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Faculty of Health Sciences, Institute of Community Medicine

Concentrations and predictors of persistent organic pollutants in pregnant women and associations with maternal and infant thyroid homeostasis

The Northern Norway Mother-and-Child Contaminant Cohort Study

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Vivian Berg

A dissertation for the degree of Philosophiae Doctor – November 2015

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Preface

Jon Øyvind Odland has been my main supervisor and has been an important motivator for me in performing this work. Thank you for giving me this opportunity and for your support and good advice.

Torkjel Manning Sandanger has been my supervisor and the one guiding me throughout this work. Thank you for always pushing me to do even better when I really don't want to. Some of your comments which immediately appear to make no sense to me always reappear in my head after a couple of days like a light bowl as "I get it". Thank you for your time, advice and good ideas.

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Content

Summary

During the 20th century, humans have been exposed to an increasing number of persistent organic pollutants (POPs). Two important groups of POPs are poly- and perfluoroalkyl substances (PFASs) and organochlorines (OCs). Each group has its own history of production and the time period when emissions peaked varies between the two groups. However, due to restrictions on use and the banning of several POPs, environmental concentrations of OCs and PFASs have decreased since the 1980s and early 2000, respectively.

POPs are transferred to humans primarily through diet although concentrations in specific food items are generally low. Further, POPs accumulate in humans and are transferred from the mother to the foetus during pregnancy and to infants through breastfeeding. High exposures to POPs have been demonstrated to cause harmful effects in humans, but potential negative health effects of background exposures in the general population is not investigated thoroughly. Concerns for possible endocrine disrupting effects of POPs on thyroid functions have been raised, especially in pregnant women, foetuses and children as these groups are more vulnerable to endocrine disrupting chemicals due to pregnancy- and growth-related stress on the thyroid gland.

The overarching aim of this thesis was to investigate concentrations and predictors of PFASs and a selection of OCs in pregnant women, and to assess the effect of exposure to these POPs on thyroid function in mother-child pairs. The thesis papers are based on personal and lifestyle information reported by pregnant woman from The Norwegian mother-and-child contaminant cohort study (n=391) sampled in the period 2007-2009, as well as serum samples and blood spot samples from these women and their children, respectively. Maternal serum samples donated during the 2nd trimester were analysed for a suite of PFASs and OCs, whereas ten thyroid parameters were analysed in serum donated at three time points; 2nd trimester, three days and 6 weeks postpartum. Concentrations of thyroid stimulating hormone (TSH) in infants were obtained from the Newborn Screening program, performed in blood spots sampled approximately three days after birth. POPs, biomarkers, predictors and covariates included in the present work were evaluated by multivariate methods to assess the overall effects on maternal and infant thyroid function of multipollutant exposures. Effect sizes were reported in mixed models and multiple linear regressions.

This thesis demonstrate that parity, sampling date, birth year and diet influenced maternal concentrations of PFASs in the time period 2007-2009, where parity was the most important predictor for all PFAS concentrations. Further, we identified sampling date to be an important predictor of several PFASs, where concentrations declined throughout the recruitment period. This observation is probably a reflection of temporal trends, where environmental concentrations of PFASs have been decreasing rapidly from 2002 and were likely still declining during the study period.

This work demonstrates associations between several POPs and maternal TSH and thyroid hormones (THs) in early pregnancy, 3 days and 6 weeks postpartum, where variables related to metabolic changes due to pregnancy (e.g. total lipid, thyroxine binding proteins (TH-BPs) and thyroxine binding capacity) were important predictors for TSH and TH concentrations at all sampling points. The association of individual POPs with thyroid function was dependent on proper adjustment for covariates in respective models, where most associations between individual POPs and TSH or THs were no longer significant after mutual adjustments for other POPs or pregnancy related covariates. Accordingly, summed POPs were positively associated to TSH concentrations, and summed OCs, perfluorodecanoic acid (PFDA) and perfluoroundecanoic acid (PFUnDA) were inversely associated to the THs. Finally, maternal POP concentrations did not influence infant TSH concentrations, but maternal TSH and FT4 were positively and inversely associated to infant TSH respectively which may be secondary to the influence of POPs on maternal TSH and THs. However, the clinical relevance of observed variations in TSH and THs is not clear, as all concentrations varied within normal reference ranges.

This work highlights challenges in establishing effects of POPs on thyroid functions due to the complexity of the thyroid system as well as the intricacy of multiple exposures of POPs. However, the results indicate an influence of background exposures to POPs on maternal thyroid function which may influence foetal and infant thyroid function, and prompt the need to drastically expand research on current environmental concentrations and mixtures of POPs.

Sammendrag

Mennesker har vært eksponert for et økende antall miljøgifter de siste 70 år. To viktige grupper av miljøgifter er organokloriner (OCer) og perfluorerte organiske forbindelser (PFASer). Disse to gruppene har ulike historiske utslipp og bruksområder, men etter at det ble innført restriksjoner for bruk av mange av dem, har konsentrasjonene i miljøet generelt gått ned fra og med 1980-tallet for OCer og fra år 2000 for PFASer.

Når miljøgifter produseres og tas i bruk havner de raskt i miljøet, i dyr, planteliv og avlinger. Selv om det er relativt lave konsentrasjoner av miljøgifter i ulike matvarer, så er det maten vi spiser som er hovedkilden til miljøgifter i mennesket. Noen miljøgifter akkumuleres i mennesket fordi de er lite nedbrytbare og overføres videre til fosteret i gravide kvinner og til spebarn gjennom morsmelk hos de som ammer. Det er blitt vist at høye konsentrasjoner av miljøgifter kan være skadelig for mennesker og dyr, men det er også en økt bekymring for langtidseffekter av de lave konsentrasjonene som er måles i blodet i den generelle befolkningen. Det er bekymring for at miljøgiftene kan forstyrre stoffskiftet hos mennesker. Gravide kan være spesielt sårbare for forstyrrelser av miljøgifter på grunn av et naturlig stress på stoffskiftet som følge av graviditeten. Fosterets er avhengig av mors stoffskifte hormoner og fosterutviklingen kan dermed påvirkes av mors miljøgifter.

Hovedmålet for denne avhandlingen har vært å undersøke konsentrasjoner av miljøgifter i gravide kvinner og hvilke faktorer (prediktorer) som beskriver kvinners høye eller lave konsentrasjoner i blodet. Samtidig ville vi se om konsentrasjonene kunne settes i sammenheng med uregelmessigheter i stoffskiftet hos mor og barn. Arbeidet baserer seg på opplysninger om kosthold og livstil hos 391 gravide kvinner som deltok i studien Miljøgifter i Svangerskapet og i Ammeperioden (MISA) i perioden 2007-2009, og blodprøver fra disse kvinnene og deres barn. Miljøgifter ble målt i mors blod tidlig i svangerskapet og en rekke stoffskifte parametere ble målt tidlig i svangerskapet, men også tre dager og 6 uker etter fødselen. Konsentrasjoner av thyroid stimulerende hormon (TSH) ble målt i barna tre dager etter fødsel av Nyfødtscreeningen på Universitetssykehuset i Oslo. Miljøgifter, prediktorer, stoffskifteparametere og viktige faktorer for naturlig variasjon i stoffskiftet ble videre evaluert med multivariate statistiske metoder for å vurdere hvordan miljøgiftene samlet påvirket balansen i stoffskiftet til mor og barn.

I dette arbeidet observerte vi at antall barnefødsler, dato og år for blodprøvetakingen, mors fødselsår og mors kostholdsvaner var viktige forklaringsfaktorer for konsentrasjonene av PFASer i studie årene 2007-2009. Antall barn kvinnene hadde født hadde sterkest påvirkning på miljøgiftskonsentrasjoner, der kvinner med flere barn hadde lavere konsentrasjoner enn kvinner med et barn eller ingen fra før. Konsentrasjonene av flere PFASer sank gjennom rekrutteringsperioden og kan sannsynligvis forklares av at konsentrasjonene av disse miljøgiftene i miljøet også sank i løpet studieperioden og kvinner som ga blodprøven sent i studiet hadde derfor lavere konsentrasjoner.

Flere miljøgifter viste en sammenheng med mors stoffskifte tidlig i graviditeten samt 3 dager og 6 uker etter fødselen. Mors stoffskifte var samtidig påvirket av de naturlige fysiologiske endringene som skjer i graviditeten og etter fødsel, og miljøgiftenes påvirkning på hormonnivåene må derfor vurderes i lys av disse naturlige endringene. Det var utfordrende å evaluere betydningen av individuelle miljøgifter i forhold til påvirkning på stoffskiftet siden miljøgiftene er sterkt korrelerte, men høye konsentrasjoner av PFASer og OCer var assosiert med høyere konsentrasjoner av TSH, og høyere konsentrasjoner av OCer var assosiert med lavere konsentrasjoner av stoffskiftehormonene fritt og bundet tyrosin (FT4 og T4) og fritt og bundet triiodotyronin (FT3 of T3). Mødrenes konsentrasjoner av miljøgifter i svangerskapet hadde ingen direkte påvirkning på deres barns TSH-nivåer, men mødre med de høyeste TSH verdiene fødte de barna som hadde de høyeste-TSH verdiene og miljøgiftene kan dermed ha en indirekte virkning på barnets stoffskifte. Allikevel, var alle forskjeller i stoffskiftet som følge av påvirkning av miljøgifter små og innenfor naturlig variasjon i nivåer for en populasjon, og vi kan dermed ikke si om resultatene er av klinisk betydning for kvinnene eller barna.

Dette arbeidet viser at det er vanskelig å evaluere miljøgifters forstyrrende effekt på stoffskiftet i gravide og deres ufødte barn, hovedsakelig på grunn av kompleksiteten av selve stoffskiftet, men også på grunn av miljøgiftenes antall og deres ulike potensiale til å forstyrre endokrine funksjoner. Resultatene viser allikevel at lave konsentrasjoner av miljøgifter viser assosiasjoner til stoffskiftet til mor og barn, og understreker viktigheten av forskning på konsentrasjoner og blandinger av miljøgifter som i dag måles i blodet til den generelle befolkning.

List of papers

This thesis is based on the following three papers, referred to in the text by their roman numerals.

I. Maternal serum concentrations of per- and polyfluoroalkyl substances and their predictors in years with reduced production and use.
Berg V, Nost TH, Huber S, Rylander C, Hansen S, Veyhe AS, Fuskevag OM, Odland JO, Sandanger TM. Environment International. 2014;69:58-66

II. Assessing the relationship between perfluoroalkyl substances, thyroid hormones and binding proteins in pregnant women; a longitudinal mixed effects approach.
Berg V, Nost TH, Hansen S, Elverland A, Veyhe AS, Jorde R, Odland JO, and Sandanger TM. Environment International. 2015;77:63-9.

III. Persistent organic pollutants and the association with maternal and infant thyroid homeostasis; a multipollutant assessment.
Berg V, Nost TH, Pettersen RD, Hansen S, Veyhe AS, Jorde R, Odland JO, Sandanger TM.
Manuscript submitted to Environmental Health Perspectives.

Abbreviations

AMAP - Arctic Monitoring and Assessment Programme

Anti-TPO - Anti-thyroid peroxidase antibodies

Ds - Deiodinases

FT3 - Free triiodothyronine

FT4 - Free thyroxine

GC - Gas chromatography

HCB - Hexachlorobenzene

HTP - Hypothalamic pituitary

LOD - Limit of detection

MISA - the Northern Norway Mother-and-Child Contaminant Cohort Study

MS - Mass spectrometry

NOWAC - Norwegian Women and Cancer Study

OCs - Organochlorines

PCBs - Polychlorinated biphenyls

PFAAs - Perfluoroalkyl acids

PFASs - Poly- and perfluoroalkyl substances

PFBA - Perfluorobutanoic acid

PFBS – Perfluorobutane sulfonic acid

PFDA - Perfluorodecanoic acid

PFHxS - Perfluorohexane sulfonic acid

PFNA - Perfluorononanoic acid

PFOA - Perfluorooctanoic acid

PFOS - Perfluorooctane sulfonic acid

PFUnDA - Perfluoroundecanoic acid

POPs - Persistent organic pollutants

POSF - Perfluorooctane sulfonyl fluoride

p,p´-DDE - 1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene

p,p´-DDT - 1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethane

QA-QC - Quality assurance- quality control

SRM - Standard reference material

TBG – Thyroxine binding globulin

Tg - Thyroglobulin

TH - Thyroid hormone

TH-BPs - Thyroid binding proteins

TR - Thyroid hormone receptor

TRH - Thyrotropin releasing hormone

TSH - Thyroid stimulating hormone

TTR - Transthyretin

T3 - Triiodothyronine

T4 - Thyroxine

UDPGT - UDP-glucuronyl transferase

UPLC - Ultra-high pressure liquid chromatography

1. Background and context

1.1 Preamble

Humans are exposed to multiple chemicals at low doses in their everyday life through digestion, absorption through skin and inhalation. Chemicals that are considered persistent, bioaccumulative, toxic, and have potential for long-range transport can be classified as persistent organic pollutants (POPs). POPs are halogenated compounds that have been directly emitted to the environment, intentionally or as by-products during their production and use (Lohmann et al. 2007; Prevedouros et al. 2006). Two major groups are poly- and perfluoroalkyl substances (PFASs) and organochlorines (OCs) which have different chemical properties and history of production and use, but are similar in their persistent nature. PFASs comprise of fluorinated carbon backbones with varying chain lengths and functional groups (Buck et al. 2011), whereas OCs are chlorinated hydrocarbons. PFASs are more recently produced and used compared to the OCs, and have been called the emerging contaminants for a decade although some of the compounds have been banned and environmental concentrations have started to decline. Still, the proportion of research on these compounds and potential human health effects is minimal compared to research targeting OCs. Therefore, the present work is mainly focused on PFASs, but also on a selection of OCs e.g. polychlorinated biphenyls (PCBs) and four pesticides (1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethylene (*p*,*p*-DDE), hexachlorobencene (HCB), *trans*- and *cis*-Nonachlor).

High exposures to POPs after accidental spills or occupational exposures have demonstrated harmful effects on human health whereas the effects in general populations have been inconsistent (Longnecker et al. 1997; Stahl et al. 2011; Wigle et al. 2008). Restrictions or full bans on use of several POPs have been implemented, resulting in a decrease in environmental concentrations. However, more recent challenges are untangling what biological relevant concentrations of POPs are, and whether current contaminant concentrations and mixtures in the human blood circulation can cause harmful effects.

POPs are transferred from the mother to the foetus via the placenta during pregnancy and from mothers milk postpartum (Liu et al. 2011). Foetuses and infants are thereby exposed to these compounds at critical developmental stages. Concentrations of POPs in maternal blood are a good indicator for the exposure to their foetuses (Verner et al. 2009). Although most studies report subtle effects on human metabolisms and the clinical importance of these effects on an adult population are debated, a most relevant concern is the effect of moderately altered thyroid functions during pregnancy and during foetal and infant development. The goal of this project was to evaluate concentrations of PFASs, important predictors for these compounds and how they affect the thyroid system during and after pregnancy. Further, we wanted to evaluate a multipollutant profile including the OCs in maternal serum and the association to maternal and infant thyroid parameters.

1.2 Persistent organic pollutants

1.2.1 Poly- and perfluorinated alkyl substances

PFASs comprise a subset of fluorinated aliphatic substances containing one or more carbon atoms where all hydrogen atoms (perfluoroalkyl substances) or at least one (polyfluoroalkyl substances) have been replaced by fluoride atoms (Buck et al. 2011). PFASs are widely used in consumer products like water and stain proofing agents, paper products and lubricants, due to their chemical and thermal stability, in addition to their hydrophobic and lipophobic nature (Lehmler. 2005). There are numerous of families of PFASs and these are described in detail by Buck et al. (2011). The most studied compounds due to their ubiquitous presence in the environment, wildlife and humans, are perfluoroalkyl acids (PFAAs). The PFAA family includes perfluoroalkyl carboxylic, sulfonic, sulfinic, phosphonic, and phosphinic acids. PFASs have been produced since the 1950s with increasing intensities from 1966 to the 1990s. The production remained relatively constant from 1990-2000 until a phase-out of perfluorooctane sulfonyl fluoride (POSF) based industry was announced in 2000 by the major manufacturer, 3M, subsequently producing replacements that were shorter-chained and not bioaccumulative (US EPA. 2002). Concerns about the persistence of PFASs in the environment, bioaccumulation potential and risk for toxicological effects in animals and humans has led to the classification of perfluorooctane sulfonic acid (PFOS) as a POP

(Stockholm convention. 2009), followed by a ban of the compound in Europe in 2011 (European Parliament. 2006) and regulated use in the US (Paul et al. 2009).

1.2.2 Organochlorines

OCs, also called legacy POPs, comprise numeral substances. PCBs have been produced for commercial uses, such as paint, plastics and electrical transformer fluids, whereas production of pesticides has been designated for control of pests and diseases in agriculture (AMAP. 2004). PCBs were mass produced from the 1930s as chemical mixtures under several trade names (e.g. Aroclor and Clophen). Production and use of these compounds was banned in many countries from the 1970s. Similar for the pesticides, these were used for several decades in the 20th century before being banned in the 1970s (van den Berg. 2009). However, use of DDT is still allowed in some countries to support malaria control (van den Berg et al. 2012).

1.3 Human exposure to POPs

The presence of POPs in the environment originates from industrial use and from abiotic or biotic degradation of precursor compounds (Paul et al. 2009; Prevedouros et al. 2006; EEA and WHO. 1999). When persistent compounds are produced and used, they rapidly end up in the food chain and diet becomes the major route of exposure (Alcock et al. 2000; Duarte-Davidson and Jones. 1994; Fromme et al. 2009; Malisch and Kotz. 2014; Vestergren and Cousins. 2009). In addition, PFASs are passed to humans through air, house dust, drinking water and water based beverages (Haug et al. 2011b; Haug et al. 2011a; Ullah et al. 2011; Eschauzier et al. 2013). POPs are transferred from the mother to the foetus and to infants through breastfeeding and due to the body mass ratio they are exposed to proportionally higher levels of certain chemicals than the mother (Liu et al. 2011). Several studies have confirmed transplacental exposure of both OCs and PFASs to the foetus and postnatal exposure through breast feeding (Apelberg et al. 2007; Inoue et al. 2004; Monroy et al. 2008; Patandin et al. 1999). Fromme et al. (2010) observed an increase of PFOS and perfluorooctanoic acid (PFOA) concentrations in infant serum through the first months of life. Concentrations of these PFASs in human milk were low, but the intake still led to a body burden at the age of six months similar to or higher than that found in adults.

In humans PFASs bind to proteins and mainly reside in blood, liver and kidneys (Butenhoff et al. 2006; Jones et al. 2003), whereas OCs are lipid soluble and accumulate in fatty tissues (Dewailly et al. 1999). Metabolism and elimination of many POPs is slow and opposed to the OCs, there is no known mammalian metabolism of PFOS (Stahl et al. 2011). Excretion of POPs occurs largely through faeces and urine (Harada et al. 2005; Schlummer et al. 1998), and in women they can additionally be excreted through breastmilk and menstruation (Harada et al. 2005; Thomsen et al. 2010; Wong et al. 2014). The half-lives of the compounds in the human body differ according to their chain length. Shorter chained PFASs usually degrade more rapidly than longer chained PFASs (Conder et al. 2008; Lau et al. 2007; Zhang et al. 2013), and lower chlorinated PCBs are more readily metabolized compared to the higher chlorinated congeners (Brown. 1994). Accordingly, estimated human half-lives of PCBs range from 1-27.5 years (Ritter et al. 2009; Shirai and Kissel. 1996), 7 and 6 years for DDT and HCB, respectively (Woodruff et al. 1994), and for PFOS and perfluorooctanoic acid (PFOA), median half-lives were estimated to be 4.6 and 3.4 years, respectively (Olsen et al. 2007).

1.3.1 Temporal trends

In Northern Europe and in the Arctic, OC concentrations in air and biota have declined parallel to the declining emissions of OCs during the 1980s and 1990s (Bignert et al. 1998; Hung et al. 2010) (Figure 1). Accordingly, declining trends have been observed in human blood during the last decades in the Northern Hemisphere (Hagmar et al. 2006; Nøst et al. 2013). For the PFASs, measurements in biota reflect a marked increase of PFASs in the environment from the 1970s, with reported doubling times for PFOS between 5.8-10 years from the 1970s and to the early 2000s (Bossi et al. 2005; Holmstrom et al. 2005). However, after the phase out of POSF based industry, human monitoring studies demonstrate a decrease of several PFASs in serum and plasma from the years 2000-2004 and onwards (Calafat et al. 2007a; Glynn et al. 2012; Haug et al. 2009; Schroter-Kermani et al. 2012; Nøst et al. 2014) (Figure 2). On the contrary, similar decreasing trend is not observed for longer chained PFASs and their potential to degrade to shorter PFAAs also renders them sources of continued exposure to PFOS and PFOA (Buck et al. 2011).

