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The Northern Norway Mother-and-Child Contaminant Cohort Study (MISA):

Population Characteristics, Dietary Intake and Predictors of Organochlorine Contaminants in Meconium and Maternal Serum, and of Essential and Toxic Elements in Mothers' Whole Blood

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Anna Sofía Veyhe

A dissertation for the degree of Philosophiae Doctor – Month 20xx

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One small anecdote during my graduate work was when one of my children did not know where mom was. "Well, the options are Norway, Sweden, Denmark or maybe Russia, but we can reach her on Skype". This has been a journey for all of us. We have lived as a cyber-family, from eating breakfast together to writing important school essays over the internet.

SUMMARY

Persistent Organic Pollutants (POPs) and toxic elements are released into the environment and are carried to the Arctic area *via* the atmosphere, oceanic currents and rivers. They have the ability to accumulate in nature and bioconcentrate in the human food chain. The primary exposure route for these contaminants is through diet, and thus circulating levels in pregnant women can give an indication of the potential risk to the developing fetus. Within countries and internationally, guidelines for safe daily intakes and for concentrations in serum or whole blood have been established to avoid health effects of POPs and toxic inorganic elements. In this context, the rationale for the MISA study was to assess exposure to a suite of environmental pollutants by women during pregnancy and to six weeks postpartum, as well of the unborn/ newborn children. Through a detailed questionnaire information was obtained on food intake (past and present), lifetime residency, education, income and other sociodemographic data, obstetrical history and pregnancy outcome.

The specific aim of the thesis was to explore the links between maternal diet and selected personal and obstetrical characteristics with concentrations of PCBs (and hydroxylated metabolites) and organochlorine (OC) pesticides in maternal serum and in newborn first stool, as well as with a selection of essential and toxic metals in maternal whole blood.

Of the 515 enrolled women, 391 completed the study protocol that included a self-administrated food frequency questionnaire (FFQ) and donation of biological samples for analyses. The FFQ information was converted into daily intake of energy, micro- and macro-nutrients. Findings were compared to a drop-out group (n = 113) and, when possible, to all delivering women from Northern Norway registered in the Medical Birth Registry of Norway (MBRN) for 2004-2006. Women who completed the study protocol were on average two years older and smoked less compared to all delivering women from Northern Norway and the drop-out group, while other characteristics were comparable between all groups including parity, gestational age, birth weight and selected obstetrical parameters and complications. Dietary intake was less than recommended by the Nordic Nutritional Recommendations (NNR), but nutrient density in terms of intake of micronutrients per mega joule (MJ) complied well. Only minor differences in dietary intake occurred between the study cohort and the drop-out group.

The entire MISA cohort (n = 498) was characterized for sources and predictors of POPs using principal component analysis (PCA), while for the elements alone it involved 279 participants, and for all the POPs and elements data combined n = 498. The PCA for the combined group revealed three prominent axes (i.e., new variables) with robust loadings of: (i) all POPs; (ii) arsenic (As), mercury (Hg) and selenium (Se); and (iii) cadmium (Cd) and lead (Pb). In the multivariable linear regression models, the major predictors identified were as follows: age, parity and consumption of fish and local traditional foods for new variable (i); marine fish for (ii); and cigarette smoking, consumption of grains & cereals, and local foods based on hunting for variable (iii). The PCA analysis of the POPs alone separated the contaminants in two new distinct groups, namely PCBs *plus p,p'*-DDE and the other OC pesticides measured. This grouping was interpreted to reflect different longitudinal trends and the relative contributions (respectively major/minor) to the sum of all POPs.

Meconium proved to be useful for measuring fetal exposure to pesticides, PCBs and hydroxylated PCBs. Multivariable linear regression analyses confirmed that maternal serum was the most consistent predictor of meconium concentrations, with gestational age and time of meconium sampling improving the models. Although lipid determinations in meconium is analytically challenging, when comparing lipid-adjusted OC concentrations in meconium and in maternal serum the correlation between them was enhanced, as well as the fractional change in concentrations in meconium per unit change in maternal serum. Our measurement of hydroxylated PCBs in meconium constitutes novel information, and lipid-adjusted OC concentrations in meconium are viewed as a sensitive and informative fetal exposure index.

