSCCPs ratios. These ratio variations also indicate the accumulation of different patterns of CPs to be different in general populations, which may reflect the sources and consumption of SCCPs and MCCPs varying between countries and during the different time periods and matrix used.

Sensitivity analyses by excluding the pool 10 with non-pregnant women obtained the equivalent results for temporal trends (Data not shown).

3.4. Strengths and limitations

Information regarding to human exposure to CPs is relatively scarce. Present study enhances the knowledge of exposure to CPs in Northern Norwegian women. The temporal trend of legacy POPs and emerging CPs offer novel insights of variation in human exposure over a decade. The methods and analytical approaches employed in our study is validated in AMAP and the analytical laboratory has participated successfully in the most recent AMAP Analytical Ring Test (INSPQ). The use of pooled sample is advantageous as a cost-effective approach, which reduces the time and resources required. The pools in our study were selected based on postpartum women in MISA 1 and pregnant and non-pregnant women in MISA 2. According to both time and

Table 4
Summary of pooled serum concentration (μg/L wet weight) of chlorinated paraffins of women in the MISA 1 and MISA 2 study during period 2007–2009 and 2019, respectively.

MISA studies	Pool #	n	Average age (years)	Age (Min-Max)	SCCPs		MCCPs			ΣCPs
					C11H19Cl5	C11H18Cl6	C14H23Cl7	C14H22Cl8	C15H25Cl7	
LOD					0.01	0.01	0.01	0.01	0.01	
MISA 1	1[a]	11	29.9	19–37	0.005	0.03	0.02	0.01	0.01	0.08
	2[a]	11	29.7	22–39	0.02	0.03	0.005	0.01	0.01	0.08
	3[a]	10	33.1	25–40	0.005	0.005	0.005	0.01	0.005	0.03
	4[a]	10	33	29–40	0.005	0.01	0.01	0.01	0.005	0.04
	5[a]	10	29.2	22–34	0.02	0.03	0.005	0.005	0.005	0.07
	6[a]	10	33.4	28–41	0.005	0.01	0.01	0.005	0.01	0.04
MISA 2	7[b,*]	9	31.9	25–40	0.01	0.03	0.02	0.03	0.01	0.1
	8[b,*]	9	28.9	23–38	0.02	0.02	0.02	0.02	0.01	0.09
	9[b,*]	10	28.3	20–32	0.005	0.005	0.01	0.02	0.005	0.05
	10[b, †]	10	21.2	19–24	0.02	0.03	0.08	0.09	0.04	0.26
MISA 1 Total concentration					0.18 (SCCPs)		0.15 (MCCPs)			0.33
MISA 2 Total concentration					0.14 (SCCPs)		0.36 (MCCPs)			0.50
MISA 1 Geometric mean					0.02 (SCCPs)		0.02 (MCCPs)			0.05
MISA 2 Geometric mean					0.03 (SCCPs)		0.07 (MCCPs)			0.10

n is the number of individual samples in each pool. For abbreviations of the compounds, see the abbreviations list. [a] MISA 1, 3 days postpartum; [b] MISA 2; * Pregnancy, [†]Non-pregnant women.

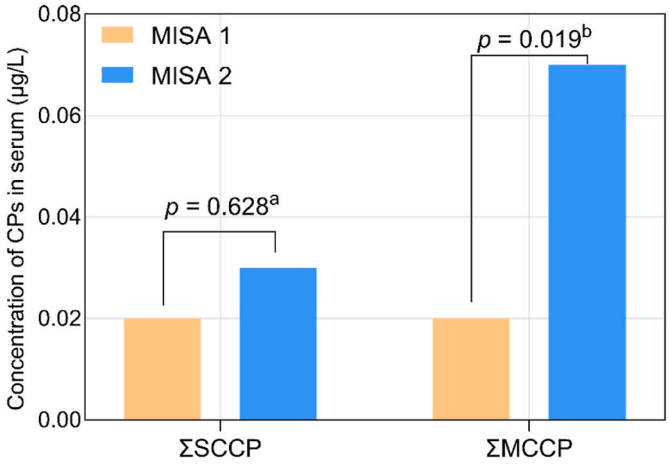

Fig. 4. Comparisons of geometric mean serum concentrations (μg/L) of the short and medium chain chlorinated paraffins in the pooled samples of MISA 1 and MISA 2 within period 2007–2009 and 2019, respectively. [a] Independent sample *t*-test was applied to compare the levels of SCCPs between MISA 1 and MISA 2. [b] Mann Whitney *U* test was used for trend analysis of MCCPs across MISA 1 to MISA 2. For abbreviations of the compounds, see the abbreviations list.

reproductive period, the samples were randomly allocated in each pool to provide the best possible overall picture of POPs exposure. No easier pooling strategy exists to extract study sample than the simple random sample pooling. Despite the strengths, present study also has some limitations. The major limitations of this study are the very small sample size and large number of chemicals which were below the limits of detection. It is therefore important that our study results are replicated in larger studies among different sample groups. In addition, previous studies have reported that blood concentrations of PCDD/Fs, organochlorine pesticides and PCBs increased with age (Hansen et al., 2017; Rawn et al., 2012). Educational level acts as proxies for socioeconomic status of the samples, and it was found to be associated with POPs levels in several studies (Lauritzen et al., 2016; Steinholt et al., 2020). The variance of individual samples concentration might reflect the difference of age and socioeconomic status. In such case, pooling sample randomly may not be representative of target sampling. A previous study in MISA 1 cohort found that the concentrations of POPs varied slightly between the women at the second trimester and postpartum (Hansen et al., 2010). However, the effects of different sampling period and geographical locations on the concentrations of POPs in MISA 1 and 2 were less concerned in this study, which might bring potential bias to this study. Furthermore, selection bias might occur in this study, as the selected non-pregnant women were university students. Therefore, our study suggests to include random participants in the future studies, thus minimizing selection bias.

4. Conclusion

The current study analyzed and reported concentrations of dioxins and dioxin-like PCBs, hexachlorobenzene (HCB), p,p'-dichlorodiphenyldichloroethylene (p,p'-DDE), short and medium chain chlorinated paraffins in pooled serum samples from women (postpartum, pregnant and non-pregnant) between MISA 1 (2007–2009) and MISA 2 study (2019). Overall, our results indicate that the blood concentrations of the selected POPs in Northern Norwegian women were at the low range compared to other international population. Decreasing temporal trends of legacy POPs were observed in our study which agree with the national and international regulations. The increasing serum concentrations of emerging contaminant MCCPs suggest a particular concern for MCCPs exposure to humans. Future studies with a broader range of CPs measurements and large sample size are warranted to replicate our findings.

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Credit author statement

Shanshan Xu: Formal analysis, Validation, Visualization, Writing - original draft. Solrunn Hansen: Data curation, Writing - review and editing. Arja Rautio, Marjo-Riitta Järvelin, Khaled Abass, Jaana Rysä, Saranya Palaniswamy, Sandra Huber and Joan O. Grimalt: Writing - review and editing. Pierre Dumas: Chemical analysis, Writing - review and editing. Jon Øyvind Odland: Conceptualization, Methodology,

Supervision, Writing - review and editing.

Author statement

The data used in the current manuscript is available in the report from the Norwegian Environment Agency (Persistent Organic Pollutants (POPs) in Human Samples from The MISA study (Northern Norway) - Miljødirektoratet (miljodirektoratet.no). The data analysis and interpretations were however done for this manuscript alone.

Declaration of competing interest

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

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2021.111980.

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