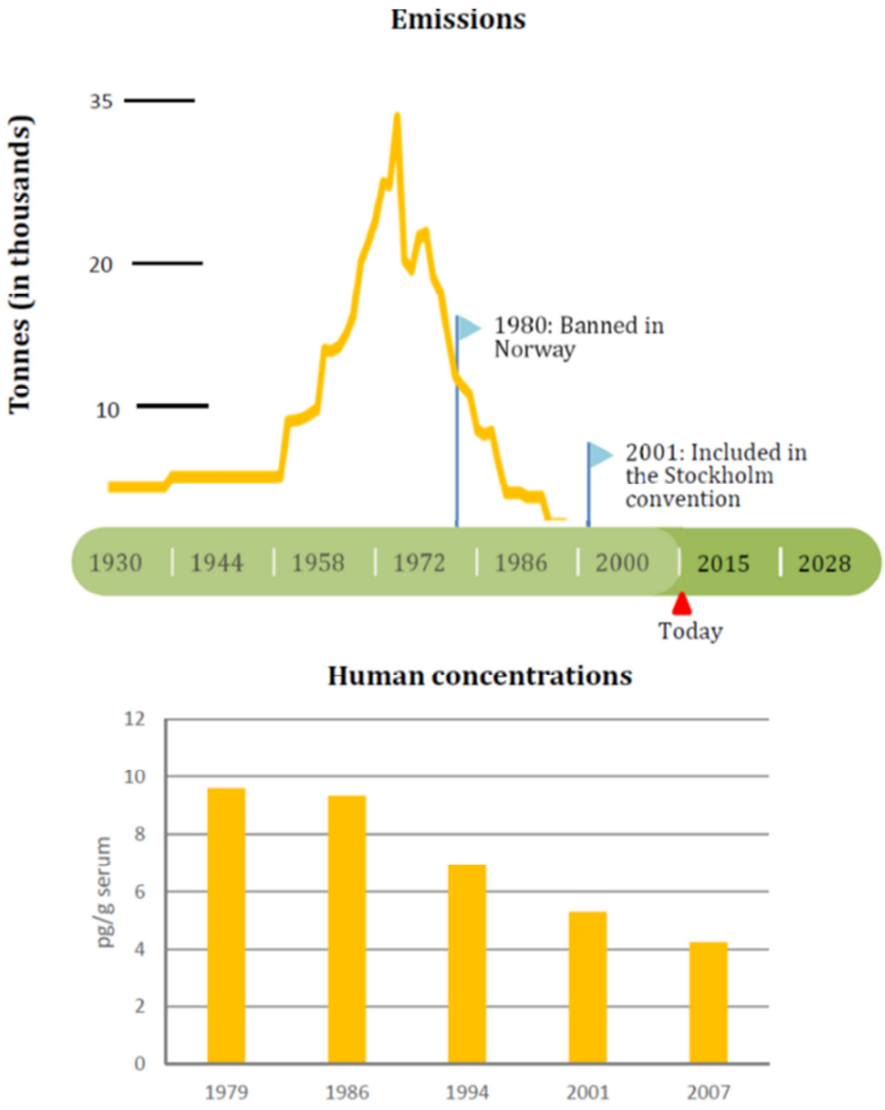

Figure 1: Estimated global emissions of sum PCBs (22 congeners) from 1930 to 2020 (yellow line in graph on top) adapted from Breivik et al. (Breivik et al. 2007) with permission, and events regarding PCBs (Norwegian Ministry of the Environment. 2006). The bottom graph displays serum concentrations of PCB153 in a population from the Tromsø study sampled at five time points by Nøst et al. (2013).

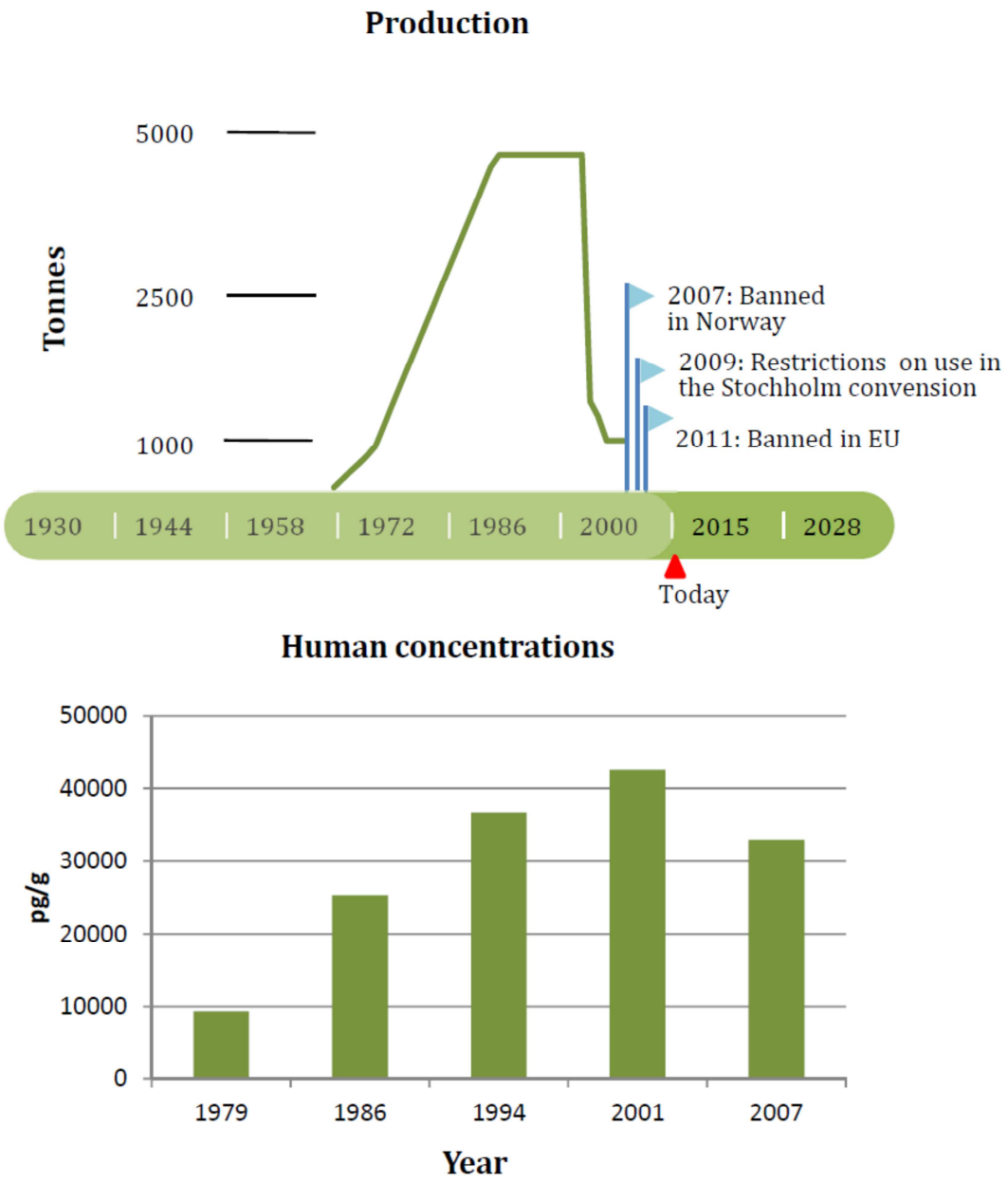

Figure 2. Estimated global production volumes of PFOS-related products from 1940 to 2010 (green line in graph on top) adapted from Paul et al. (Paul et al. 2009) with permission, and events regarding PFOS (Norwegian Ministry of the Environment. 2005; US EPA. 2002). The bottom graph displays serum concentrations of PFOS in a population from the Tromsø study sampled at five time points by Nøst et al. (2014).

1.3.2 Predictors of POP concentrations

Biomonitoring studies have reported dietary and lifestyle predictors of POP concentrations in humans mainly with cross sectional design, where age, birth year and BMI are frequently associated with OCs (Hardell et al. 2010; Rylander et al. 2012; Wolff et al. 2007; Brauner et al. 2012; Fei et al. 2007; Hardell et al. 2010). Similar associations have been inconsistent for PFASs (Calafat et al. 2007a; Calafat et al. 2007b; Haug et al. 2009; Kato et al. 2011; Olsen et al. 2008). Commonly, parity has been demonstrated as an important predictor for concentrations of both OCs and PFASs among women (Brauner et al. 2011; Fei et al. 2007; Hardell et al. 2010), as well as the consumption of marine food in the general population in Norway (Brantsaeter et al. 2013; Furberg et al. 2002; Haug et al. 2010b; Rylander et al. 2009a; Rylander et al. 2009b).

In humans, lifetime exposure to POPs represent the cumulative exposure over the lifetime of the individual resulting from prenatal, postnatal, childhood and adult exposure (Alcock et al. 2000; Moser and McLachlan. 2002; Ritter et al. 2009). Considering historical time-variant emissions of PFASs, a post-ban situation will result in different predictors of PFAS concentrations in the general population compared to an environment of increasing exposures. This is described in detail for the PCBs (Quinn et al. 2011) which indicates different exposure scenarios under constant and time-variant emissions. Potential biodegradation and continued production of PFASs including PFOS and PFOA in some countries like China (Wang et al. 2009), indicates that the interpretation of temporal trends for PFASs can be complex and can differ between contries.

1.3.3 Health concerns of POPs

Extensive research regarding hazardous effects of POPs performed in rodents has demonstrated toxic effects on the liver and immune and endocrine systems (Lau et al. 2007; Winneke. 2011). Concerns for possible effects of POPs on thyroid function also in humans have been raised, especially because of the importance of the TH homeostasis during foetal neurodevelopment. Epidemiological studies have indicated possible adverse effects of prenatal POPs exposure on foetal and infant development, and an influence on maternal and foetal thyroid function has been suggested as an explanation. Studies on the influence of OCs on maternal and foetal TH function have been extensively investigated and are reviewed in

several publications (Hagmar. 2003; Hartoft-Nielsen et al. 2011; Jugan et al. 2010; Goodman et al. 2010), whereas similar studies of PFASs are limited (Chen et al. 2013; de Cock et al. 2014).

Human exposure to POPs is characterised by low levels of a myriad of chemicals, and approaches used by regulatory bodies for safety assessment (e.g. evaluating single chemicals at high doses) are not suitable for current mixtures of POPs (Kortenkamp. 2008). Recent animal studies have suggested that low-dose POP mixtures may be a relevant research focus, as effects in animals are observed at concentrations and mixtures similar to those humans are currently exposed to (Ruzzin et al. 2010). Hence, the long term effects on human health and the potential mixture effects of these low background levels are of concern, especially their potential to perturb maternal hormonal homeostasis and subsequently affect pregnancy outcome and foetal and infant development (Boas et al. 2012; Morreale De et al. 2000; Morreale De et al. 2004; Stahl et al. 2011).

1.4 The thyroid system

The thyroid endocrine system is critical for regulating energy homeostasis, metabolic pathways and the growth and differentiation of many tissues and organs. THs like triiodothyronine (T3) and thyroxine (T4), are involved in numerous physiological processes e.g. regulation of metabolism, bone remodelling, cardiac function and mental status (Morreale De et al. 2004). T3 and T4 are produced in the thyroid gland, and transported to peripheral target tissues aided by thyroid hormone binding proteins (TH-BPs) e.g. thyroid binding globulin (TBG), transthyretin (TTR), and albumin (Figure 3 and Table 1). The thyroid function is regulated by negative feedback mechanisms, in which thyroid stimulating hormone (TSH) stimulates the thyroid gland to synthesize T3 and T4. TSH is in turn regulated by thyrotropin releasing hormone (TRH) from the hypothalamus, as well as by the levels of circulating T3 and T4 (Feldt-Rasmussen et al. 1980). Hence, the thyroid function is regulated to secure a constant equilibrium in the thyroid homeostasis. In healthy individuals, serum levels of thyroid parameters are maintained relatively stable with individuals having his or her specific set point (Feldt-Rasmussen et al. 1980). Accordingly, individual variations in levels of TSH, THs and TH-BPs are large whereas variations within individuals are small, hence normal reference ranges are relative broad and differ according to analytical method and populations, the latter due to factors like lifestyle, age, dietary habits and iodine status.

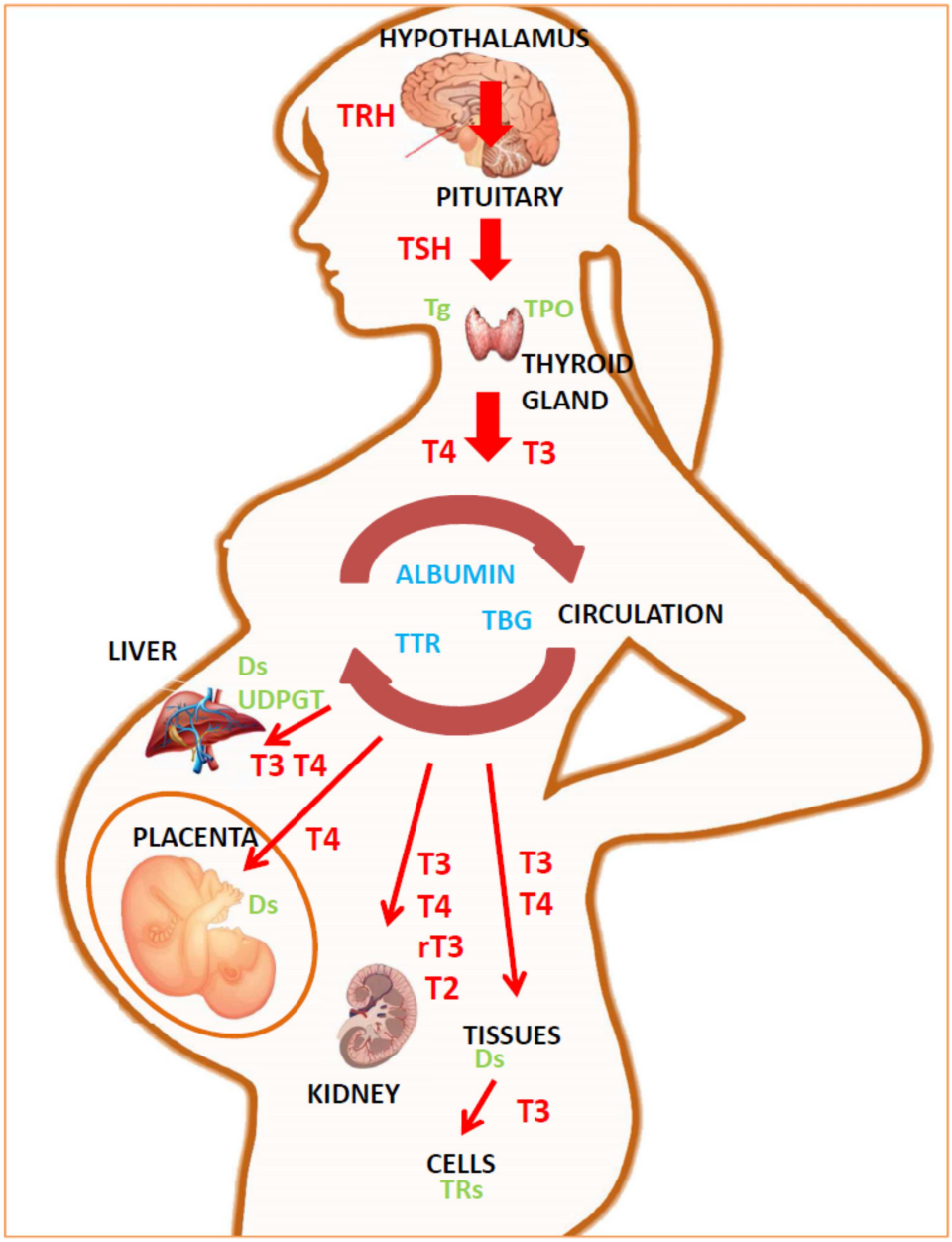

Figure 3. The thyroid system

TRH stimulates the production of TSH resulting in the formation of the THs, T3 and T4. T3 and T4 are formed by iodotyrosine coupling and iodination of thyrosine residues by thyroglobulin (Tg), a process catalysed by thyroid peroxidase (TPO). In the circulation, THs bind to and are transported by TBG, albumin, and TTR. T4 is deodinated to T3 in the liver and tissues by deiodinases (Ds) and T3 are further transported into cells by membrane bound transporters where it binds to nuclear thyroid hormone receptors (TRs) (Preau et al. 2014). In the liver THs are metabolized by UDP-glucuronyl transferase (UDPGT) and the metabolites (rT3 and T2) are excreted in the urine. In the pregnant woman, supply of T3 to the foetus is maintained by the placenta which metabolizes maternal T4 (Colicchia et al. 2014).

Table 1: Thyroid parameters and functions

Parameter	Abbreviation	Function
Thyrotropin releasing hormone	**TRH**	Regulate pituitary release of TSH (Jackson. 1982).
Thyroglobulin	**Tg**	Acts as a substrate in the synthesis of T3 and T4. Is a storage protein for the inactive forms of thyroid hormone (T3, T4) and iodine (Van Herle et al. 1979).
Thyroid stimulating hormone	**TSH**	Stimulates the synthesis of T4 and T3 (Glinoer and Spencer. 2010).
Total and free thyroxine	**T4 and FT4**	Controls the metabolism of cells and tissues. FT4 is the metabolic active form and constitutes 0.3 % of the total T4 in blood (Feldt-Rasmussen and Feldt-Rasmussen. 2007).
Total and free triiodothyronine	**T3 and FT3**	Controls the metabolism of cells and tissues. FT3 is the metabolic active form and constitutes 0.03 % of the total T3 in blood. FT3 is four times more potent than FT4 (Feldt-Rasmussen and Feldt-Rasmussen. 2007).
Thyroxin binding globulin	**TBG**	Transports 70% of T3 and T4 in the blood and acts as a buffer for the metabolic inactive form. (Feldt-Rasmussen and Feldt-Rasmussen. 2007).
Transthyretin	**TTR**	Transports 10-15% of T4 in the blood and acts as a buffer for the metabolic inactive form. (Feldt-Rasmussen and Feldt-Rasmussen. 2007).
Albumin		Transports 15-20% of T3 and T4 in the blood and acts as a buffer for the metabolic inactive form (Feldt-Rasmussen and Feldt-Rasmussen. 2007).
Thyroxine binding capacity (T3 uptake)		A measure of the TBG that is unsaturated with thyroid hormone. Degree of unsaturated TBG increases with decreased circulating levels of thyroid hormones (Blackburn. 2013).
Anti-thyroid peroxidase antibodies	**Anti-TPO**	Autoantibodies targeted against one or more components of the thyroid system. Predictor for risk of thyroid disease (Fitzpatrick and Russell. 2010).

1.4.1 The thyroid system during pregnancy

Changes in thyroid function during pregnancy are important as it parallels the altered carbohydrate, protein and lipid metabolism and increase in basal metabolic rate. Accordingly, there are marked changes in the maternal hypothalamic pituitary (HTP) thyroid axis to increase the availability of THs. During the first two trimesters of pregnancy, these changes lead to a two- to three-fold increase in TBG production and a subsequent decrease in levels of free thyroxin (FT4) and free triiodothyronine (FT3) followed by an increased production of T3 and T4. The large increase in TBG compared to T4, results in a decreased T4/TBG ratio, creating a state of relative hypothyroxinemia, but thyroid function per se does not change during pregnancy. Changes in individual TH levels throughout pregnancy varies by gestational age, number of foetuses and study population, but generally, the woman achieves a new steady state in HTP function at the end of 2nd trimester which is maintained until delivery. After delivery, the alterations in thyroid processes are gradually reversed over 4-6 weeks (Blackburn. 2013).

1.4.2 Maternal TH homeostasis and foetal and infant development

For the embryo and foetus, the THs are crucial in all developmental stages. THs play an important role in the development of the central nervous system and brain maturation e.g. differentiation and migration of neural and glial cells, and myelinisation (Bernal. 2007). The foetal thyroid is fully functional from approximately 18 weeks gestation, and thus prior to this, maternal T4 is the sole source of TH to the developing foetal brain (Obregon et al. 2007). Still, the foetus relies on maternal THs throughout the gestational period, and this supply is also important for supporting TH storages in the newborn. In the infants, HTP thyroid function gradually changes during infancy and childhood, hence adequate TH production is crucial for continued central nervous system (CNS) maturation and bone growth. The critical period of TH influence on CNS continues 6 to 8 months after birth (Blackburn. 2013).

1.4.3 Thyroid disease

Thyroid function abnormalities during pregnancy affect up to 10% of all women, including overt (symptomatic) and subclinical (mild and asymptomatic) hypothyroidism with the

worldwide prevalence of 0.5% and 3%, respectively (Hartoft-Nielsen et al. 2011). Hypothyroidism is characterised by a depleted supply of THs, where the thyroid gland is unable to produce adequate amounts of thyroid hormone to meet the requirements of peripheral tissues. A drop in serum concentrations of THs causes an increased secretion of TSH to stimulate TH production. Subclinical hypothyroidism is defined by an elevated TSH concentration in the presence of normal serum FT4 and FT3 concentrations and may progress to overt hypothyroidism (Biondi and Cooper. 2008; Cooper and Biondi. 2012). Today there is no population screening program for hypothyroidism in pregnant women, but women with known familial thyroid disease are tested. No therapeutic actions are taken when subclinical hypothyroidism is indicated in pregnant women (Fitzpatrick and Russell. 2010; Lazarus. 2011). The clinical importance of moderately low TH concentrations is unclear, but subtle discrepancies in maternal TH during early pregnancy are of particular concern, where subclinical changes in maternal THs may affect embryonic and foetal development. Accordingly, decreases in childhood intellectual performance can occur if a pregnant woman's hypothyroidism is subclinical and marginally low T4 levels in the pregnant woman could cause reduced cognitive functions of the offspring (Berbel et al. 2009; Pop et al. 2003; Haddow et al. 1999). In Norway and several other countries, all newborns are screened for thyroid disease with TSH levels above 8 mlU/L as a limit for further investigation (Norwegian Newborn Screening. 2015), but little is known about the clinical relevance of subclinical hypothyroidism in infants (TSH >5.0 mlU/L) (Kaplowitz. 2010). However, discrepancies in maternal thyroid homeostasis during pregnancy can increase the difficulties encountered by the newborn in meeting their postnatal hormone requirements, including those of the developing brain (Morreale De et al. 2000).