It is evident that maternal serum concentrations of pesticides, PCBs and hydroxylated PCBs were generally low compared to results from other countries, but comparable to findings from Norway. It is concluded that they are not of clinical importance, and thus were of no special concern to the study participants. Similarly, the observed concentrations of essential elements in maternal whole blood may be considered normal in the clinical chemistry context and those for the toxic elements are judged to be relatively low and of no clinical concern.

Nevertheless, the MISA study provides an opportunity to follow-up the development of the children, and it is recommended to include measurement of the body burdens of the most prominent POPs, toxic and essential elements examined in the current study, as well as any new environmental toxins.

SAMMENDRAG

Tungt løselige organiske miljøgifter og giftige metaller slippes ut i miljøet hvorpå de fraktes til Arktiske strøk via luft, havstrømmer og elver. De har evne til å akkumulere i naturen og oppkonsentreres derfor i næringskjeden. Av denne grunn ansees kosten som den viktigste eksponeringsveien. Miljøgiftsnivåer målt i blodprøver hos gravide kvinner kan således gi en indikasjon på den mulige risikoen for fosterets utvikling. Både lokalt og internasjonalt finnes retningslinjer for tolerabelt daglig inntak av både giftige organiske-og uorganiske forbindelser, samt nivåer av disse i blodet som kan gi negative helseeffekter. Dette er bakgrunnen og begrunnelsen for forskningsprosjektet *Miljøgifter i svangerskap og i ammeperioden* (MISA-studien), der vi har vurdert eksponering for en rekke miljøgifter hos kvinner under graviditeten og etter fødselen, samt hos deres nyfødte barn. Gjennom et detaljert spørreskjema ble kvinnene bedt om å oppgi matinntak (tidligere og nåværende), bosted siden fødsel, utdanning, inntekt og andre sosiodemografiske data, obstetrisk historie og svangerskapsutfall. I tillegg donerte både mor og det nyfødte barnet biologiske prøver til analyser.

Hovedformålet med avhandlingen var å undersøke sammenhengen mellom mors kosthold og utvalgte svangerskapsutfall, med vekt på konsentrasjoner av forskjellige persistente organiske miljøgifter (POPer) som PCB (polyklorerte bifenyler), hydroksylerte PCB-metabolitter og pesticider i mors serum og i den første avføring fra nyfødte (mekonium), samt et utvalg av essensielle og giftige elementer i mors fullblod.

Av de 515 kvinnene som deltok i prosjektet fullførte 391 studieprotokollen som innebar at de alle hadde besvart spørreskjema, inkludert kostholdskartlegging, samt avlevert biologisk materiale for kjemiske analyser. Kostholdet ble vurdert ut fra daglig inntak av næringsstoffer, hvor både mikro- og makro-næringsstoffer ble beregnet. Resultatene for de 391 kvinnene som fullførte, ble sammenlignet med gruppen som ikke fullførte studie protokollen (drop-out; n =113). En sammenligning ble også gjort med alle fødende kvinner fra Nord-Norge registrert i Medisinsk fødselsregister (MFR) i perioden 2004-06. MISA-kvinner som fullførte studien var i gjennomsnitt to år eldre og røkte mindre i forhold til både drop-out gruppen og fødende kvinner fra Nord-Norge. Mens obstetriske utfall, som for eksempel paritet, svangerskapslengde, fødselsvekt og ulike fødselskomplikasjoner, var sammenlignbare for alle tre grupper. Kostinntaket var mindre enn anbefalt av Nordiske kostanbefalinger (NNR), men næringsstoffinntak per mega joule (MJ) (nutrient density) passet godt til gjeldende

anbefalinger. Kun små forskjeller i kostholdet mellom kvinnene som fullførte studien og drop-out gruppen ble observert.

Hele MISA kohorten, i alt 498 kvinner, ble analysert for kilder og prediktorer til ved hjelp av Principal Component Analysis (PCA). Analysen for essensielle og giftige elementer involverte 279 deltakere, og for alle POPer og elementer kombinert n = 266 deltakere. PCA analysen for den kombinerte gruppen avdekket tre prominente akser (dvs. nye variabler) med robuste utfall for: (i) alle POPer; (ii) arsen (As), kvikksølv (Hg) og selen (Se); og (iii) kadmium (Cd) og bly (Pb). De multivariable lineære regresjonsmodellene viste følgende tydelige prediktorer: alder, paritet og inntak av fisk og lokale tradisjonelle matvarer for (i); marin fisk for (ii); røyking, inntak av kornprodukter og lokal tradisjonell mat basert på jakt for (iii). PCA analysen som kun inkluderte POPer delte forurensningsstoffene i to nye separate grupper, nemlig PCB og *p, p′*-DDE i én og de andre pesticidene i den andre gruppen. Denne grupperingen ble tolket til å gjenspeile ulike langsgående trender og det relative bidraget (henholdsvis større/mindre) til summen av alle miljøgifter.