1.4.4 Evaluation of thyroid parameters

TSH levels can reflect mild thyroid functional impairment even when T4 and T3 concentrations are within normal ranges. Hence, disruption of the thyroid function is often investigated in regards to hypothyroidism with the reporting of TSH concentrations. Still, hypothyroxinemia (low T4 concentrations) can occur with normal TSH and T3 concentrations and in the absence of assessment of the overall thyroid function; the clinical importance of individual THs is unclear (Braverman and Utiger. 1986). Measurement of anti-thyroid peroxidase antibodies (anti-TPO) can be a valuable adjunct in patients with subclinical hypothyroidism because it predicts a higher risk of developing overt hypothyroidism. Further,

pregnancy-induced changes in thyroid physiology affect laboratory interpretation and presently no universally accepted reference ranges for thyroid parameters exist (Fitzpatrick and Russell. 2010). For example, increased concentrations of TH-BPs give rise to misinterpretation of most of the measurements of serum levels of TH by available techniques. Therefore, interpreting thyroid function in pregnant women should include measurements of TSH, both bound and free THs, as well as TH-BPs or available binding sites on TH-BPs (thyroxine binding capacity)(Fitzpatrick and Russell. 2010).

1.4.5 Thyroid disruption by POPs

Like THs, POPs are also halogenated molecules, and their chemical structure resembles those of the THs. Hence, POPs could influence the thyroid function through all the segments of the thyroid system by; i) stimulating or inhibiting enzyme functions which mediates iodine uptake of the thyroid gland in the synthesis of THs; ii) disturbing TSH signalling through TSH receptors in the thyroid gland; iii) displacing THs from their binding proteins subsequently being transported themselves to thyroid dependent tissues; iii) transmitting agonistic or antagonistic signals through TRs on target cells; and iv) affecting metabolism of TH in the liver causing increased clearance of THs (Boas et al. 2012; Takser et al. 2005). Different POPs can have different potencies in regards to interference with thyroid functions; hence, a challenge lies in the assessment of combination effects from large number of chemicals with endocrine disrupting abilities with varying impact. This means that elucidation of any causality in impairment of thyroid function by POPs is complicated by a complex correlation of exposures. Most studies include selected POPs when effects of individual compounds are studied. Associations between OCs, particularly PCBs, and health outcomes in humans have been extensively studied and reviewed (Hagmar. 2003; Jugan et al. 2010; Langer. 2008), whereas similar studies on PFASs and OCs and PFASs together have been sparse (Boas et al. 2009; Boas et al. 2012).

1.4.6 Thyroid complexity

Interference of POPs with thyroid function may result in small changes in serum concentrations of THs and may be difficult to detect in small clinical studies, additionally, a single measurement may not capture transient change in TH levels. The thyroid system may also be able to compensate for adverse effects through the negative feedback mechanisms,

where discrete alterations in THs may not be detected by evaluating levels of individual thyroid parameters. The negative health effects during pregnancy on thyroid function that have been associated with POP exposures, resemble those related to iodine deficiency (eg. decreased maternal FT4 and increased maternal TSH, increased risk of prematurity, spontaneous abortion, and neurodevelopmental impairment) (Morreale De et al. 2000; Morreale De et al. 2004; Stahl et al. 2011). In addition, iodine status affects the variation in TH concentrations throughout the pregnancy, where the degree of iodine sufficiency or deficiency affects individual TH set points and changes in concentrations throughout the pregnancy (Blackburn. 2013; Morreale De et al. 2004). Hence, iodine status may modify the degree of thyroid disruption by chemicals. Therefore, it is important to include the major thyroid parameters in studies on the overall influence by POPs on thyroid function, in addition to considering lifestyle variables, age and iodine status. Unfortunately, this is seldom performed in studies.

2. Aims of the thesis

The main objective of this doctoral thesis was to assess the effect of background exposures of POPs on thyroid function in mother-child pairs in Norway. Concentrations and predictors of PFASs and a selection of OCs are investigated in pregnant women, and a multipollutant assessment of POPs and their associations to concentrations of maternal and infant THs are evaluated.

Specific objectives:

- Explore concentrations and predictors of PFASs in a maternal population in a period of decreasing environmental concentrations.
- Assess associations between PFAS concentrations in early pregnancy and thyroid parameters in early pregnancy, 3 days and 6 weeks postpartum.
- Evaluate the overall relationship between POPs (PFASs and OCs), maternal and infant thyroid status and important covariates, applying a multipollutant approach.

3. Materials and methods

3.1 The Northern Norway Mother-and-Child Contaminant Cohort Study

The Northern Norway Mother-and-Child Contaminant Cohort Study (MISA) was initiated in 2007 to address exposure of environmental contaminants experienced by women during pregnancy and postpartum and also by their newborn (Veyhe et al. 2012). The recruitment period was from May 2007 to June 2009 and included 2600 invited women from Northern Norway (Figure 4), where 20 % was initially included in the study and 15 % completed. The present project includes the 391 women who completed the study. The participants answered a comprehensive questionnaire on personal information and food frequency consumption (FFQ) (Appendix), and donated blood at three time points: during pregnancy (mean gestational week 18, range 10-32), three days and six weeks postpartum. Blood from their newborn were collected three days after birth (Figure 6).

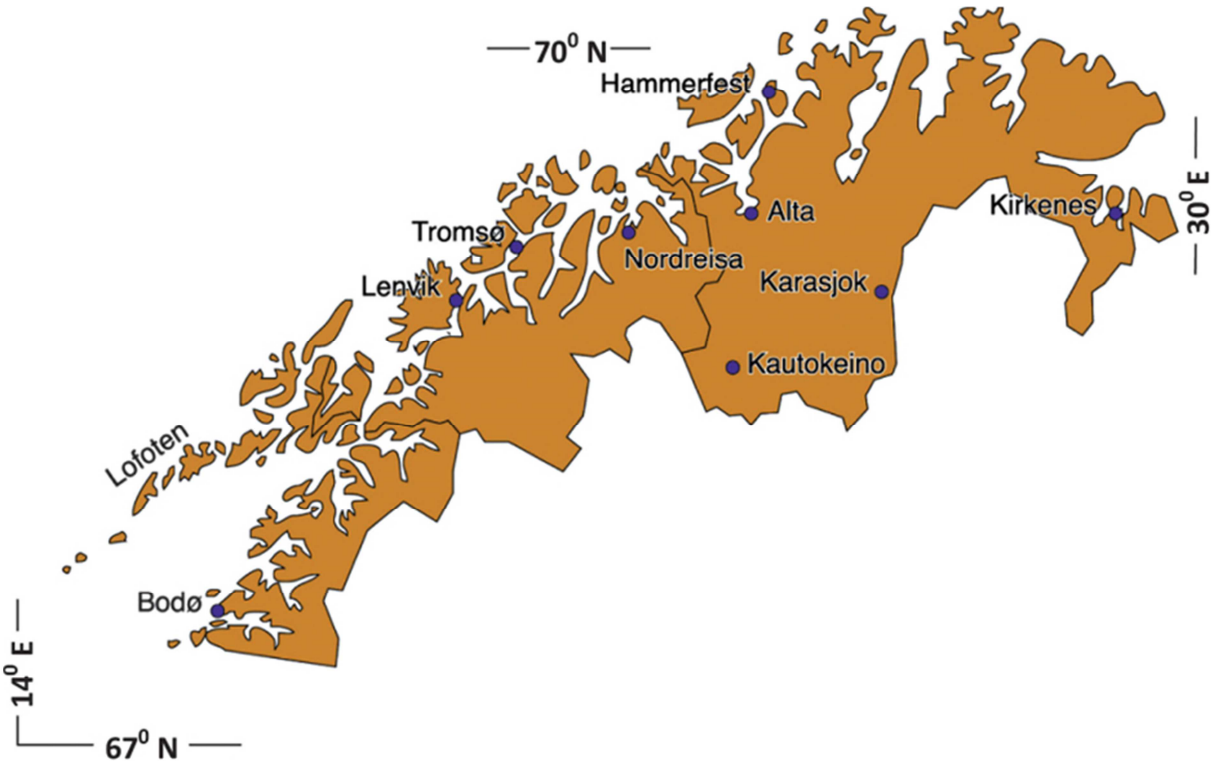

Figure 4. Map of the MISA cohort study area (reproduced from Veyhe et al., 2012 with permission).

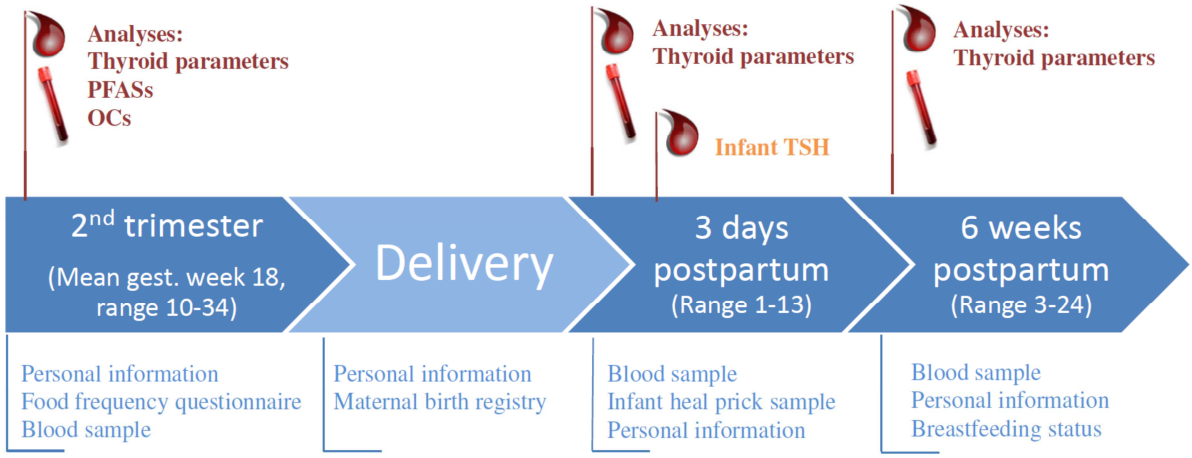

Figure 5. Flow chart for the events in the MISA cohort study

3.2 Demographic and lifestyle information

At enrolment, all the participants completed a detailed questionnaire about personal characteristics, obstetric history, diet and lifestyle (Appendix). In addition, information about current diet, smoking and alcohol habits, medications and dietary supplements, were obtained at all blood sampling time points. The participants also completed a separate questionnaire about breastfeeding.

Food consumption was self-reported and calculations were based on standardized portions and national food composition tables. The FFQ was the same as used for the Norwegian Women and Cancer Study (NOWAC) supplemented with 12 questions about fish and shellfish (Hansen et al. 2010) and has previously been validated (Hjartaker et al. 2007) and submitted to a retest (Parr et al. 2006).

3.3 Sampling procedures

Contaminant analyses were targeted in serum from the second trimester, while thyroid hormones were analysed in serum from all three sampling points. Infant TSH concentrations were acquired from the National newborn screening program.

The women in the MISA study were requested to fast or eat a light, non-fatty breakfast no later than 2 hours before the blood sampling (Hansen et al. 2010). Venous blood was collected in BD vacutainers (SST II Plus Advance 10/8.5 ml). Vacutainers were transported to the Univeristy of Tromsø where serum was transferred to appropriate storage vials according to analyses; i) glass vials pre-rinsed with n-hexane and acetone for the contaminant analyses, and ii) cryotubes for analyses of biomarkers. The serum was stored at minus 20 ºC until analysis. Blood spots from infant heel prick was collected on filter paper three days after birth and shipped to the University Hospital of Oslo as part of the newborn screening program.

3.4 Analytical methods

3.4.1 Analyses of PFASs

Analyses of PFASs were conducted for paper I, II and III by the candidate at NILU-Norwegian Institute of Air Research. Detailed analytical methodology and a list of compounds are presented in Paper I. The extraction method was modified from Powley et al. (2005). Briefly, PFASs were extracted from serum samples with internal standards using sonication-facilitated liquid–liquid extraction, activated ENVI-carb clean-up. Recovery standard were added to the extracts which were analysed by ultrahigh pressure liquid chromatography triple–quadrupole mass-spectrometry (UHPLC-MS/MS). Quantification was conducted with the LC Quan software.

3.4.2 Analyses of OCs

Analyses of OCs were applied in Paper III, and the analytical details as well as concentrations are presented therein and previously published by Veyhe at al. (Veyhe et al. 2012). Briefly,

internal standards, formic acid and deionised water were added to 2 ml serum sample and left in the fridge over night before being extracted through an HLB solid phase (SPE) column using dichloromethane. Further clean-up involved elution of compounds from Florisil columns with n-hexane/dichloromethane. OCs were identified and quantified in the extracts with a gas chromatograph/mass spectrometer operated in electron impact mode. Assessment of isotopic mass ratios, blank samples and standard reference materials ensured the quality of the results. Finally, lipids were detemined enzymatically and the summed amount of lipids was calculated as described by Akins et al. (1989).

3.4.3 Analyses of thyroid parameters

Analyses of THs, TH-BPs, anti-TPO and thyroxine binding capacity were conducted for Paper II and III and were performed by laboratory staff at the University Hospital of Northern Norway, Department of Laboratory Medicine. A detailed methodological description and list of analytes are described in Paper II. The laboratory is certified according to ISO 151810 (Norwegian accreditation. 2014) and all reagents, calibrators and equipment were CE-approved. Quality controls are run at three different concentrations every day and additionally the laboratory participates in the LabQuality external quality assessment program (Labquality Finland. 2014).

Infant TSH concentrations were determined by the National Newborn Screening program and applied in Paper III, and a detailed methodological description is presented therein.

3.5 Statistical analyses

The statistical approaches in all three papers were performed in SPSS statistic software (IBM SPSS Inc. Chicago, IL, USA), in addition to the freely available, open source software R (R Development Core Team, available at **http://www.cran.r-project.org**) in paper III. The general statistical approaches are described below, but details on the different methods are described in each respective paper.

3.5.1. Analyses of multidimensional data

With the large number of POPs and biomarkers measured in human blood as well as the reporting of many potential predictors and covariates, a collection of multivariate analyses were performed. We selected statistical methods which allow highly correlated variables as exploratory models for; i) evaluating the impact of the demographic and dietary variables simultaneously on serum concentrations of PFASs for Paper I and; ii) to evaluate the overall relationship between contaminant and covariate variables with levels of THs in papers II and III. PCA and PLS were used for data reduction and for selecting variables of specific interest in all the papers. Additionally, hierarchical clustering was applied in Paper III to reduce the dimensional structure of POPs and to create summed contaminant groups.

3.5.2 Effect sizes

To investigate the impact of demographic and dietary variables with large influence on POP concentrations (identified from the PLS regression) while mutual adjusting for important covariates, analysis of covariance (ANCOVA) was applied in Paper I. In paper II we applied mixed effects linear models with three repeated measurements of thyroid parameters. Women were assigned to PFASs quartiles which were included as fixed factors along with THs, covariates (identified from PLS regression) and a quadratic time variable in five separate TH models. Finally, in Paper III we applied multiple linear regression models with either individual POPs or summed POP groups as dependent variables including important covariates (linear regression method: Enter). Mutual adjustments were performed by including individual or summed groups of POPs as covariates.

3.6 Ethical considerations

According to ethical guidelines and human research regulations the MISA study has been approved by the Regional Ethics committee (REK) and approvals for storing personal information and biological materials in a biobank, were obtained before starting the study (Veyhe et al. 2012). Participation was voluntary, and the participants signed an informed consent before entering the study. Information on the study participants was obtained from the cohort data bases at the University of Tromsø and internal security and confidentiality

requirements were fulfilled. The identification of all samples and questionnaire information was depersonalized.

Reports and storage of results will be according to requirements of the cohort procedures. Results have been and are intended to be published in peer-reviewed journals. The co-authors of the three papers reported no conflicts of interest.

4. Results – Summary of papers

Paper I

Concentrations and predictors of PFASs in pregnant women from the MISA study

This study investigated concentrations and demographic and dietary predictors of 26 PFASs in pregnant women who donated a blood sample in their second trimester during a recruitment period of 867 days (June 2007 to December 2009). Predictors were evaluated with PLS regression and effect sizes were reported by ANCOVA.

Seven PFASs was detected in over 80% of serum samples where PFOS was the dominating compound followed by PFOA, PFNA, PFHxS, PFUnDA, PFDA and PFHpS. Results demonstrated parity, sampling date and birth year to be the most important predictors of maternal PFAS concentrations in years following reduced production and use of PFASs. Parity was the strongest significant predictor for all the investigated PFASs, and nulliparous women had higher concentrations compared to multiparous women (10 ng/mL versus 4.5 ng/mL (median PFOS), respectively). Further, serum concentrations of PFOS and PFOA of women recruited day 1–100 were 25% and 26% higher, respectively, compared to those women recruited in the last 167 days of the study (day 601–867). Dietary predictors varied in importance according to compound, and were stronger predictors for the longest chained PFASs, explaining up to 17% of the variation in concentrations.

Paper II

Associations between PFAS and thyroid parameters during pregnancy and the postpartum period in women from the MISA study

This study investigated the relationship between serum concentrations of seven PFASs in the women from paper I, and TSH, THs and TH-BPs in 2nd trimester, three days and 6 weeks postpartum. Associations were assessed by graphical and mixed model analyses.

The specific study population reference range (2.5–97.5th percentile) for ten thyroid parameters in women during and after pregnancy are presented in this paper. The specific

reference ranges at each sampling point were within the normal non-pregnant population reference ranges all the respective parameters. The results demonstrated consistently higher mean TSH concentrations (24%) in women within the highest PFOS quartile compared to women in the lowest quartile throughout the three sampling points. Similarly, women in the highest PFDA and PFUnDA quartiles had lower T3 and FT3 concentrations, respectively. Thyroxine binding capacity was significantly associated with all the THs and the individual binding proteins, and was selected as covariate to adjust for elevated levels of TH-BPs as a proxy for the pregnancy related alterations in blood THs when considering the effects of POPs in statistical models.

Paper III

Associations between POPs and maternal and infant TSH and TH in mother-child pairs from the MISA study

This study investigated the association of a broad range of POPs (seven PFASs and twelve OCs) with maternal TSH and THs and infant TSH. A multipollutant approach was applied using multivariate analyses; hierarchical clustering, PCA and PLS regression, and effect sizes were reported with multiple linear regression.

The concentrations of PFASs were tenfold higher compared to the OCs on a wet weight basis. Hierarchical clustering demonstrated two distinct clusters, dividing the PFASs and OCs into two groups, where correlations within the OCs were stronger as compared to the correlations within the PFASs. Further, the results indicated that PFASs and OCs may differentially alter the circulating levels of THs in pregnant women, which in turn may influence infant TSH concentrations. omen within the extreme POP quartile had significantly higher (8%) TSH concentrations compared to women within the lowest quartile, whereas women within the extreme summed OC quartile had significantly lower (2-4%) T3, T4 and FT4 concentrations compared to women within the lowest quartile. Further, maternal TSH and FT4 levels were positively and inversely associated to infant TSH, respectively. However, differences in TSH and TH concentrations were small between quartiles, and varied within what is considered normal reference ranges for healthy non-pregnant and infant populations, thus the clinical relevance of the observations is not clear.

5. Discussion

5.1 Major findings

This work report the concentrations of 10 thyroid parameters, 26 PFASs, and 12 OCs along with detailed information on 391 pregnant women (e.g. a total of 152 demographic and lifestyle variables were evaluated). Throughout the papers we have included the most important covariates in statistical models, allowing for proper adjustment and interpretation of maternal PFASs concentrations and influence of summed groups of POPs on maternal and infant thyroid function:

- Parity, sampling date and birth year were the most important predictors for maternal PFAS concentrations in years with decreasing environmental concentrations.
- Our data indicate that background concentrations of POPs influenced maternal concentrations of TSH and THs consistently in early pregnancy, 3 days and 6 weeks postpartum.
- Maternal concentrations of TSH and THs were influenced by levels of TH-BPs and thyroxine binding capacity throughout the sampling period.
- Individual POPs were correlated, complicating the statistical evaluation of the relative importance of individual compounds.
- Clinical relevance was not established due to that maternal and infant TSH and TH concentrations varied within normal reference ranges.

5.2 Concentrations of POPs

5.2.1 Regional and international comparisons

Overall, the concentrations of POPs in the MISA population can be considered low and reflect a background exposed population. Median concentrations in the MISA population are lower compared to populations from earlier studies in approximate regions. Table 2 present PFAS concentrations reported in women from Northern Europe in the period 1992-2012 (Barrett et al. 2015; Glynn et al. 2012; Jensen et al. 2015; Liew et al. 2015; Vestergaard et al. 2012; Wang et al. 2013) and demonstrate a general decrease in population medians with study year, which complies with temporal trends reported for the same time period (Glynn et al. 2012; Haug et al. 2009; Nøst et al. 2014). In regards to OC concentrations, these are comparable to those reported in other pregnant populations in Nordic countries when considering fish consumption and the year of sampling (Glynn et al. 2007; Halldorsson et al. 2008b). Based on knowledge of trends for emissions and environmental concentrations, the exposures to humans are indicated to continue to decrease or level off in the coming years. However, there are large differences between continents where continued production of PFASs including PFOS and PFOA in some countries contribute to increasing exposures in some populations (Wang et al. 2009). This was apparent in a study of a Swedish population from Uppsala, where median PFHxS concentrations increased from 2007-2009 and was related to that these women had recently been exposed to increasing levels of PFHxS-related compounds (Table 2) (Glynn et al. 2012).

Table 2. Median concentrations of PFASs (ng/mL) in pregnant women and women of childbearing age in Northern Europe.

Study year	N	Population	Details	PFOS	PFHxS	PFHpS	PFOA	PFNA	PFDA	PFUnDA	Reference
2010-2012	336	Pregnant women	Odense child cohort, Denmark.	7.85	0.28	-	1.59	0.68	0.26	-	Jensen et al. 2015
2007-2009	391	Pregnant women	The MISA study, Northern Norway.	8.03	0.44	0.10	1.53	0.56	0.23	0.26	Current study
2009*	30	Nursing women	Pooled serum samples, 3 weeks after delivery, Sweden.	8.24	4.84	-	1.91	0.65	0.32	0.27	Glynn et al. 2012
2008*	30	Nursing women	Pooled serum samples, 3 weeks after delivery, Sweden.	10.25	4.36	-	2.09	0.72	0.28	0.24	
2007*	30	Nursing women	Pooled serum samples, 3 weeks after delivery, Sweden.	14.06	4.12	-	2.06	0.60	0.26	0.22	
2003-2004	903	Pregnant women	Pregnant women, MoBa cohort, Norway.	12.81	0.60	0.13	2.15	0.39	0.09	0.22	Wang et al. 2013
2000-2002	88	Women of childbearing age	Parous woman, Northern Norway.	12.65	0.71	0.10	2.03	0.55	0.22	0.39	Barrett et al. 2015
	90	Women of childbearing age	Nulliparous women, Northern Norway.	14.78	1.05	0.13	3.36	0.61	0.23	0.36	
1996-2002	545	Pregnant women	The Danish National Birth Cohort, Denmark	26.80	0.84	0.30	4.06	0.42	0.15	-	Liew et al. 2015
1992-1995	222	Women of childbearing age	Woman of childbearing age, Denmark.	36.02	1.17	-	5.60	0.48	0.11	-	Vestergaard et al. 2012

*Concentrations reported as ng/g serum

5.2.2 POP concentrations and patterns

Concentrations of PFASs were tenfold higher than the OCs as would be expected regarding the different history of production and use for the two contaminant groups (Bignert et al. 1998; Hung et al. 2010; Paul et al. 2009). Statistical analyses (e.g. hierarchical clustering and correlation analyses) in Paper III demonstrated two distinct clusters dividing the PFASs and OCs into two groups (Figure 6) and reflect difference in concentrations and a stronger correlation between components within each group. Further, correlations within the OCs were stronger as compared to the correlations within the PFASs and might be explained by similarities within the two groups with respect to physicochemical properties of the compound groups and their temporal trends (Nøst et al. 2013; Nøst et al. 2014). In addition, this could also reflect production, where the OCs, particularly the PCBs, was produced in mixtures containing several congeners, whereas individual PFASs have been produced from different precursor compounds. Accordingly, within the PFAS group, two clusters separated the longest chained PFASs ($C_{9\text{-}11}$) from the shortest chained PFASs ($C_{6\text{-}8}$). This tendency was also demonstrated throughout the papers; In statistical analyses the longest chained PFASs covaried with regard to predictors in Paper I, associations to different thyroid parameters in Paper II and clustering in Paper III, whereas the shortest chained PFASs covaried in regards to different predictors, thyroid parameters and clusters compared to the longest chained PFASs. These observations are also in line with environmental pathways of the different PFASs where longer half-lives and different temporal trends are observed for the longest chained PFASs (Glynn et al. 2012; Kato et al. 2011).

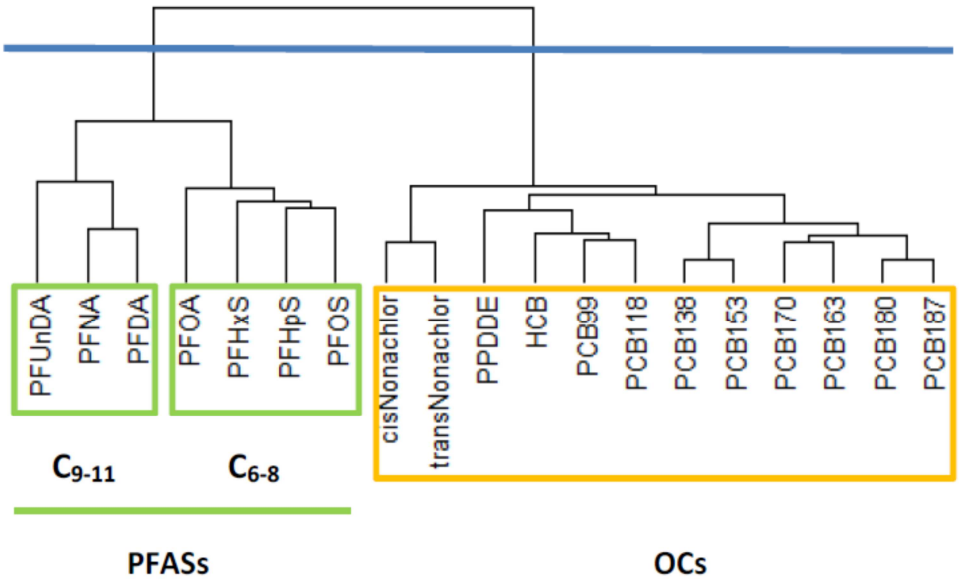

Figure 6. Hierarchical clustering of 19 POPs based on concentrations in 370 samples from early pregnancy. The figure depicts the hierarchical structure obtained on the distance between concentrations (method: complete linkage). The vertical blue line represents the manually selected cut-off for the number of clusters.

5.3 Predictors of contaminant concentrations

5.3.1 Date and year of sampling

In Paper I we demonstrated that sampling date was inversely associated with concentrations of PFHxS, PFHpS, PFOS and PFOA due to continuously decreasing environmental concentrations of these PFASs during the recruitment period. Sampling date was not important for the OC concentrations as the decrease in environmental concentrations of OCs has slowed down considerably (Nøst et al. 2013). The relative importance of predictors is likely modified according to changes in environmental concentrations of the different POPs, and could differ in pre- and post-ban periods. Accordingly, sampling year and sampling date, especially within studies with prolonged recruitment periods, are important to consider in the assessment of POP concentrations and their predictors, and when comparing results from different studies.

5.3.2 Parity, birth year and BMI

Parity was the strongest significant predictor for concentrations of all the PFASs, while birth year and BMI were of varying importance according to compound. Similar, parity, birth year, and BMI were important predictors for the OCs (Veyhe et al. 2015). These observations are in accordance with predictors identified in other studies on POP concentrations in women from similar study years (Brantsaeter et al. 2013; Polder et al. 2009). PFNA, PFDA, PFUnDA and the OCs were positively associated to birth year and may reflect more intense exposure to these compounds in older women or possible age dependent elimination patterns (Armitage et al. 2009; Zhang et al. 2013). Increasing OC concentrations with increasing age likely reflects birth year dependent past exposure as OC exposures have varied across the birth years of the MISA women (Alcock et al. 2000; Moser and McLachlan. 2002; Nøst et al. 2013; Ritter et al. 2009).

5.3.3 Dietary predictors

Several dietary predictors of PFAS concentrations were identified and varied in importance according to compound. The largest increase in explained variance by including diet in statistical models was observed for concentrations of PFNA, PFDA and PFUnDA. This observation may be in accordance with increasing biomagnification with chain length with the current relative time trends and correlations for PFASs in biota (Vestergren and Cousins. 2009). Higher concentrations of PFASs were observed in high consumers of marine food, game and white meat and comply with observations reported in other Nordic studies (Halldorsson et al. 2008a; Haug et al. 2010b; Rylander et al. 2009a; Rylander et al. 2009b). Further, Veyhe et al. (2015) identified dietary intakes of freshwater fish, fat fish, fish liver and reindeer as significant predictors of a selection of OCs in the present study population.

The dietary predictors identified in this association study are food items with high concentrations and/or food items with large differences in intake between individuals. Accordingly, the associations observed in the present study are in line with studies on PFAS concentrations in different food groups in general which demonstrate that high consumers of marine food and meat have the highest PFAS concentrations as well as large variation in intake (Cornelis et al. 2012; Domingo et al. 2012; Haug et al. 2010a; Noorlander et al. 2011; Tittlemier et al. 2007; Trudel et al. 2008; Vestergren et al. 2012; Hlouskova et al. 2013;

Herzke et al. 2013). However, we did not observe associations between PFAS concentrations and food categories that are general high consumption foods like vegetables, cereal products and dairy products. Still, these food groups have been reported to contribute considerably to the total daily intake of PFASs (Haug et al. 2010a; Noorlander et al. 2011), and small differences in intake in the population and/or their relative low concentrations of PFASs could explain that they are not apparent as statistical predictors (Vestergren et al. 2012).

5.4 Concentrations of thyroid parameters and their predictors

5.4.1 Concentrations during pregnancy and in postpartum periods

Specific reference ranges for thyroid parameters in the present study population, during and after pregnancy, were within what is considered normal reference ranges in healthy non-pregnant individuals (Norwegian Medical Association. 2015). Further, the difference in concentrations of the thyroid parameters between the sampling points were consistent with what has been previously described across the pregnancy (Blackburn. 2013). Briefly, i) median concentrations of maternal TSH, T3, T4, TBG and thyroxine binding capacity were slightly increased three days after delivery compared to the second trimester, whereas concentrations six weeks postpartum had decreased close to pre-pregnancy levels (normal non-pregnant levels), six weeks postpartum; ii) median concentrations of FT3 and FT4 remained relative unchanged throughout the three sampling points, and complies with the expected transient increase in individual levels of FT3 and FT4 in the first trimester with levels being relative stable until delivery (Lazarus. 2011); iii) median TTR concentrations were unchanged; and finally, iv) albumin decreased after delivery compared to the 2nd trimester but increased to pre-pregnancy levels six weeks postpartum. TPO antibodies have been indicated to be markers for increased risk of infertility, miscarriage and preterm delivery, but are not necessarily reflected in TSH and TH levels (Stagnaro-Green and Glinoer. 2004). Twenty-two women were positive for anti-TPO in the 2nd trimester and these women had TH concentrations within 95% confidence interval for the population, and including or excluding them did not alter the study population reference ranges for any of the thyroid parameters. For the infants, the TSH concentrations varied according to what is considered normal in healthy infant populations (Kapelari et al. 2008).

5.4.2 Predictors of maternal TSH and TH concentrations

Important predictors for maternal TSH and TH concentrations (Paper II and III) were parity, age, BMI and variables related to physiological changes during pregnancy and postpartum periods (e.g. gestational week, total lipids, TH-BPs and thyroxin binding capacity). These observations demonstrate the dependency of concentrations of TSH and THs to the pregnancy-related increase in total lipids, TH-BPs and thyroxine binding capacity compared to non-pregnant women. Importantly, and as described in the introduction, these variables influence individual variations in TSH and TH concentrations and must be regarded when interpreting laboratory analyses (Fitzpatrick and Russell. 2010) and assessing thyroid homeostasis in pregnant women.

5.5 Background exposures of POPs and associations with thyroid function

5.5.1 Associations between POPs and maternal TSH and THs

This work demonstrated that women with the highest serum concentrations of summed PFASs and OCs had 8% higher concentrations of TSH compared to women with the lowest contaminant concentrations. Further, women with the highest serum concentrations of summed OCs had 2-4% lower concentrations of T3, T4 and FT4. These associations were consistent at all sampling points, where the contaminant quartile differences in TSH and TH concentrations were the same in early pregnancy, 3 days and 6 weeks postpartum. Table 3 presents an overview of comparable studies and their observations, and demonstrates that our findings partly comply with other studies; one study included repeated measurements of thyroid hormones in mixed models (Takser et al. 2005) similar to what we performed in Paper II, and also observed several OCs to be positively and inversely associated with TSH and T3, respectively. Several studies have also reported inverse associations between OCs and THs (Abdelouahab et al. 2013; Chevrier et al. 2008; Darnerud et al. 2010; Koopman-Esseboom et al. 1994). The magnitude of associations or estimated effects, are difficult to compare between the different studies due to different statistical methods and interpretation of effect sizes. Still, the magnitude of the effects on concentrations of TSH and THs are very low and concentrations vary within normal reference ranges. Finally, several studies report both positive and negative associations and no associations at all.

The difference in analysed POPs and biomarkers between studies complicates the conclusion on effects on thyroid function. Additionally, single measurements of blood POP concentrations are most often used in epidemiological studies (Lee et al. 2006; Steenland et al. 2010; Wigle et al. 2008). POP concentrations in early pregnancy represent the biologically available concentrations and are good biomarkers of internal exposure doses in the mother. However, concentrations change with time, where past or cumulative exposures are not necessarily strongly correlated to single measurements at different time points (Nost et al. 2015). Therefore, discrepancies in thyroid homeostasis during pregnancy can be a result of thyroid disruption at earlier stages in the womens life, where POP measurements in pregnancy may not adequately reflect exposure at the time endocrine disruption in the mother actually occurred.

5.5.2 Associations between maternal POPs and infant TSH

We did not detect any associations between maternal POP concentrations and infant TSH concentrations three days after delivery. However, interpreting TSH concentrations three days after birth in regards to dysregulation of infant TH homeostasis may be too early after birth to indicate thyroid impairment, and that divergences in the thyroid homeostasis due to maternal POP exposures could develop throughout childhood. Also, concentrations of maternal TSH and FT4 were positively and inversely associated to infant TSH, respectively, and indicate an influence of maternal TSH and TH levels on the infant TSH levels that could be secondary to POP influence on the maternal thyroid homeostasis.

Table 3. Thyroid-disrupting properties of PFASs and OCs in human studies on pregnant woman and infants

Study period	Population	N	Sampling time	Organic contaminants[a]	Thyroid parameters[b]	Covariates[c]	Indicated effect	Reference
2007-2009	Pregnant women	391	2nd trimester	PFHxS, PFHpS, PFOS, PFOA, PFNA, PFDA, PFUnDA,p,p'-DDE, HCB, PCB 99, 118, 138, 153, 163, 170, 180, 187, t-Nonachlor, c-Nonachlor	TSH, T3, FT3, T4, FT4, TBG, TTR, Albumin, TPOAb, Thyroxin binding capacity (Maesured: 2nd trimester, 3 days and 6 weeks postpartum)	Age, BMI, parity, thyroxine binding capacity, pregnancy vector, physical activity, sum of PFASs and sum of Ocs	↑TSH, ↓T3, ↓FT3, ↓T4, ↓FT4	Current study
	Infants	370	48-120 hours			Maternal total lipid, infant age at sampling, birthweight, gestational length and gender.	No effect	
1990-1992	Pregnant women	105	3rd trimester	PCB-118, 138, 153, 180	TSH, T3, T4, FT4		↓T3, ↓T4	Koopman-Esseboom et al. 1994
	Infants	105	2 weeks and 3 months	PCB-118, 138, 153, 180	TSH, T3, T4, FT4		↑TSH	
2005	Pregnant women	101	1st and 2nd trimester	PCB-99, 118, 138, 153, 156, 170, 180, 183, 187, t-Nonachlor, oxychlordane, HCB, DDT, p,p-DDE	TSH, T3, FT4 (Measured: First and second trimester and at delivery)	Gestational age at blood draw, age, smoking, total lipid and sum of PCBs.	↑TSH, ↓T3	Takser et al. 2005
	Cord blood	92		PCB-138, 153, 180, HCB, p,p-DDE	TSH, T3, FT4		No effect	
2000-2002	Pregnant women	165	3rd trimester	Non-ortho PCB, mono-ortho PCB	TSH, T3, FT3, T4, FT4	Nationality, length of gestation, alcohol, smoking, thyroid-disease, iodotherapy,first pregnancy, lead, cadmium, selenium.	No effect	Wilhelm et al. 2008
	Cord blood	127			TSH, T3, FT3, T4, FT4		No effect	
2004-2008	Pregnant women	1090	1st trimester	HCB, β-HCH, p,p'-DDT, p,p'-DDE, PCB-28, 118, 138, 153, 180	TSH, T3, FT4	Age, weight, parity, smoking, educational level and gestational age at sampling.	↓T3, ↑FT4	Alvarez-Pedrerol et al. 2009
1995-2001	Pregnant women	120	Delivery	PCB-153, HCB, ∑HO-PCBs	TSH, T3, FT4, TBG	Age, alcohol, cigarettes/day, serum and lipid concentrations.	↑T3	Dallaire et al. 2009b
	Cord blood	95		PCB-153, HCB, ∑HO-PCBs	TSH, T3, FT4, TBG	Gestational age, cord selenuim, smoking and lipid concentrations.	↓TBG, ↓FT4	
	Infants	130	7 months	PCB-153, HCB	TSH, T3, FT4, TBG	Breastfeeding status, lipid concentrations.	No effect	
2004-2005	Cord blood	289		PCB-118, 138, 153, 180	TSH, T4, FT4	Gender, gestational age, maternal age, race, prepregnancy BMI and smoking.	↓T4, ↓FT4	Herbstman et al. 2008
	Infants	265	18 days		T4	Gender, gestational age, maternal age, race, prepregnancy BMI, smoking, infant age at sampling.	↓T4	
1999-2000	Pregnant women	333	2nd trimester	PCB-18,28,44,49,52,66,74,99,101,118,138,146, 153,156,180,183,187,194,199, p,p-DDT, o,p-DDT, p,p-DDt, p,p-DDE, HCB	TSH, T4, FT4	Age, prepregnancy BMI.	↓T4, ↓FT4	Chevrier et al. 2008
1996-1999	Pregnant women	325	3rd trimester	LPCBs, Di-ortho PCBs, PCB-153, p,p-DDE	TSH, T3, FT4	Age, Pre-pregnacy BMI, education, smoking, season, alcohol.	↓T3	Darnerud et al. 2009
	Infants	150	3 weeks		TSH, T3, FT4	Maternal age, gender, birth weight, maternal education, smoking alchohol, breastfeeding and sampling season.	↓T3	
2007-2008	Pregnant women	380	2nd trimester	PCB-138, 153, 180	TSH, T3, FT3, T4, FT4, TPOAb	Gestational age,maternal age, selenium, iodine, BMI, Anti-TPO	↓T3	Abdelouahab et al. 2013
	Cord blood	260			TSH, T3, FT3, T4, FT4, TPOAb	Gestational age delivery, maternal age, selenium, iodine, BMI	No effect	
2000-2001	Pregnant women	285	3rd trimester	PFOS, PFUnDA, PFOA, PFNA, PFHxS, PFDeA, PFDoDA	TSH, T3, T4, FT4	Age, education and parity.	↑TSH, ↓T4, ↓FT4	Wang et al. 2014
	Cord blood	116			TSH, T3, T4, FT4	Maternal age, education, parity, neonatal sex and type of delivery.	↓T3, ↓T4	
2011-2013	Infants	83	4-7 days	DDT, PCB-153, PFOS, PFOA (measured in cord blood)	T4	Birth weight, type of delivery, maternal weight gain, gestational age, parity, BMI, age, smoking and alcohol.	↑T4 in girls	de Cock et al. 2014
2005-2006	Pregnant women	974	2nd trimester	PFHxS, PFOA, PFOS	TSH, FT4	Age, weight, race, gestational age at blood draw.	No effect	Chan et al. 2011
2003-2004	Pregnant women	903	2nd trimester	PFOS, PFOA, PFHxS, PFNA, PFUnDA, PFHpS, PFDA	TSH	Age, gestational age at blood draw, HDL concentrations, seafood intake, parity and inter-pregnancy interval.	↑TSH	Wang et al. 2013
2006-2008	Pregnant women	152	2nd trimester	PFHxS, PFOS, PFOA, PFNA	TSH, T4, FT4	Sampling time and TPOAb status.	↑TSH in in TPOAb+ women	Webster et al. 2014

[a]POPs were measured in blood at unless otherwise stated

[b]Thyroid parameters were mesured at the same sampling time as the organic contaminants unless otherwise stated.

[c]Covariates included in statistical models of significant findings.

5.5.3 Inclusion of relevant covariates

In the assessment of associations between POPs and maternal thyroid homeostasis, parity and thyroxine binding capacity were important covariates in the TSH models, whereas age, BMI and variables related to physiological changes during pregnancy were important covariates in models for T3, FT3, T4 and FT4. Regression analyses in Paper II demonstrated that without proper adjustment for covariates in respective models, we could have concluded on significant associations between several PFASs and T4 and FT4. Accordingly, Wang et al. reported PFUnDA to be significant inversely associated with FT4 and T4, but did not report on adjustments for gestational week or elevated levels of TH-BPs. However, several studies include gestational week as a covariate to adjust for pregnancy related influence on THs. Table 3 describes thyroid parameters and the covariates included in the different studies. The table demonstrate large variations in included covariates between studies and to our knowledge, TH-BPs or thyroxine binding capacity are not included in previous studies on pregnant woman. Hence, inconsistence in investigated covariates may account for some of the discrepancies in observed relationships between POPs and THs.

A sufficient iodine supply is crucial for supporting the increasing demand for THs in pregnancy. Iodine deficient women may be more susceptible to thyroid disruption and assessment of iodine status when investigating associations between thyroid disruptors and THs is apparent. Additionally, the negative health effects during pregnancy of disrupted thyroid function that has been associated to POP exposures can resemble those related to iodine deficiency (Morreale De et al. 2000; Morreale De et al. 2004; Stahl et al. 2011). In the present work, maternal iodine status (evaluated from dietary intake and iodine measured in urine) did not influence the observed associations between POPs and THs and was not included as a covariate in the final models. This has also been demonstrated in other studies (Abdelouahab et al. 2013; Alvarez-Pedrerol et al. 2009). However, iodine status may affect the variance in TH concentrations, as the degree of iodine sufficiency or deficiency affects individual TH set points and relative changes in concentrations throughout the pregnancy (Blackburn. 2013; Morreale De et al. 2004). This could not be observed in our cohort as the variation in iodine status was low but may influence any effects of POPs on thyroid function in population with large variances in iodine status, as well as when comparing effects between populations with different iodine status.

5.6 Mixture effects

Paper III displayed correlation coefficients as high as 0.95 between different POPs; hence, if a single compound is likely to cause a biological effect, linking this effect to a single compound will be difficult. Accordingly, PFOS was the dominating contaminant for the association of PFASs with maternal TSH in Paper II, where associations between PFHxS and PFOA with TSH lost their significance in models including PFOS as a covariate. In the reciprocal models, including PFOA or PFHxS in PFOS models did not alter the association between PFOS and TSH. These observations reflect the strong correlations between these PFASs, and complicate the interpretation of their individual effect on maternal thyroid homeostasis. This was further acknowledged in Paper III were the inclusion of specific OCs in statistical models, made it impossible to conclude if the variance in TSH concentrations were explained by either PFOS, PCBs or nonachlors. This was also the case for the PCBs, HCB and nonachlors and their individual associations to T3, T4 and FT4 after mutually adjustments. This has also been addressed in other studies (Dallaire et al. 2009; Chevrier et al. 2008; Takser et al. 2005), were the authors state that they were unable to evaluate the individual effect of OCs on TH status by controlling for other OCs because of the high intercorrelations between these compounds.

In the present study, we cannot exclude that the observed associations between POPs and concentrations of TSH and THs are related to other contaminants not included in the statistical analyses. Nevertheless, several epidemiological studies interpret findings from the different POPs that emerge as statistically significant, despite that specific POPs that display association to THs in a given study may partly or largely reflect the influence of other POPs rather than the role of that POP itself. It is likely that observed associations between POPs and thyroid functions could be related to a combined effect of several POPs, and there is growing awareness of the challenge of studying such multipollutant effects on human health (Borg et al. 2013; Kortenkamp. 2008; Lenters et al. 2015). An approach applied by several studies as well as in the present, is to include summed contaminant groups in statistical models. However, summing the concentrations of POPs assumes equal potencies and no synergistic effects, which may not be appropriate either. In the present population, women in the highest PFOS quartile demonstrated 24% higher TSH concentrations than women in the lowest

quartile (Paper II), while women within the highest summed POPs quartile had 8% higher TSH concentrations compared to women in the lowest quartile (Paper III). This observation indicate that summed contaminant groups may disguise individual effects and the strength of associations, and therby the interpretation of clinical relevance.

The nineteen POPs included in this work were in the same pmol/L concentrations as the THs (Figure 7), but single POPs have been indicated to exert lower potencies towards functions in the thyroid system compared to the THs, and the concentrations of individual POPs are therefore not regarded as hazardous in relation to competing with TH functions. Modelling of human thyroid function *in vitro*, demonstrates that some PFASs can compete with T4 binding to TTR which is most the important carrier protein for thyroid hormone to the brain and developing foetus (Weiss et al. 2009). However, PFOS and PFOA had individually a binding capacity for TTR of only one tenth compared to T4 in that study, hence they will likely not affect T4 binding to TTR in a pronounced way (Weiss et al. 2009). Still, the increased number of chemicals humans are exposed to may exert thyroid disrupting potencies through different mechanisms of the thyroid system, as well as combinational effects (Weiss et al. 2009).

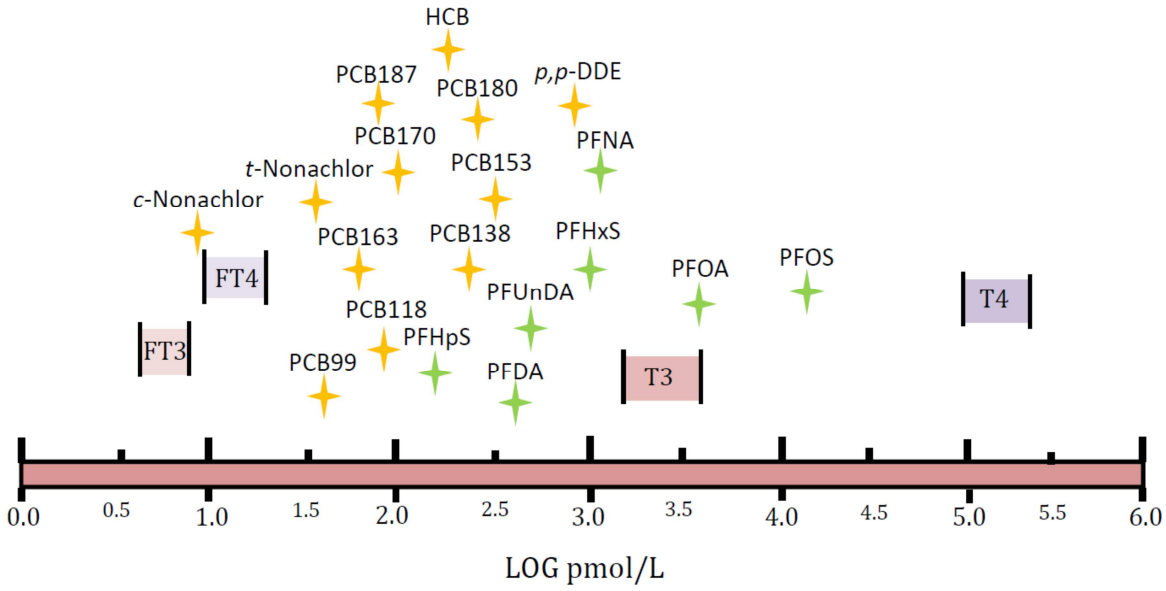

Figure 7. Serum concentrations of THs (2.5 and 97.5 percentiles are represented by lines on the end of the boxes), and median POP concentrations in serum from pregnant women. Concentrations are in pmol/L on a LOG scale.

5.7 Clinical relevance of findings

5.7.1 Clinical relevance of associations between POPs and maternal TSH and THs

Although associations between several POPs and TSH and THs were statistically significant, concentrations of all thyroid parameters varied within normal reference ranges. Hence, the indicated POP induced changes on hormone concentrations may not be of clinical relevance in the pregnant women. However, as pregnancy-induced changes in thyroid physiology alters maternal TH and TH-BP levels, this can affect laboratory interpretations, complicating the evaluation of thyroid function in pregnant women. In addition, changes in individual TH levels throughout pregnancy varies by gestational age, number of foetuses and study population (Blackburn. 2013). Hence, the clinical relevance of individual levels might be masked in non-pregnant population reference ranges, and gestational normative reference ranges for thyroid function tests are required for proper interpretation of any abnormalities (Lazarus. 2011). Still, population specific reference ranges for the THs indicate that ranges for the THs are within the mid to high end of normal reference ranges in non-pregnant populations (Table 4), and can be considered low for pregnant women since they are expected to have an increase in levels by 40-100% (Blackburn. 2013). Therefore, higher TSH concentrations in women with the highest POP concentrations may indicate inadequate T4 concentrations in these women, as TSH quickly responds to subtle changes in T4 concentrations resulting in elevation in TSH (Lazarus. 2011). Noteworthy, higher TSH levels, within the normal reference ranges, have been associated with an increased risk of miscarriages, foetal and neonatal distress, and preterm delivery (Benhadi et al. 2009; Stagnaro-Green and Glinoer. 2004; Stagnaro-Green et al. 2005), whereas marginally low T4 levels in the pregnant woman have been indicated to cause reduction in cognitive functions of the offspring (Berbel et al. 2009; Pop et al. 2003; Haddow et al. 1999).

Table 4. Reference ranges for thyroid parameters

Parameters	Method specific reference ranges[a]	International guidelines for reference ranges[b]	Study pop reference ranges[c]
TSH (mlU/L)	0.20-4.30	0.50-3.60	0.44-4.48
T3 (nmol/L)	1.30-3.10	1.70-2.70	1.97-3.73
T4 (nmol/L)	66.0-181	Refers to method	111-190
FT3 (pmol/L)	2.80-7.10	Refers to method	3.66-5.79
FT4 (pmol/L)	9.0-22.0	8.00-20.0	10.0-17.0
TBG (mg/L)[e]	47.0-59.0[f]	27.0-66.0[g]	26.2-53.3
TTR (g/L)	0.15-0.29	0.23-0.39	0.15-0.25
Albumin (g/L)	39.7-49.4	36.0-48.0	36.0-46.0
Thyroxin binding capacity (TBI)	0.80-1.30	Refers to method	1.07-1.43
Anti-TPO IU/ml	Negative < 34 < Positive	Refers to method	Negative < 34 < Positive

[a]Reference ranges (2.5-97.5th percentiles) are those recommended by the manufacturer (Roche)
[b]Reference ranges are those recommended by Norwegian Medical association (Norwegian Medical Association, 2015) for a non-pregnant population unless otherwise stated.
[c]Defined as the 2.5 percentile (lower range) and 97.5 percentile (upper range) in 2nd trimester for this population
[e]TBG reference ranges are reported for pregnant populations
[f]Reference ranges for pregnant women in 3rd trimester
[g]Reference ranges for pregnant women 2nd trimester

5.7.2 Clinical relevance of the influence of maternal thyroid homeostasis on infant TSH

Children born by mothers within the highest TSH quartile and lowest FT4 quartile had 10% (0.2 mlU/L) higher median concentrations of TSH compared to children born by mothers in the lowest and highest TSH and FT4 quartiles, respectively. This difference is small and in a magnitude comparable to normal variance within healthy infants, and may not be of clinical relevance. Further, the physiological importance of subtle deviations in infant TH levels or subclinical hypothyroidism in infants is not established in the literature. The limit for clinical action is a TSH concentration above 8 mlU/L according to the Norwegian Newborn Screening program (Knudtzon J et al. 1997; Norwegian Newborn Screening. 2015), and no actions are taken when TSH levels are mildly elevated (5-8 mlU/L). However, a concern is that mildly elevated TSH levels with normal FT4 levels increases the risk of developing hypothyroidism and subsequently developmental delay, but no studies have yet fully supported this concern (Kaplowitz. 2010). Noteworthy, there are almost a complete lack of paediatric randomized controlled trials investigating the effect of treating subclinical hypothyroidism with synthetic THs compared to no treatment. Further, whether or not mildly elevated TSH levels poses a risk for the infant and developing child is still debated (Chu and Crapo. 2001; McDermott and Ridgway. 2001)

6. Methodological considerations

6.1 Study design, population and validity

All the papers were based upon the MISA cohort study which has both cross-sectional and longitudinal aspects. Paper I and III applied a cross-sectional study design where exposure and outcome were measured at early pregnancy, whereas Paper II applied a longitudinal examination of thyroid parameters during and after pregnancy in regards to PFAS concentrations at early pregnancy. The internal validity of the MISA population was considered acceptable by Veyhe at al. (2012) although the participation rate among invited women was low. The participation rate was 20 % and when comparing the participants to the general Norwegian pregnant population using the Medical Birth Registry of Norway (MFR), the MISA population is slightly older (two years), smoked less and were better educated, but otherwise similar to the general pregnant population in Norway (Veyhe et al. 2012).

The internal validity of the personal and dietary information is considered good based on previous validation of the FFQ (Hjartaker et al. 2007) and intake of total energy and micronutrients are comparable to those in similar age groups in the Norwegian population (Table 5) (Norwegian Directorate of Health. 2012; Norwegian Directorate of Health. 2014; Veyhe et al. 2012). Hence, the MISA women can be cosidered representative for other pregnant women in Norway with similar dietary habits. The internal validity of the chemical analyses was strengthened by high quality exposure assessment, including a wide range of POPs, as well as including several thyroid parameters analysed with accredited methods by personnel at the hospital laboratory. Contaminant concentrations in the MISA population are representative for the general female population in Norway since POP burdens are similar and thus an indicator of exposure to future infants. Further, the study specific reference ranges for thyroid parameters at the three sampling points are likely representative for pregnant women in Norway.

The internal validity of statistical assessments of the association between POPs and TH-homeostasis, are strengthened by a large sample size, as well as the large number of POPs,

demographic and lifestyle variables, and thyroid parameters considered. The observed associations between concentrations of POPs and THs are likely not transferable to non-pregnant populations as thyroid physiology is different from non-pregnant women, and the pregnant thyroid function could be more sensitive to disruption due to increased thyroid stress. Additionally, the generalizability to other pregnant populations is dependent on variance in organic contaminant concentrations and iodine supply. However, the POP concentrations in maternal serum and association to maternal and infant concentrations of TSH and THs could reflect actual health risk for foetuses and children in general.

Table 5. Energy intake and distribution of energy (E %) in the MISA cohort compared to women in Norkost 3. Mean, percentiles and recommended intake.

	MISA women (n=387)					Norkost 3 women[a] (n=925)					Recommended
	Mean (SD)	P25	P50	P75	P95	Mean (SD)	P25	P50	P75	P95	intake[b]
Energy, MJ/d	8.0 (2.0)	6.7	8.1	9.4	11	8.0 (2.4)	6.3	7.8	9.5	12	
Protein, E%	17.4 (2.0)	16	17	19	21	18 (4.0)	15	17	20	24	10-20
Fat, E%	34.0 (4.6)	31	34	37	42	34 (7.0)	30	34	39	46	25-35
Saturated fat, E%	13.9 (2.3)	12	14	15	18	13 (3.0)	11	13	16	20	<10
Monounsaturated fat, E%	10.8 (1.7)	9.8	10	12	17	12 (3.0)	9.3	11	13	17	10-15
Polyunsaturated fat, E%	6.6 (1.6)	5.4	6.4	7.4	9.7	6.2 (2.3)	4.5	5.9	7.4	10	5-10
Carbohydrate, E%	46 (4.8)	43	46	49	55	44 (8.0)	39	44	49	56	50-60
Added sugar, E%	5.8 (2.7)	4.1	5.2	6.9	11	7.4 (5.1)	3.8	6.4	9.7	17	<10

[a]National report on dietery intake in Norwegian men and women between 18-70 of age (Norwegian Directorate of Health, 2012)
[b]Recommended intake from the Norwegian Directorate of Health (Norwegian Directorate of Health, 2000)

6.2 Chemical analyses

As epidemiological effect studies address the potential association between an exposure and an outcome and where these are of measurable scale, the quality of measurements is critical in determining the validity of such studies. Systematic errors in measurement were controlled for and minimized by quality assurance-quality control (QA-QC) efforts. For the analyses of thyroid parameters, random errors were minimized by automatic high throughput technology and samples were reanalysed if values differed from normal reference ranges. However, possible errors due to switching of sample identity and pipetting serum into the wrong tubes cannot be disregarded. In regard to POPs, the sample preparation is more manual and thus prone to more random error.

Exposure assessment included 12 OCs that were initially analysed for a different study (Veyhe et al. 2015) and a total of 26 PFASs that was screened for in a subset of 50 serum samples (Paper I). Concentrations of 10 PFASs were determined and presented in all samples (N=391) while the detection frequency of the remaining 16 PFASs were low and thus not quantified. Perfluorobutane sulfonic acid (PFBS) and perfluorobutanoic acid (PFBA) were not presented due to methodological limitations at the time of analysis with only one transition ion for the compounds. These results could have contributed to valuable information as the production and use of these are reported to have increased in later years (Buck et al. 2011).

The chemical analyses of POPs employed in these studies are well established. QA-QC measures indicated good quality for reported concentrations which confirm that good internal validity for these results was achieved; i) Evaluation of analyses of standard reference materials (SRMs) where agreement between the measured value and a certified value ensured the accuracy of analyses; ii) The repeated analysis of SRMs throughout sample processing evaluated the precision of the results; iii) Analyses of blank samples served to assess potential laboratory contamination and to determine a threshold to avoid false positive detections of low concentrations; iv) The laboratory at the Norwegian Institute for Air Reseach routinely participates in the international AMAP Ring Test for Persistent Organic Pollutants in Human Serum and has performed well (within ± 20% for PFASs and ± 15% for OCs, of assigned

values); v) A high number of internal standards was added to ensure that the method was adequate for compounds with different properties; vi) Quantification based on the internal standard method corrects for any loss of sample during sample extraction: vii) Quantified results of OCs were rejected when the isotopic mass ratios deviated by > 20% from those in quantification standards, and viii) For PFASs, the presence of two masses were regarded qualitatively to confirm the compound identity.

The chemical analyses of THs, TH-BPs, thyroxine binding capacity and anti-TPO are well-established routine analyses used in the clinic for diagnostic purposes. The quality assurance involves routinely running a three level commercial control in addition to the analyses of pooled serum from blood donors. The analytical variation was well within 10 % (% variation in concentrations calculated form repeated analyses of the same donor control for a year) for all the analytes.

6.3 Statistical methods and sample size

Values that are below a threshold for which concentrations are considered accurate are a challenge in environmental studies. In the present work we chose to only include POPs with detection frequencies above 80% in statistical analyses, and concentrations below limit of detection (LODs) were replaced by LOD/$\sqrt{2}$ (Anda et al. 2007). Further, participants with missing values for POPs or thyroid parameters were excluded from the analyses.

Analyses of biomarkers as well as POPs in human blood are expensive, thus many association studies on the relationship between POPs and thyroid parameters are challenged with limited number of samples. Sample size calculations for simple bivariate correlation and multiple linear regression, demonstrated that significant associations (P<0.05) between POPs and THs, with a statistical power of 80 %, could be detected with 190 and 360 women, respectively, and indicated adequate size of the present study population.

In Paper I, food variables were summed and included in statistical models to reduce the number of independent variables in the statistical models and thus reducing the random variation in the regression equations. This might have concealed the importance of single food items as predictors. However the variables that were summed were selected based on their correlations and proximity in the PLS-plots.

Due to the strong correlation between POPs and their joint explanation of the outcome, it is challenging to isolate the variance in THs explained by individual POPs in statistical models. Several studies apply numerous statistical models including individual POPs one by one as independent variables in regression analyses (Table 3). To avoid multicollinearity issues, we applied multivariate analyses throughout the papers to assess the simultaneous relationship between POPs, demographic and dietary predictors and thyroid parameters. In addition, individual POPs were mutually adjusted for in models, and highly correlated compounds were investigated and summed based on cluster analyses.

Due to the pregnancy-dependent change in thyroid function throughout the gestational period, the difference in gestational week between participants was adjusted for by including either thyroxine binding capacity or a pregnancy related vector depending on the outcome variable in Paper II and III. The model predictions for the total population were also confirmed by repeated analyses of subset of women in gestational week 18 and 20.

To be able to compare the contaminant groups, the wet-weight concentrations of OCs were applied in statistical models in Paper III as PFASs are not associated to lipids. Increased lipid concentrations during pregnancy leads to increase in OC concentrations and both lipids and wet-weight OC concentrations peaked at birth and were the lowest at 6 weeks postpartum in the present population. However, when the OC concentrations were lipid-adjusted, this peaking was no longer evident (Hansen et al. 2010). However, THs are involved in lipid metabolism (Al-Tonsi et al. 2004), and to take into consideration the effect of OCs on THs in statistical models, total lipid concentration was included as a covariate and thereby adjusted for in the model as opposed to lipid adjusting the OC concentrations prior to analysis (Paper III).

7. Concluding remarks

This work allowed for an extensive assessment of the influence of POPs on thyroid function in mother-child pairs from Norway. The work especially highlights the challenges in establishing effects of POPs on thyroid functions due to the complexity of the thyroid system as well as the intricacy of multiple exposures of POPs.

The results demonstrate relative low maternal POP concentrations, where PFASs are currently the group with the highest concentrations in human blood. Maternal POP concentrations are influenced by demographic and dietary variables, where child birth and breastfeeding are important sources of maternal elimination of POPs. Accordingly, foetuses and infants are exposed to POPs during sensitive developmental periods throughout the gestational period and after birth.

The summed POP concentrations were associated with TSH and THs, where maternal TSH and TH concentrations appeared to influence infant TSH concentrations after birth. However, all the observed differences in thyroid parameters were small and varied within the normal reference ranges for non-pregnant individuals and infant populations, and we cannot conclude on the clinical relevance of the findings.

This research effort contributes to the understanding of multipollutant exposures and the potential of environmentally relevant pollutant mixtures to influence maternal and infant thyroid function. However, the clinical manifestation of subtle influence on hormone concentrations both in adults, foetuses and infants should be explored in longitudinal effect studies.

8. Future perspectives

An increased focus should be on the exposome, where the totality of human environmental exposures from conception and onwards can advance understanding of disease aetiology.

A larger number of contaminants could have been included in this work. In particular metals, brominated flame retardants, hydroxylated PCBs and other PFASs compounds, to further enhance our understanding on substance mixtures and intragroup correlations in humans. Taking the complexity of mixtures one step further would to determine the exposome rather than single compounds.

Increased effort in identifying emerging contaminants could enhance the understanding of potential future health hazards.

The importance of single food items for PFASs body burdens, and subsequent dietary advice for pregnant women should be investigated in relation to the relative importance of single food items in regards to absolute intake amounts.

Further studies should include several blood samples throughout the gestational period to assess possible transient change in hormone concentrations in pregnant women.

Effect studies should combine basic research as well as population studies, where potential effects are investigated with epigenetics, biomarkers and disease development.

Studies should elucidate exposures during sensitive developmental periods and time until development of disease.

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Errata

Paper II

Supplemental material Table S1: Reference range “TBG 47-45 mg/L” should have been “47-59 mg/L”.

APPENDIX

Invitation letter

Questionnaires

Enquiry

Til deg som er gravid

Universitetet i Tromsø · Romssa universitehta
Senter for samisk helseforskning, Institutt for samfunnsmedisin, Universitetet i Tromsø

Til deg som vil delta

Du må kontakt **ditt nærmeste** innsamlingssted for å avtale tid for oppstart. Du kan starte opp umiddelbart eller **helst** innen uke 20. Du kan også avtale å starte opp i forbindelse med ultralydundersøkelsen (ca. uke 18).

Innsamlingssted	Telefonnummer
Kirkenes fødeavdeling	78 97 32 35
Hammerfest fødeavdeling	78 42 15 12
Alta Fødestue	78 45 54 00
Karasjok legesenter	78 46 85 00
Kautokeino legesenter	78 48 72 50
UNN barselavdeling	77 62 64 60
Sonjatun fødestue	77 77 08 25
Fødestua i Midt-Troms, Lenvik	77 87 14 90
Lofoten fødestue	76 06 01 22
Gynekologisk senter, Bodø	75 52 39 00

Ved oppstart:
Du skal måle blodtrykk og vekt, ta blodprøve og levere urinprøve. Vi ber deg derfor om å:

- Møte fastende. Om du ikke klarer å faste, kan du spise en lett, fettfattig frokost (brød, salat, grøt) uten kaffe.
- Ta med en morgenurinprøve tatt på følgende måte: Den første porsjon av urinstrålen kastes, den neste porsjon urin samles i egnet beholder og den siste porsjon urin kastes.
- Ta med "Helsekort for gravide" da vi vil merke helsekortet med prosjektets ID

Før oppstart ber vi deg om å sende inn underskrevet samtykke (Miljøgifter i svangerskapet og i ammeperioden + Morsmelksundersøkelsen) i vedlagte svarkonvolutt til Universitetet i Tromsø.

Dersom du har spørsmål, kan du ta kontakt med:
solrunn.hansen@ism.uit.no
Telefon 920 69 700

På forhånd takk og vel møtt!

Vennlig hilsen
Solrunn Hansen
Prosjektleder / Jordmor

http://uit.no/med-nord/misa

Forespørsel om deltakelse i forskningsprosjekt

Miljøgifter i svangerskapet og i ammeperioden

Det er for tiden økende fokus på miljøgifter og hvilke effekter disse har på omgivelsene og helsen til oss mennesker. Befolkningen i arktiske områder er spesielt utsatt siden miljøgifter fra den øvrige verden fraktes nordover til våre områder med globale hav- og luftstrømmer. Nivået av miljøgifter i Norge er sammenlignet med andre land, generelt lave.

Kosten er den viktigste kilden for spredning av miljøgifter i tillegg til det vi finner i miljøet forøvrig. Vi er særlig sårbare for miljøgifter på fosterstadiet og i de første årene av livet. Fettløselige, organiske miljøgifter passerer lett fra mor til foster gjennom morkaka og navlesnora, og de utskilles også i morsmelk. Nivåene av disse stoffene i mors blod gjennom svangerskapet og senere i brystmelk, gir indikasjoner på den risiko vi utsetter våre barn for. Målinger viser at de fleste miljøgifter heldigvis er på vei ned, men vi har mangelfull kunnskap om hvordan mennesker påvirkes over tid.

Vi har ennå liten informasjon om situasjonen i Nord-Norge. Vi ønsker derfor å gjennomføre en undersøkelse som skal måle nivåer av disse langsomt nedbrytbare stoffene hos om lag 1000 gravide og ammende mødre i vår landsdel.

Hensikten er å:

- Kartlegge miljøgifter i mors blod, navlestrengsblod og morsmelk.
- Undersøke hvilken risiko gravide og nyfødte utsettes for gjennom påvirkning av miljøgifter og spesielt hva som tilføres gjennom kostholdet og morsmelk.
- Se om det er noen sammenheng mellom miljøgifter og helsen til mor og barn.
- Å lage grunnlag for retningslinjer i forebyggende helsearbeid for å beskytte mennesker mot miljøgifter og spesielt kostholdsråd for gravide, ammende og kvinner i fertil alder.
- Lage grunnlag for oppfølgingsstudier til barna når 12-årsalder.
- Lagre prøvemateriale i biobank for å ha mulighet til å analysere på "nye" miljøgifter eller faktorer som kan virke beskyttende mot skadelige effekter av miljøgifter.
- Prosjektet vil spesielt sammenligne den samiske og den norsk etniske befolkningen.
- Tilleggsundersøkelse: Undersøke om det er forskjell mellom den samiske og den norske befolkning vedrørende fostermål utført ved ultralyd ved 18. svangerskapsuke.

Forespørsel om å delta sendes til alle gravide som:

- Har time hos jordmor eller time til rutineultralyd
- Er i første halvdel av svangerskapet
- Skal føde ved følgende fødesteder: Kirkenes, Hammerfest, Alta, UNN, Sonjatun, Lenvik, Lofoten eller Bodø.

Frivillig deltagelse

Deltakelse i undersøkelsen er frivillig og bygger på skriftlig informert samtykke. Alle data behandles strengt fortrolig, og resultater blir formidlet slik at ingen opplysninger kan føres tilbake til enkeltpersoner. Dersom du blir med, kan du trekke deg uansett tidspunkt, og du kan be om at dine opplysninger og prøveresultater slettes inntil data er publisert.
Du trenger ikke å begrunne hvorfor du trekker deg, og det medfører ingen konsekvenser for deg. Om du trekker deg i løpet av svangerskapet eller etter fødselen, ber vi deg om å gi tilbakemelding for å unngå utsendelse av nye spørreskjema/innsamlingsutstyr og purring.

Hvis du blir med, spør vi deg om:

1. Spørreskjema:

- Å svare på et spørreskjema i første halvdel av svangerskapet

2. Prøver av deg til analyse av miljøgifter, fettstoffer og hormoner:

Tungmetaller: Kvikksølv, bly, kadmium
Organiske miljøgifter: DDT, HCH, Toxaphenes, HCB, PCB, dioksiner, bromerte flammehemmere, ftalater og PFOS
Jernlagre, kolesterol, triglyserider
Hormoner: FSH, LH, prolaktin, TSH, FT4, FT3, østradiol og progesteron

- Blodprøve i første halvdel av svangerskapet, etter fødsel og 6 uker etter fødsel
- Navlestrengsblod ved fødsel
- Hårprøve ved fødsel for biobank
- Urinprøve ved hver blodprøvetaking til biobank
- Blodtrykk, høyde og vekt i forbindelse med prøvetaking

3. At vi av ditt nyfødte barn kan få:

- Måle omkretsen rundt magen og genitale lengdemål
- Avføringsprøve (mekonium) til biobank
- Blodprøve av barnets hæl til eventuelt hormonanalyse og biobank. Blodprøven tas samtidig med rutineprøven "Nyfødtscreening" 3. dag etter fødselen. Vi ber dersom det er nødvendig, å få stikke barnets hæl en ekstra gang for å få nok blod.

4. Morsmelkundersøkelsen:

- Å levere en morsmelksprøve samlet i løpet av barnets første levemåned, til analyse av miljøgifter
- I forbindelse med morsmelksundersøkelsen spør vi deg også om å svare på spørreskjema når barnet er 1, 6 og 12 måneder og 2, 7 og 12 år gammel.

Folkehelseinstituttet (FHI) er ansvarlig for denne delen av prosjektet. Personopplysninger utlevers til FHI, slik at de kan kontakte deg direkte for utlevering av utstyr og spørreskjema. Vi ber deg om å lese eget vedlagt informasjonsskriv med egen samtykkeerklæring.

5. Ditt samtykke:

- Til å oppbevare prøvematerialet av deg selv og barnet i biobank. Blod- og urinprøver, navlestrengsblod, mekonium og hårprøve vil lagres i en biobank til utgange av år 2022 ved Universitetet i Tromsø med prosjektansvarlig som ansvarlig.
- Til at prøvematerialet kan sendes avidentifisert til utlandet når det er nødvendig av hensyn til å få utført analyser av prøvene og for kvalitetskontrollanalyser (Canada).

6. Innhenting av opplysninger:

- Tillatelse til innhenting av nødvendige journalopplysninger om deg og ditt barn i forbindelse med svangerskapet og fødselen. Kopi av svangerskapsjournal, ultralydskjema, barnets epikrise som sendes til helsestasjonen og skjema til Medisinsk Fødselsregister. Alle opplysninger behandles etter at personopplysninger er fjernet og erstattet med et ID-nummer før utlevering til Universitetet.

7. Tillatelse til å koble innsamlede opplysninger om deg:

- Fra denne delen av prosjektet mot data fra Morsmelksundersøkelsen og Mor-/barnundersøkelsen.
- Mot Medisinsk Fødselsregister vedrørende data fra pågående og eventuelt tidligere svangerskap og fødsler.
- Mot Norsk pasientregister som registrerer diagnoser barnet ditt har fått ved innleggelse på sykehus.
- Mot Nyfødtscreeningregisteret som gir prøvesvar på barnets stoffskifte (TSH).
- Datatilsynet har godkjent disse koblingene.

8. Kontakte deg senere for å:

- Invitere dere til ekstra undersøkelse når barnet er blitt eldre. Du forplikter deg ikke til å delta i dette, men kan ta stilling til dette når du får invitasjonen som vil inneholde detaljert informasjon om hva vi ønsker å undersøke.

Utstyr, ID-nummer
Ditt og barnets navn og fødselsdato er byttet ut (avidentifisert) med et nummer når det brukes i forskning. Ved oppstart får du utlevert alt utstyr merket med et ID-nummer. Både prøver og innsamlet informasjon blir derfor avidentifisert på innsamlingsstedet dersom du har med ID-merket utstyr. Om du ikke har med forhåndsmerket utstyr, skjer avidentifiseringen etter ankomst Universitetet i Tromsø. Data vil anonymiseres etter prosjektslutt år 2022.

Din sikkerhet og tilbakemelding

Opplysninger du gir og svar på prøver du tar, blir kun brukt til forskning. Vi forplikter oss til å gi tilbakemelding til deg dersom du ønsker svar på dine egne blodprøver. Du får svar på for eksempel nivåer av miljøgifter, hormoner og fettstoffer. Vi gir deg automatisk svar på avvikende fettstoffer og hormonprøver vedrørende stoffskifte. Din fastlege får også prøvesvar dersom du tillater det, og fastlege kan gi deg videre oppfølging. Det tar noen måneder før resultatene foreligger pga. tidkrevende analyser.
Vi lager rapporter fra prosjektet, og hvis du ønsker det, kan gir vi deg prosjektets resultater og konklusjoner. Datainnsamlingen pågår fra juni 2007 til høsten 2008, og de første rapporter beregnes ferdig i 2009.

Godkjenninger

Undersøkelsen er godkjent av Regional komité for medisinsk og helsefaglig forskningsetikk (REK Nord) og Datatilsynet. Hvis det senere blir aktuelt å bruke prøvene til andre problemstillinger enn de som er skissert her, skjer det kun etter ny godkjenning fra datatilsynet og ny vurdering av REK.

Ansvarlig

Ansvarlig for dette prosjektet er dr. med. Jon Øyvind Odland ved Institutt for samfunnsmedisin, Universitetet i Tromsø. Oppdragsgiver er Institutt for samfunnsmedisin og Senter for samisk helseforskning ved Universitetet i Tromsø. Norges Forskningsråd, Norske Kvinners Sanitetsforening, Helse Nord og Senter for samisk helseforskning ved UiT finansierer prosjektet.

Påmelding, samtykke

Dersom du sier ja til å delta i studien, ber vi deg om å avtale tid for oppstart med ditt innsamlingssted (se oversikt side 2). Før oppstart ber vi deg om å underskrive samtykke og returnere de i vedlagte returkonvolutt. Du beholder selv ett eksemplar.

Dersom du har behov for mer informasjon før oppstart eller har spørsmål underveis, ta kontakt med:

- Prosjektets kontakttelefon:
  920 69 700
- Prosjektansvarlig Jon Øyvind Odland:
  E-post jon.oyvind.odland@ism.uit.no
  telefon 909 53 887
- Prosjektleder Solrunn Hansen:
  E-post solrunn.hansen@ism.uit.no
  telefon 77 64 48 36 / 992 71 762

Du kan også finne informasjon om prosjektet på vår nettside: http://uit.no/med-nord/misa

Vennlig hilsen

Jon Øyvind Odland (sign.),
Prosjektansvarlig / Dr. med.,
Institutt for samfunnsmedisin, UiT

Merete Eggesbø (sign.),
Prosjektleder Morsmelksundersøkelsen/ Dr. med,
Divisjon for epidemiologi, Folkehelseinstituttet

Solrunn Hansen (sign.),
Prosjektleder / Jordmor,
Institutt for samfunnsmedisin, UiT

Samtykke [din kopi]

Miljøgifter i svangerskapet og i ammeperioden

ID- nummer:

Fornavn:.....

Etternavn:.....

Adresse:.....

Postnummer:.....

Poststed:.....

Fødselsnummer 11 siffer:....

E-post:.....

Telefon privat:.....

Telefon mobil:.....

Termin (DD|MM|ÅÅÅÅ):.....

Sett kryss:

☐ Jeg har lest informasjon om prosjektet og samtykker til å delta.

Dato: _____ Signatur: _____

Dato: _____ Signatur foresatte: _____

Dersom du er under 16 år, må du også ha underskrift fra din foresatte.

Tilbakemeldinger

☐ Jeg ønsker tilbakemelding om mine egne prøveresultater.

☐ Jeg ønsker tilbakemelding om prosjektets resultater og konklusjoner.

☐ Jeg tillater at min fastlege får resultater på avvikende prøvesvar med hensyn til hormoner og fettstoffer.

Navn på fastlege: _____

Adresse: _____

2007
KONFIDENSIELT

MILJØGIFTER I SVANGERSKAPET OG I AMMEPERIODEN

Følgende opplysninger fylles ut i forbindelse med blodprøvetaking.

Dette skjema **må** følge blodprøven!

Skjemaet skal leses optisk. Vennligst bruk blå eller sort penn. Du kan ikke bruke komma, bruk blokkbokstaver.

ID-nr:

LAB-kobling.

Urinprøve levert i dag: Ja: ☐ Nei: ☐ **Prøvesett:** P1: ☐ P5: ☐ P6: ☐

PRØVETAKINGSDAGEN

Fyll inn tidspunkt når blodprøven er tatt: dag mnd

Dato ..... | | | | |

Klokkeslett ..... | | | | |

Prøvetakingssted .....

STILLING NÅR BLODPRØVEN BLE TATT

☐ Sittende ☐ Liggende

MÅLTID FØR BLODPRØVEN

Når spiste du siste måltid før blodprøven ble tatt: dag mnd

Dato ..... | | | | |

Klokkeslett ..... | | | | |

Når drakk du siste kaffe før blodprøven ble tatt: dag mnd

Dato ..... | | | | |

Klokkeslett ..... | | | | |

RØYKEVANER SISTE UKEN

Har du røykt i løpet av siste uke?

☐ Ja ☐ Nei

Hvis ja: Hvor mange sigaretter røykte du? Antall

I dag ..... | | |

I går ..... | | |

ALKOHOL SISTE UKEN

	Antall Siste uke	Antall i går
Øl *(0,4 l)*, rusbrus		
Vin *(glass)*		
Brennevin *(drinker/shots)*		
Likør/Hetvin		

HØYDE OG VEKT

Hvor høy er du *(cm)* ..... | | |

Er høyden målt i svangerskapet?

☐ Ja ☐ Nei

Hvor mye veier du i dag? *(I hele kg)* ..... | | |

Er vekten tatt i dag?

☐ Ja ☐ Nei

Hvor ble den i så fall tatt:

☐ Lab ☐ Legekontor ☐ Fødeenhet/fødestue

MEDISINER SISTE UKEN

Har du tatt medisiner i løpet av siste uke?

☐ Ja ☐ Nei

Hvis ja: Angi medikament og dato for siste tablett

dag mnd

Dato ..... | | | | |

Preparatnavn: .....

(Ikke skriv her →) | | | | | | |

dag mnd

Dato ..... | | | | |

Preparatnavn: .....

(Ikke skriv her →) | | | | | | |

dag mnd

Dato ..... | | | | |

Preparatnavn: .....

(Ikke skriv her →) | | | | | | |

dag mnd

Dato ..... | | | | |

Preparatnavn: .....

(Ikke skriv her →) | | | | | | |

TRAN OG FISKEOLJE SISTE UKEN

Har du brukt flytende tran/omega-3/fiskeolje i løpet av siste uke?

☐ Ja ☐ Nei

Hvis ja: Angi dato du sist tok flytende tran/Omega-3/fiskeolje

dag mnd

Dato .....

Preparatnavn: .....

(Ikke skriv her →)

Preparatnavn: .....

(Ikke skriv her →)

Angi mengde

☐ 1 ts ☐ 1/2 ss ☐ 1+ ss

Har du brukt kapsler/piller med tran/omega-3/fiskeolje i løpet av siste uke?

☐ Ja ☐ Nei

Hvis ja: Angi dato du sist tok kapsler/piller med tran/Omega-3/fiskeolje

dag mnd

Dato .....

Preparatnavn: .....

(Ikke skriv her →)

Angi mengde

☐ 1 stk ☐ 2 stk ☐ 3 stk

dag mnd

Dato .....

Preparatnavn: .....

(Ikke skriv her →)

Angi mengde

☐ 1 stk ☐ 2 stk ☐ 3 stk

KOSTTILSKUDD SISTE UKEN

Har du brukt andre kosttilskudd (vitaminer/mineraler) i løpet av siste uke?

☐ Ja ☐ Nei

Hvis ja: Angi dato for siste tablett

dag mnd

Dato .....

Preparatnavn: .....

(Ikke skriv her →)

dag mnd

Dato .....

Preparatnavn: .....

(Ikke skriv her →)

dag mnd

Dato .....

Preparatnavn: .....

(Ikke skriv her →)

dag mnd

Dato .....

Preparatnavn: .....

(Ikke skriv her →)

dag mnd

Dato .....

Preparatnavn: .....

(Ikke skriv her →)

dag mnd

Dato .....

Preparatnavn: .....

(Ikke skriv her →)

dag mnd

Dato .....

Preparatnavn: .....

(Ikke skriv her →)

Takk for hjelpen!

2007
KONFIDENSIELT

MILJØGIFTER I SVANGERSKAPET OG I AMMEPERIODEN

ID-nr:

Universitetet i Tromsø

Romssa universitehta

Universitetet i Tromsø — Romssa universitehta

MILJØGIFTER I SVANGERSKAPET OG I AMMEPERIODEN

Vi ber deg fylle ut spørreskjemaet så nøye som mulig.

Skjemaet skal leses optisk. Vennligst bruk blå eller sort penn. Du kan ikke bruke komma, forhøy 0,5 til 1. Bruk blokkbokstaver.

Dersom du får for liten plass på enkelte spørsmål, vennligst noter på siste side, eller ta i bruk et ekstra ark.

Venligst besvar skjema innen en uke etter oppstart i prosjektet. Sendes sammen med blodtrykkssjema til UiT i vedlagte returkonvolutt.

Dato for utfylling av spørreskjema: dag mnd år

Dato .....

SOSIALE FORHOLD

Hva er ditt postnummer? .....

Hva er ditt fødselsår: .....

Hvor mange års skolegang/utdanning har du i alt,
ta også med grunnskole og videregående? Antall år

Hvor mange personer er det i ditt hushold? Voksne Barn

Hvor høy er den samlede bruttoinntekten i ditt hushold?

- ☐ Under 150 000 kr
- ☐ 150 000-300 000 kr
- ☐ 301 000-450 000 kr
- ☐ 451 000-600 000 kr
- ☐ 601 000-750 000 kr
- ☐ 751 000-900 000 kr
- ☐ Over 900 000 kr

Hva er ditt yrke?

.....

(Ikke skriv her →)

Beskriv kort din arbeidsplass og arbeidsoppgaver så nøyaktig som mulig:
(Eksempel: skole/undervisning, sykehus/ pasientarbeid/cellegift, butikk/ klær, renseri/renser klær, kontor/dataarbeid, frisør/kunder)

.....

(Ikke skriv her →)

Hva er din arbeidssituasjon? (Sett om nødvendig flere kryss)

- ☐ Arbeider heltid
- ☐ Arbeider deltid
- ☐ Hjemmeværende
- ☐ Under utdanning
- ☐ Arbeidssøkende
- ☐ Under attføring
- ☐ Uføretrygdet

Er du sykemeldt? (Sett ett kryss i hver kolonne)

- ☐ Nei
- ☐ Delvis sykemeldt
- ☐ Fullt sykemeldt

Hvordan er du sykemeldt?

- ☐ Sykemeldt korttids
- ☐ Sykemeldt langtids

OPPVEKST

Hva var din bostedskommune da du ble født, og i hvilke kommuner i Norge har du bodd lengre enn ett år?

Kommune	Fra årstall	Til årstall	*(Ikke skriv her →)*
1 Ved fødsel:			
2			
3			
4			
5			
6			
7			

FAMILIE- OG SPRÅKBAKGRUNN

I Nord-Norge bor det folk med ulik etnisk bakgrunn. Det vil si at de snakker ulike språk og har ulike kulturer. Eksempler på etnisk bakgrunn eller etnisk gruppe er norsk, samisk og kvensk.

Hvilket hjemmespråk har/hadde du, dine foreldre og besteforeldre? (sett ett eller flere kryss)

	Norsk	Samisk	Kvensk	Annet	Vet ikke	Dersom annet beskriv
Morfar	☐	☐	☐	☐	☐	.....
Mormor	☐	☐	☐	☐	☐	.....
Farfar	☐	☐	☐	☐	☐	.....
Farmor	☐	☐	☐	☐	☐	.....
Far	☐	☐	☐	☐	☐	.....
Mor	☐	☐	☐	☐	☐	.....
Jeg selv	☐	☐	☐	☐	☐	.....

Hva er din, din fars og din mors etniske bakgrunn?
(sett ett eller flere kryss)

	Norsk	Samisk	Kvensk	Annet	Vet ikke	Dersom annet beskriv
Min bakgrunn	☐	☐	☐	☐	☐	.....
Mors bakgrunn	☐	☐	☐	☐	☐	.....
Fars bakgrunn	☐	☐	☐	☐	☐	.....

Hva regner du deg selv som? (sett ett eller flere kryss)

Norsk ☐ Samisk ☐ Kvensk ☐ Annet ☐ Dersom annet beskriv .....

SVANGERSKAPET

Var dette svangerskapet planlagt?

☐ Ja ☐ Nei

Dersom JA, hvor mange måneder tok det før du ble gravid?

Antall mnd. ☐☐

Trengte du hjelp til å bli gravid i dette svangerskapet?
(Behandlet for barnløshet; hormonstimulering, IVF, mikroinjeksjon ol.)

☐ Ja ☐ Nei

Dersom JA, hva var årsaken?

.....

Hvilken behandling fikk du da?

.....

MORSMELK SOM BABY

Ammet din mor deg da du var baby?

☐ Ja ☐ Nei

Dersom JA, hvor mange måneder til sammen fikk du morsmelk?

Totalt antall mnd. med morsmelk ☐☐ Vet ikke ☐

SELVOPPLEVD HELSE

Oppfatter du din helse som:

☐ Meget god ☐ God ☐ Dårlig ☐ Meget dårlig

VEKT

Hvor mye veide du før svangerskapet? *(I hele kg)*.... ☐☐☐

Hva var din egen fødselsvekt som nyfødt baby?

(Gram) ☐☐☐☐ Vet ikke ☐

Har du noen gang hatt vekttap på 5 kg eller mer, i så fall hvor mange ganger?

☐ Ja ☐ Nei Antall ganger ☐☐

FYSISK AKTIVITET

Vi ber deg angi din fysiske aktivitet etter en skala fra svært liten til svært mye ved 14 års alder, før svangerskapet og i dag. Skalaen nedenfor går fra 1-10. Med fysisk aktivitet mener vi både arbeid i hjemmet og i yrkeslivet samt trening og annen fysisk aktivitet som turgåing ol.

	Svært lite									Svært mye
Alder	1	2	3	4	5	6	7	8	9	10
14 år.....	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Før svangerskapet.....	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
I dag.....	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

RØYK OG ALKOHOL

Beskriv dine røykevaner før og i dette svangerskapet?
(Sett ett kryss)

	Ikke røyker	Av og til	Daglig
6 mnd før svangerskapet.....	☐	☐	☐
Ved svangerskapets start.....	☐	☐	☐
I dag.....	☐	☐	☐

Dersom du røyker eller har røykt, angi antall pr. dag eller pr uke?

	Antall pr dag	Antallpr uke
6 mnd før svangerskapet.....	☐☐	☐☐
Ved svangerskapets start.....	☐☐	☐☐
I dag.....	☐☐	☐☐

Dersom du røyker daglig eller tidligere har røykt daglig, hvor mange år har du da røykt til sammen? Antall år ☐☐

Er du til daglig utsatt for passiv røyking?

☐ Ja ☐ Nei Antall timer daglig ☐☐

Er du totalavholdskvinne?

☐ Ja ☐ Nei

Hvis NEI, hvor ofte og hvor mye har du drukket før dette svangerskapet?
(sett ett kryss for hver linje)

	aldri/ sjelden	1 pr. mnd.	2-3 pr. mnd.	1 pr. uke	2-4 pr. uke	5-6 pr. uke	1+ pr. dag
Lettøl/cider *(0,5 l)*.....	☐	☐	☐	☐	☐	☐	☐
Øl/rusbrus *(0,5 l)*.....	☐	☐	☐	☐	☐	☐	☐
Vin *(glass)*.....	☐	☐	☐	☐	☐	☐	☐
Brennevin *(drink/shot)*.....	☐	☐	☐	☐	☐	☐	☐
Likør/Hetvin *(glass)*.....	☐	☐	☐	☐	☐	☐	☐

Dersom NEI, hvor ofte og hvor mye har du drukket i dette svangerskapet?
(sett ett kryss for hver linje)

	aldri/ sjelden	1 pr. mnd.	2-3 pr. mnd.	1 pr. uke	2-4 pr. uke	5-6 pr. uke	1+ pr. dag
Lettøl/cider *(0,5 l)*.....	☐	☐	☐	☐	☐	☐	☐
Øl/rusbrus *(0,5 l)*.....	☐	☐	☐	☐	☐	☐	☐
Vin *(glass)*.....	☐	☐	☐	☐	☐	☐	☐
Brennevin *(drink/shot)*.....	☐	☐	☐	☐	☐	☐	☐
Likør/Hetvin *(glass)*.....	☐	☐	☐	☐	☐	☐	☐

TRAN, OMEGA-3 OG FISKEOLJE

Bruker du flytende tran/omega-3/fiskeolje?

☐ Ja ☐ Nei

Hvis JA, hvor ofte tar du flytende tran/omega-3/fiskeolje?
(Sett ett kryss pr. linje)

	aldri/ sjelden	1-3 pr. mnd.	1 pr. uke	2-6 pr. uke	daglig
Om vinteren.....	☐	☐	☐	☐	☐
Resten av året.....	☐	☐	☐	☐	☐

Hvilken type flytende tran/omega-3/fiskeolje bruker du vanligvis, og hvor mye pleier du å ta hver gang?

	1 ts	½ ss	1+ ss
Navn:	☐	☐	☐
Navn:	☐	☐	☐
Navn:	☐	☐	☐

Bruker du kapsler/piller med tran/omega-3/fiskeolje?

☐ Ja ☐ Nei

Hvis JA, hvor ofte tar du kapsler/piller med tran/omega-3/fiskeolje (Sett ett kryss pr. linje)

	aldri/ sjelden	1-3 pr. mnd.	1 pr. uke	2-6 pr. uke	daglig
Om vinteren	☐	☐	☐	☐	☐
Resten av året	☐	☐	☐	☐	☐

Hvilken type kapsler/piller med tran/omega-3/fiskeolje bruker du vanligvis, og hvor mange pleier du å ta hver gang?

Navn ..... Antall ☐

Navn ..... Antall ☐

Navn ..... Antall ☐

KOSTTILSKUDD

Bruker du kosttilskudd?

☐ Ja ☐ Nei

Hvis JA, hvor ofte bruker du kosttilskudd? (Sett ett kryss pr. linje)

Navn på kosttilskudd	aldri/ sjelden	1-3 pr. mnd.	1 pr. uke	2-6 pr. uke	daglig
.....	☐	☐	☐	☐	☐
.....	☐	☐	☐	☐	☐
.....	☐	☐	☐	☐	☐
.....	☐	☐	☐	☐	☐

KOSTHOLD

Påvirker noen av følgende forhold kostholdet ditt?
(Sett om nødvendig flere kryss)

- ☐ Er vegetarianer/veganer
- ☐ Spiser ikke norsk kost til daglig
- ☐ Har allergi/intoleranse
- ☐ Kronisk sykdom
- ☐ Har anoreksi
- ☐ Har bulimi
- ☐ Prøver å gå ned i vekt
- ☐ Lav glykemisk mat

Vi er interessert i å få kjennskap til hvordan kostholdet ditt er vanligvis. Kryss av for hvert spørsmål om hvor ofte du i gjennomsnitt siste året har brukt den aktuelle matvaren, og hvor mye du pleier å spise/drikke hver gang.

DRIKKE

Hvor mange glass melk drikker du vanligvis av hver type?
(Sett ett kryss pr. linje)

	aldri/ sjelden	1-4 pr. uke	5-6 pr. uke	1 pr. dag	2-3 pr. dag	4+ pr. dag
Helmelk *(søt, sur)*	☐	☐	☐	☐	☐	☐
Lettmelk *(søt, sur)*	☐	☐	☐	☐	☐	☐
Ekstra lettmelk	☐	☐	☐	☐	☐	☐
Skummet *(søt, sur)*	☐	☐	☐	☐	☐	☐

Hvor mange kopper kaffe/te drikker du vanligvis av hver sort?
(Sett ett kryss for hver linje)

	aldri/ sjelden	1-6 pr. uke	1 pr. dag	2-3 pr. dag	4-5 pr. dag	6-7 pr. dag	8+ pr. dag
Kokekaffe	☐	☐	☐	☐	☐	☐	☐
Traktekaffe	☐	☐	☐	☐	☐	☐	☐
Pulverkaffe	☐	☐	☐	☐	☐	☐	☐
Presskanne kaffe	☐	☐	☐	☐	☐	☐	☐
Anne kaffe *(latte, espresso ol.)*	☐	☐	☐	☐	☐	☐	☐
Svart te	☐	☐	☐	☐	☐	☐	☐
Grønn te	☐	☐	☐	☐	☐	☐	☐

Bruker du følgende i kaffe eller te:

	Kaffe		Te	
Sukker *(ikke kunstig søtstoff)*	☐ Ja	☐ Nei	☐ Ja	☐ Nei
Melk eller fløte	☐ Ja	☐ Nei	☐ Ja	☐ Nei

Hvor mange glass vann drikker du vanligvis?

	aldri/ sjelden	1-6 pr. uke	1 pr. dag	2-3 pr. dag	4-5 pr. dag	6-7 pr. dag	8+ pr. dag
Springvann/flaskevann	☐	☐	☐	☐	☐	☐	☐

Hvor mange glass juice, saft og brus drikker du vanligvis?
(Sett ett kryss pr. linje)

	aldri/ sjelden	1-3 pr. uke	4-6 pr. uke	1 pr. dag	2-3 pr. dag	4+ pr. dag
Appelsinjuice	☐	☐	☐	☐	☐	☐
Annen juice	☐	☐	☐	☐	☐	☐
Saft/brus med sukker	☐	☐	☐	☐	☐	☐
Saft/brus sukkerfri	☐	☐	☐	☐	☐	☐

YOGHURT/KORNBLANNING

Hvor ofte spiser du yoghurt (1 beger)? (Sett ett kryss)

- ☐ Aldri/sjelden
- ☐ 1 pr. uke
- ☐ 2-3 pr. uke
- ☐ 4+ pr. uke

Hvor ofte spiser du kornblanding, havregryn eller müsli?
(Sett ett kryss)

- ☐ Aldri/sjelden
- ☐ 1-3 pr. uke
- ☐ 4-6 pr. uke
- ☐ 1+ pr. dag

BRØDMAT

Hvor mange skiver brød/rundstykker og knekkebrød/ skonrokker spiser du vanligvis?
(1/2 rundstykke = 1 brødskive) (Sett ett kryss for hver linje)

	aldri/ sjelden	1-4 pr. uke	5-7 pr. uke	2-3 pr. dag	4-5 pr. dag	6+ pr. dag
Grovbrød	☐	☐	☐	☐	☐	☐
Kneip/halvfint	☐	☐	☐	☐	☐	☐
Fint brød/baguett	☐	☐	☐	☐	☐	☐
Knekkebrød o.l.	☐	☐	☐	☐	☐	☐

Nedenfor er det spørsmål om bruk av ulike påleggstyper. Vi spør om hvor mange brødskiver med det aktuelle pålegget du pleier å spise. Dersom du også bruker matvarene i andre sammenhenger enn til brød (f. eks. til vafler, frokostblandinger, grøt), ber vi om at du tar med dette når du besvarer spørsmålene.

På hvor mange brødskiver bruker du? (Sett ett kryss pr. linje)

	aldri/ sjelden	1-3 pr. uke	4-6 pr. uke	1 pr. dag	2-3 pr. dag	4+ pr. dag
Syltetøy	☐	☐	☐	☐	☐	☐
Brunost helfet	☐	☐	☐	☐	☐	☐
Brunost halvfet/mager	☐	☐	☐	☐	☐	☐
Hvitost helfet	☐	☐	☐	☐	☐	☐
Hvitost halvfet/mager	☐	☐	☐	☐	☐	☐
Kjøttpålegg, leverpostei	☐	☐	☐	☐	☐	☐
Rekesalat, italiensk o.l.	☐	☐	☐	☐	☐	☐

På hvor mange brødskiver pr. uke har du i gjennomsnitt siste året spist? (Sett ett kryss pr. linje)

	aldri/ sjelden	1 pr. uke	2-3 pr. uke	4-6 pr. uke	7-9 pr. uke	10+ pr. uke
Makrell i tomat, røkt makrell	☐	☐	☐	☐	☐	☐
Kaviar	☐	☐	☐	☐	☐	☐
Sild/ansjos/sardiner	☐	☐	☐	☐	☐	☐
Laks/ørret *(gravet/røkt)*	☐	☐	☐	☐	☐	☐
Svolværpostei/Lofotpostei	☐	☐	☐	☐	☐	☐
Krabbepålegg	☐	☐	☐	☐	☐	☐
Annet fiskepålegg	☐	☐	☐	☐	☐	☐

Hva slags fett bruker du vanligvis på brødet?

- ☐ Bruker ikke fett på brødet
- ☐ Smør
- ☐ Hard margarin *(f. eks. Per, Melange)*
- ☐ Myk margarin *(f. eks. Soft, Vita, Solsikke)*
- ☐ Smørblandet margarin *(f.eks. Bremyk)*
- ☐ Brelett
- ☐ Lettmargarin *(f. eks. Soft light, Letta, Vita Lett)*
- ☐ Middels lett margarin *(f. eks. Olivero, Omega)*

Dersom du bruker fett på brødet, hvor tykt lag pleier du å smøre på? (En kuvertpakke med margarin veier 12 gram).
(Sett ett kryss)

- ☐ Skrapet (3 g)
- ☐ Tynt lag (5 g)
- ☐ Godt dekket (8 g)
- ☐ Tykt lag (12 g)

FRUKT OG GRØNNSAKER

Hvor ofte spiser du frukt? (Sett ett kryss pr. linje)

	aldri/ sjelden	1-3 pr. mnd.	1 pr. uke	2-4 pr. uke	5-6 pr uke	1 pr dag	2+ pr dag
Epler/pærer	☐	☐	☐	☐	☐	☐	☐
Appelsiner o.l.	☐	☐	☐	☐	☐	☐	☐
Bananer	☐	☐	☐	☐	☐	☐	☐
Annen frukt	☐	☐	☐	☐	☐	☐	☐

Hvor ofte spiser du ulike typer grønnsaker? (Sett ett kryss pr. linje)

	aldri/ sjelden	1-3 pr. mnd.	1 pr. uke	2 pr. uke	3 pr uke	4-5 pr uke	6-7 pr uke
Gulrøtter	☐	☐	☐	☐	☐	☐	☐
Kål	☐	☐	☐	☐	☐	☐	☐
Kålrot	☐	☐	☐	☐	☐	☐	☐
Brokkoli/blomkål	☐	☐	☐	☐	☐	☐	☐
Blandet salat	☐	☐	☐	☐	☐	☐	☐
Tomat	☐	☐	☐	☐	☐	☐	☐
Grønnsakblanding *(frossen)*	☐	☐	☐	☐	☐	☐	☐
Løk	☐	☐	☐	☐	☐	☐	☐
Andre grønnsaker	☐	☐	☐	☐	☐	☐	☐

For de grønnsakene du spiser, kryss av for hvor mye du spiser hver gang: (Sett ett kryss for hver sort):

Gulrøtter *(stk)*	☐ ½	☐ 1	☐ 1 ½	☐ 2+
Kål *(dl)*	☐ ½	☐ 1	☐ 1 ½	☐ 2+
Kålrot *(dl)*	☐ ½	☐ 1	☐ 1 ½	☐ 2+
Brokkoli/blomkål *(buketter)*	☐ 1-2	☐ 3-4	☐ 5+	
Blandet salat *(dl)*	☐ 1	☐ 2	☐ 3	☐ 4+
Tomat *(stk)*	☐ ¼	☐ ½	☐ 1	☐ 2+
Grønnsakblanding *(frossen) (dl)*	☐ ½	☐ 1	☐ 2	☐ 3+

Hvor mange poteter spiser du vanligvis (kokte, stekte, mos)?
(Sett ett kryss)

- ☐ Aldri/sjelden
- ☐ 1-4 pr uke
- ☐ 5-6 pr. uke
- ☐ 1 pr dag
- ☐ 2 pr dag
- ☐ 3 pr dag
- ☐ 4+ pr dag

RIS, SPAGHETTI, GRØT, SUPPE

Hvor ofte bruker du ris og spaghetti/makaroni?
(Sett ett kryss pr. linje)

	aldri/ sjelden	1-3 pr. mnd.	1 pr. uke	2 pr. uke	3+ pr uke
Ris	☐	☐	☐	☐	☐
Spaghetti, makaroni, nudler	☐	☐	☐	☐	☐

Hvor ofte spiser du grøt?
(Sett ett kryss pr. linje)

	aldri/ sjelden	1 pr. mnd.	2-3 pr. mnd.	1 pr. uke	2-6 pr. uke	1+ pr. dag
Risengrynsgrøt	☐	☐	☐	☐	☐	☐
Annen grøt *(havre o.l.)*	☐	☐	☐	☐	☐	☐

Hvor ofte spiser du suppe?
(Sett ett kryss pr. linje)

	aldri/ sjelden	1-3 pr. mnd.	1 pr. uke	2 pr. uke	3+ pr uke
Som hovedrett	☐	☐	☐	☐	☐
Som forrett, lunsj eller kveldsmat	☐	☐	☐	☐	☐

FISK

Vi vil gjerne vite hvor ofte du pleier å spise fisk, og ber deg fylle ut spørsmålene om fiskeforbruk så godt du kan. Tilgangen på fisk kan variere gjennom året. Vær vennlig å markere i hvilke årstider du spiser de ulike fiskeslagene.

	aldri/ sjelden	like mye hele året	vinter	vår	sommer	høst
Torsk, sei, hyse, lyr	☐	☐	☐	☐	☐	☐
Steinbit, flyndre, uer	☐	☐	☐	☐	☐	☐
Laks, ørret	☐	☐	☐	☐	☐	☐
Kveite	☐	☐	☐	☐	☐	☐
Makrell	☐	☐	☐	☐	☐	☐
Sild	☐	☐	☐	☐	☐	☐
Tunfisk *(ikke på boks)*	☐	☐	☐	☐	☐	☐
Ferskvannsfisk (*Abbor, gjedde, røye, sik, harr)*	☐	☐	☐	☐	☐	☐
Annen fisk	☐	☐	☐	☐	☐	☐

Med tanke på de periodene av året der du spiser fisk, hvor ofte pleier du å spise følgende til middag? (Sett ett kryss pr. linje)

	aldri/ sjelden	1 pr. mnd.	2-3 pr. mnd.	1 pr. uke	2+ pr uke
Kokt torsk, sei, hyse, lyr	☐	☐	☐	☐	☐
Stekt torsk, sei, hyse, lyr	☐	☐	☐	☐	☐
Steinbit, flyndre, uer	☐	☐	☐	☐	☐
Laks, ørret	☐	☐	☐	☐	☐
Kveite	☐	☐	☐	☐	☐
Makrell	☐	☐	☐	☐	☐
Sild	☐	☐	☐	☐	☐
Tunfisk *(ikke på boks)*	☐	☐	☐	☐	☐
Ferskvannsfisk (*Abbor, gjedde, røye, sik, harr)*	☐	☐	☐	☐	☐
Annen fisk	☐	☐	☐	☐	☐

Dersom du spiser fisk, hvor mye spiser du vanligvis pr. gang? (1 skive/stykke = 150 gram)

Kokt fisk *(skive)*	☐ 1	☐ 1,5	☐ 2	☐ 3+
Stekt fisk *(stykke)*	☐ 1	☐ 1,5	☐ 2	☐ 3+

Hvor mange ganger pr. år spiser du fiskeinnmat? (Sett ett kryss for hver linje)

	aldri	1-3	4-6	7-9	10-15	16+
Rogn	☐	☐	☐	☐	☐	☐
Fiskelever	☐	☐	☐	☐	☐	☐

Dersom du spiser fiskelever, hvor mange spiseskjeer pleier du å spise hver gang? (Sett ett kryss)

☐ 1 ☐ 2 ☐ 3-4 ☐ 5-6 ☐ 7+

Hvor ofte bruker du følgende typer fiskemat? (Sett ett kryss pr. linje)

	aldri/ sjelden	1 pr. mnd.	2-3 pr. mnd.	1 pr. uke	2+ pr uke
Fiskekaker/pudding/boller	☐	☐	☐	☐	☐
Plukkfisk/fiskegrateng	☐	☐	☐	☐	☐
Frityrfisk/fiskepinner	☐	☐	☐	☐	☐
Andre fiskeretter	☐	☐	☐	☐	☐

Hvor stor mengde pleier du vanligvis å spise av de ulike rettene? (Sett ett kryss for hver linje)

Fiskekaker/pudding/boller *(stk.)* *(2 fiskeboller=1 fiskekake)*	☐ 1	☐ 2	☐ 3	☐ 4+
Plukkfisk, fiskegrateng *(dl)*	☐ 1-2	☐ 3-4	☐ 5+	
Frityrfisk, fiskepinner *(stk.)*	☐ 1-2	☐ 3-4	☐ 5-6	☐ 7+

I tillegg til informasjon om fiskeforbruk er det viktig å få kartlagt hvilket tilbehør som blir servert til fisk.
Hvor ofte bruker du følgende til fisk? (Sett ett kryss pr. linje)

	aldri/ sjelden	1 pr. mnd.	2-3 pr. mnd.	1 pr. uke	2+ pr uke
Smeltet/fast smør	☐	☐	☐	☐	☐
Smeltet/fast margarin/fett	☐	☐	☐	☐	☐
Seterrømme *(35%)*	☐	☐	☐	☐	☐
Lettrømme *(20%)*	☐	☐	☐	☐	☐
Saus med fett *(hvit/brun)*	☐	☐	☐	☐	☐
Saus uten fett *(hvit/brun)*	☐	☐	☐	☐	☐

For de ulike typene tilbehør du bruker til fisk, vær vennlig å kryss av for hvor mye du vanligvis pleier å spise.

Smeltet/fast smør *(ss)*	☐ ½	☐ 1	☐ 2	☐ 3	☐ 4+
Smeltet/fast margarin *(ss)*	☐ ½	☐ 1	☐ 2	☐ 3	☐ 4+
Seterrømme *(ss)*	☐ ½	☐ 1	☐ 2	☐ 3	☐ 4+
Lettrømme *(ss)*	☐ ½	☐ 1	☐ 2	☐ 3	☐ 4+
Saus med fett *(dl)*	☐ ¼	☐ ½	☐ ¾	☐ 1	☐ 2+
Saus uten fett *(dl)*	☐ ¼	☐ ½	☐ ¾	☐ 1	☐ 2+

Hvor mange ganger i året spiser du hval-/selkjøtt? (Sett ett kryss)

aldri	1-3	4-6	7-9	10-15	16+
☐	☐	☐	☐	☐	☐

Hvor mange ganger i året spiser du det brune kjøttet i krabbe (utenom krabbepålegg)? (Sett ett kryss)

aldri	1-3	4-6	7-9	10-15	16+
☐	☐	☐	☐	☐	☐

Hvor mange ganger i året spiser du andre skalldyr (reker og skjell)? (Sett ett kryss)

aldri	1-3	4-6	7-9	10-15	16+
☐	☐	☐	☐	☐	☐

Hvor mange måseegg eller egg fra annen sjøfugl spiser du i året? (Sett ett kryss)

aldri	1-3	4-6	7-9	10-15	16+
☐	☐	☐	☐	☐	☐

KJØTT

Hvor ofte spiser du følgende viltprodukter? (Sett ett kryss pr. linje)

	aldri/ sjelden	1 pr. mnd.	2-3 pr. mnd.	1 pr. uke	2-3 pr. uke	4+ pr. uke
Reinkjøtt	☐	☐	☐	☐	☐	☐
Andre matvarer fra rein *(lever, nyre, margebein, hjerte, tunge, blod og annet)*	☐	☐	☐	☐	☐	☐
Elgkjøtt, andre matvarer fra elg	☐	☐	☐	☐	☐	☐
Rype, annen viltfugl	☐	☐	☐	☐	☐	☐

Hvor ofte spiser du følgende kjøtt- og fjærkreretter? (Sett ett kryss for hver rett)

	aldri/ sjelden	1 pr. mnd.	2-3 pr. mnd.	1 pr. uke	2+ pr uke
Steik *(okse, svin, får)*	☐	☐	☐	☐	☐
Koteletter	☐	☐	☐	☐	☐
Biff	☐	☐	☐	☐	☐
Kjøttkaker, karbonader	☐	☐	☐	☐	☐
Pølser	☐	☐	☐	☐	☐
Gryterett, lapskaus	☐	☐	☐	☐	☐
Pizza med kjøtt	☐	☐	☐	☐	☐
Kylling	☐	☐	☐	☐	☐
Bacon, flesk	☐	☐	☐	☐	☐
Innmat får/storfe	☐	☐	☐	☐	☐
Andre kjøttretter	☐	☐	☐	☐	☐

Dersom du spiser følgende retter, oppgi mengden du vanligvis spiser: (Sett ett kryss for hver linje)

Steik *(skiver)*	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5+
Koteletter *(stk.)*	☐ ½	☐ 1	☐ 1 ½	☐ 2+	
Kjøttkaker, karbonader *(stk)*	☐ 1	☐ 2	☐ 3	☐ 4+	
Pølser *(stk à 150g)*	☐ ½	☐ 1	☐ 1 ½	☐ 2+	
Gryterett, lapskaus *(dl)*	☐ 1-2	☐ 3	☐ 4	☐ 5+	
Pizza m/kjøtt *(stykke à 100 g)*	☐ 1	☐ 2	☐ 3	☐ 4+	

Hvilke sauser bruker du til kjøttretter og pastaretter?
(Sett ett kryss pr. linje)

	aldri/ sjelden	1 pr. mnd.	2-3 pr. mnd.	1 pr. uke	2+ pr uke
Brun saus	☐	☐	☐	☐	☐
Sjysaus	☐	☐	☐	☐	☐
Tomatsaus	☐	☐	☐	☐	☐
Saus med fløte/rømme	☐	☐	☐	☐	☐

Hvor mye bruker du vanligvis av disse sausene?
(Sett ett kryss for hver linje)

Brun saus *(dl)*	☐ ¼	☐ ½	☐ ¾	☐ 1	☐ 2+
Sjysaus *(dl)*	☐ ¼	☐ ½	☐ ¾	☐ 1	☐ 2+
Tomatsaus *(dl)*	☐ ¼	☐ ½	☐ ¾	☐ 1	☐ 2+
Saus med fløte/rømme *(dl)*	☐ ¼	☐ ½	☐ ¾	☐ 1	☐ 2+

ANDRE MATVARER

Hvor mange egg spiser du vanligvis i løpet av en uke (stekte, kokte, eggerøre, omelett)? (Sett ett kryss)

☐ 0 ☐ 1 ☐ 2 ☐ 3-4 ☐ 5-6 ☐ 7+

Hvor ofte spiser du iskrem (til dessert, Krone-is osv.)?
Sett ett kryss for hvor ofte du spiser iskrem om sommeren, og ett kryss for resten av året

	aldri/ sjelden	1 pr. mnd.	2-3 pr. mnd.	1 pr. uke	2+ pr uke
Om sommeren	☐	☐	☐	☐	☐
Resten av året	☐	☐	☐	☐	☐

Hvor mye is spiser du vanligvis pr. gang? (Sett ett kryss)

☐ 1 dl ☐ 2 dl ☐ 3 dl ☐ 4+ dl

Hvor ofte spiser du bakevarer som boller, kaker, wienerbrød eller småkaker? (Sett ett kryss pr. linje)

	aldri/ sjelden	1-3 pr. mnd.	1 pr. uke	2-3 pr. uke	4-6 pr. uke	1+ pr. dag
Gjærbakst *(boller ol.)*	☐	☐	☐	☐	☐	☐
Wienerbrød, kringle	☐	☐	☐	☐	☐	☐
Kaker	☐	☐	☐	☐	☐	☐
Pannekaker	☐	☐	☐	☐	☐	☐
Vafler	☐	☐	☐	☐	☐	☐
Småkaker, kjeks	☐	☐	☐	☐	☐	☐
Lefser, lomper	☐	☐	☐	☐	☐	☐

Hvor ofte spiser du dessert? (Sett ett kryss pr. linje)

	aldri/ sjelden	1 pr. mnd.	2-3 pr. mnd.	1 pr. uke	2-3 pr. uke	4+ pr. uke
Pudding sjokolade/karamell	☐	☐	☐	☐	☐	☐
Riskrem, fromasj	☐	☐	☐	☐	☐	☐
Kompott, fruktgrøt, hermetisk frukt	☐	☐	☐	☐	☐	☐
Jordbær *(friske, frosne)*	☐	☐	☐	☐	☐	☐
Andre bær *(friske, frosne)*	☐	☐	☐	☐	☐	☐

Hvor ofte spiser/drikker du ville bær, inkludert syltetøy og saft? (Ikke industrifremstilt)? (Sett ett kryss pr. linje)

	aldri/ sjelden	1 pr. mnd.	2-3 pr. mnd.	1 pr. uke	2-3 pr. uke	4+ pr. uke
Multebær	☐	☐	☐	☐	☐	☐
Tyttebær	☐	☐	☐	☐	☐	☐
Blåbær	☐	☐	☐	☐	☐	☐
Krøkebær	☐	☐	☐	☐	☐	☐
Andre bær	☐	☐	☐	☐	☐	☐

Hvor ofte spiser du selvplukket sopp? (Sett ett kryss pr. linje)

aldri/ sjelden	1 pr. mnd.	2-3 pr. mnd.	1 pr. uke	2-3 pr. uke	4+ pr. uke
☐	☐	☐	☐	☐	☐

Hvor ofte spiser du sjokolade? (Sett ett kryss pr. linje)

	aldri/ sjelden	1-3 pr. mnd.	1 pr. uke	2-3 pr. uke	4-6 pr. uke	1+ pr. dag
Mørk sjokolade	☐	☐	☐	☐	☐	☐
Lys sjokolade	☐	☐	☐	☐	☐	☐

Dersom du spiser sjokolade, hvor mye pleier du vanligvis å spise hver gang? Tenk deg størrelsen på en Kvikk-Lunsj sjokolade, og oppgi hvor mye du spiser i forhold til den.

☐ ¼ ☐ ½ ☐ ¾ ☐ 1 ☐ 1 ½ ☐ 2+

Hvor ofte spiser du snacks? (Sett ett kryss pr. linje)

	aldri/ sjelden	1-3 pr. mnd.	1 pr. uke	2-3 pr. uke	4-6 pr. uke	1+ pr. dag
Potetchips	☐	☐	☐	☐	☐	☐
Peanøtter	☐	☐	☐	☐	☐	☐
Andre nøtter	☐	☐	☐	☐	☐	☐
Annen snacks	☐	☐	☐	☐	☐	☐

VARM MAT

Hvor mange ganger i løpet av en måned spiser du varm mat?

Til frokost ____ Til middag ____
Til lunch ____ Til kvelds ____

KOSTHOLD GJENNOM ULIKE LIVSFASER

Det kan være vanskelig å huske eksakt hva du har spist gjennom tiden, men fyll ut sånn omtrent.

Hvor ofte har du spist fisk? (Sett ett kryss pr. linje)

	aldri/ sjelden	1 pr. mnd.	2-3 pr. mnd.	1 pr. uke	2-3 pr. uke	4+ pr. uke
Barndom	☐	☐	☐	☐	☐	☐
Ungdom 13-19	☐	☐	☐	☐	☐	☐
Voksen *(før siste året)*	☐	☐	☐	☐	☐	☐

Når du har spist fisk, hvor ofte har du da spist fet fisk (laks, ørret, kveite, makrell, sild, ål)? (Sett ett kryss pr. linje)

	aldri/ sjelden	1 pr. mnd.	2-3 pr. mnd.	1 pr. uke	2-3 pr. uke	4+ pr. uke
Barndom	☐	☐	☐	☐	☐	☐
Ungdom 13-19	☐	☐	☐	☐	☐	☐
Voksen *(før siste året)*	☐	☐	☐	☐	☐	☐

Når du har spist fisk, hvor ofte har du da spist ferskvannsfisk (abbor, gjedde, røye, sik, harr)? (Sett ett kryss pr. linje)

	aldri/ sjelden	1 pr. mnd.	2-3 pr. mnd.	1 pr. uke	2-3 pr. uke	4+ pr. uke
Barndom	☐	☐	☐	☐	☐	☐
Ungdom 13-19	☐	☐	☐	☐	☐	☐
Voksen *(før siste året)*	☐	☐	☐	☐	☐	☐

Hvor ofte har du spist fiskepålegg (Makrell, sild, ansjos, sardiner, røkt eller gravet laks/ørret, kaviar, fiskeleverpostei (Lofotpostei, Svolværpostei) krabbepålegg)?
(Sett ett kryss pr. linje)

	aldri/ sjelden	1 pr. mnd.	2-3 pr. mnd.	1 pr. uke	2-3 pr. uke	4-6 pr. uke	Daglig
Barndom	☐	☐	☐	☐	☐	☐	☐
Ungdom 13-19	☐	☐	☐	☐	☐	☐	☐
Voksen *(før siste året)*	☐	☐	☐	☐	☐	☐	☐

Hvor mange ganger i året har du spist fiskelever?
(Sett ett kryss pr. linje)

	aldri	1-3	4-6	7-9	10-15	16+
Barndom	☐	☐	☐	☐	☐	☐
Ungdom 13-19	☐	☐	☐	☐	☐	☐
Voksen *(før siste året)*	☐	☐	☐	☐	☐	☐

Hvor mange ganger i året har du spist hval-/selkjøtt?
(Sett ett kryss pr. linje)

	aldri	1-3	4-6	7-9	10-15	16+
Barndom	☐	☐	☐	☐	☐	☐
Ungdom 13-19	☐	☐	☐	☐	☐	☐
Voksen *(før siste året)*	☐	☐	☐	☐	☐	☐

Hvor mange ganger i året har du spist det brune kjøttet i krabbe (utenom krabbepålegg)? (Sett ett kryss pr. linje)

	aldri	1-3	4-6	7-9	10-15	16+
Barndom	☐	☐	☐	☐	☐	☐
Ungdom 13-19	☐	☐	☐	☐	☐	☐
Voksen *(før siste året)*	☐	☐	☐	☐	☐	☐

Hvor mange måseegg eller egg fra annen sjøfugl har du spist i året? (Sett ett kryss pr. linje)

	aldri	1-3	4-6	7-9	10-15	16+
Barndom	☐	☐	☐	☐	☐	☐
Ungdom 13-19	☐	☐	☐	☐	☐	☐
Voksen *(før siste året)*	☐	☐	☐	☐	☐	☐

Hvor ofte i nevnte livsfaser har du tatt tilskudd av tran/ omega-3/fiskeolje (flytende/kapsler/piller)?
(Sett ett kryss pr. linje)

	Aldri	1-3 pr. mnd.	1 pr. uke	2-6 pr. uke	Daglig
Barndom vinter	☐	☐	☐	☐	☐
Barndom resten av året	☐	☐	☐	☐	☐
Ungdom 13-19 vinter	☐	☐	☐	☐	☐
Ungdom 13-19 resten av året	☐	☐	☐	☐	☐
Voksen vinter *(før siste året)*	☐	☐	☐	☐	☐
Voksen resten av året *(før siste året)*	☐	☐	☐	☐	☐

BARNEFAR

I forbindelse med sammenligning av ultralydmål, er det viktig å ha noen opplysninger om far til barnet i dette svangerskapet:

Hva var barnefars fødselsvekt som nyfødt baby?
(Gram) ☐☐☐☐ Vet ikke ☐

Hva er barnefars høyde i dag? *(cm)* ☐☐☐ Vet ikke ☐

Hvilket hjemmespråk har/hadde barnefar, hans foreldre og hans besteforeldre? (sett ett eller flere kryss)

	Norsk	Samisk	Kvensk	Annet	Vet ikke	Dersom annet beskriv
Morfar	☐	☐	☐	☐	☐	
Mormor	☐	☐	☐	☐	☐	
Farfar	☐	☐	☐	☐	☐	
Farmor	☐	☐	☐	☐	☐	
Far	☐	☐	☐	☐	☐	
Mor	☐	☐	☐	☐	☐	
Barnefar	☐	☐	☐	☐	☐	

Hva er barnefars, hans fars og hans mors etniske bakgrunn?
(sett ett eller flere kryss)

	Norsk	Samisk	Kvensk	Annet	Vet ikke	Dersom annet beskriv
Barnefars bakgrunn	☐	☐	☐	☐	☐	
Mors bakgrunn	☐	☐	☐	☐	☐	
Fars bakgrunn	☐	☐	☐	☐	☐	

Hva regner barnefar seg selv som? (sett ett eller flere kryss)

Norsk	Samisk	Kvensk	Annet	Vet ikke	Dersom annet beskriv
☐	☐	☐	☐	☐	

ANGÅENDE SPØRSMÅLENE

Var noen av spørsmålene vanskelige eller nærgående? Hvis ja oppgi hvilke spørsmål og evt. kommentarer.

☐ Ja ☐ Nei

Andre kommentarer:

Takk for hjelpen!

Navn _____

ID ☐

Fødseldato for barnet ☐

Spørsmålene omhandler kun barnet du fødte da du var med i miljøgiftsprosjektet (kalles her for prosjektbarnet).

Kontroll miljøgiftsprosjektet 6 uker etter fødselen

Dato ☐

Uker etter fødselen ☐

Hvor mange måneder har du til sammen ammet tidligere barn (før prosjektbarnet ble født)?

Barn	Født (årstall)	Måneder Kun amming	Måneder Amming + tillegg/grøt	Måneder Total ammelengde
1				
2				
3				
4				

Ammestatus for prosjekt-barnet ved miljøgiftskontrollen 6 uker etter fødselen

- Kun amming ☐
- Amming + morsmelkserstatning ☐
- Ammet ikke barnet, fikk morsmelkserstatning ☐

DERSOM prosjekt-barnet har fått morsmelkserstatning:
Hvor mye erstatning har barnet fått inntil miljøgiftskontrollen 6 uker etter fødselen

- Kun fått morsmelkserstatning 1-2 ganger ☐
- Fått erstatning flere enn 2 ganger, men ikke daglig ☐
- Fått erstatning daglig, men mindre enn en flaske daglig ☐
- Fått erstatning, 1-2 flasker daglig ☐
- Fått erstatning, 3-4 flasker daglig ☐
- Fått kun erstatning, aldri fått morsmelk ☐

Dersom du for prosjekt-barnet, har avsluttet amming før 6 ukers miljøgiftskontrollen, hvor mange uker var barnet da?

Barnet var ☐ uker

Hvis du aldri har ammet, skriv null (0) på uker

Telefon ☐ slik at vi kan nå deg om noe er uklart

Dato for utfylling av skjema ☐

Eventuelle kommentarer skrives på baksiden av arket

Dersom du er i tvil om noen spørsmål, ber vi deg om å ta kontakt med oss: Telefon 920 69 700

Tusen takk for hjelpen!

Navn _____

ID [ ]

Fødseldato for barnet [ ]

Spørsmålene omhandler kun barna du fødte før du var med i miljøgiftsprosjektet (kalles her for prosjektbarnet).

Hvor mange måneder har du til sammen ammet tidligere barn (før prosjektbarnet ble født)?

Barn	Født (årstall)	**Måneder** Kun amming	**Måneder** Amming + tillegg/grøt	**Måneder** Total ammelengde
1				
2				
3				
4				

Telefon [ ] slik at vi kan nå deg om noe er uklart

Dato for utfylling av skjema [ ]

Dersom du er i tvil om noen spørsmål, ber vi deg om å ta kontakt med oss: Telefon 920 69 700

Eventuelle kommentarer skrives her:

Tusen takk for hjelpen!

Universitetet i Tromsø
Romssa universitehta

Forskningsprosjektet
Miljøgifter i svangerskapet og i ammeperioden

Tromsø, den 21. oktober 2009

Kjære NN

Først vil vi takke deg for at du har deltatt i prosjektet "Miljøgifter i svangerskapet og i ammeperioden". Vi er ferdig med å samle inn data og har begynt å analysere resultatene. Men dessverre viser det seg, at vi ikke har innhentet tilstrekkelig med spørsmål vedrørende ammingen.

Fordi kvinner skiller ut en del av forurensende stoffer gjennom morsmelken, må vi vite din ammestatus for å kunne analysere nivåene av miljøgifte i blodet. Når vi skal beskrive nivået på miljøgifter vi undersøker for, må vi derfor ta hensyn til om du har ammet, delvis ammet eller ikke ammet i det hele tatt.

Vi spør deg derfor om å svare på vedlagte skjema og returnere det til oss snarest mulig i den vedlagte konvolutten. Alle opplysningene vil bli behandlet uten navn. Skjema er forelagt Den regionale komité for medisinsk og helsefaglig forskningsetikk (REK Nord).

Har du noen spørsmål angående dette, så ikke nøl med å ta kontakt på telefon: 920 69 700 eller send e-post til en av oss:

solrunn.hansen@uit.no eller anna.sofia.veyhe@uit.no

Igjen mange takk for hjelpen, og vi beklager bryderiet.

Med vennlig hilsen

Solrunn Hansen
prosjektkoordinator