Mekonium viste seg å være anvendelig for å måle fosterets eksponering for pesticider, PCB og hydroksylerte PCBer. Multivariabel lineær regresjonsanalyse bekreftet at mors serum var den klareste prediktoren for konsentrasjoner i mekonium, men når svangerskapslengde og tidspunkt for prøvetaking av mekonium ble inkludert i modellen, ble den klarere. Lipid-bestemmelse av mekonium er analytisk utfordrende. Ved å sammenligne lipid-justerte konsentrasjoner i mekonium og i mors serum, ble korrelasjonen mellom dem klarere, likeså endringen av mekoniumskonsentrasjonen per enhet relatert til endring i mors serum. Målinger av hydroksylerte PCBer i mekonium er ikke utført tidligere, og lipidjusterte konsentrasjoner i mekonium blir sett på som en god og informativ eksponeringsindikator for fosteret.

Studien konkluderer med at mors serumkonsentrasjon av pesticider (sprøytemidler), PCB og hydroksylerte PCBer generelt var lave sammenlignet med resultater fra andre land, men tilsvarende funn fra andre norske studier. Det konkluderes med at lave konsentrasjoner er uten klinisk betydning og gir dermed ikke særskilt bekymring for deltagerne i studien. Likeledes kan de observerte konsentrasjonene av essensielle elementer (sporstoffer) i mors fullblod ansees normale i klinisk sammenheng. De giftige metallene vurderes å være forholdsvis lave og har ingen klinisk betydning for den enkelte deltaker i studien. Derimot er det nødvendig å følge opp nivåer av giftige metaller og eventuelle nye giftstoffer i forhold til barnas utvikling. MISA-studien gir muligheter for slik oppfølging.

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KEY ISSUES AND OVERVIEW OF THE THESIS

Thesis context

- There are man-made chemicals in the environment that stay around for a long time and some accumulate along the human food chain and ultimately end up in our bodies. They are released into nature from industrial and agricultural processes and installations, and undergo long-range transport by way of oceanic currents, rivers and air. The Artic regions of the world have been and remain a primary recipient. International bans and regulations have helped to reduce their use and the amounts released into the environment.

- Two groups of persistent organic pollutants (short form is POPs) that are part of the focus of the current study are made up of carbon, hydrogen and chlorine. They are referred to as organochlorines (OCs) and include pesticides (e.g., DDT) and the industrial chemicals called polychlorinated hydrocarbons (or PCBs in shorthand). Because they stay around in our bodies for a long time (measured in years), they are said to be persistent and are also toxic. In the current study, the levels of these compounds are measured in maternal serum and in the first stools (meconium) of newborn babies.

- A third group of toxic chemicals that is somewhat less persistent in our bodies (but still measured in months or years), gets into the human food chain or accumulates in specific foods; it includes the toxic metals cadmium, mercury, and lead. We analysed maternal blood samples for these inorganic elements. Arsenic, a toxic non-metal, is also included in this group even though its turnover in the body is considerably quicker (expressed in days).

- A fourth group of inorganic elements was also quantified in whole blood, namely copper, manganese, molybdenum, selenium and zinc. They are naturally present in our food, are required for good health (they are essential!), are less persistent and thus need to be replenished. Therefore it is important to know their levels in our bodies.

- The POPs are stored in our fat tissues and the elements are distributed to all tissues, or accumulate in specific organs such as the kidney (e.g., cadmium) or in our bones (e.g., lead).

Thesis introduction

- The introduction begins by providing the rationale of the The Northern Norway Mother-and-Child Contaminant Cohort Study [in Norwegian: Miljøgifter i svangerskapet og i ammeperioden (the MISA study)], of which the work described in this thesis is part. A map of northern Norway identifies the locations of the delivery/antenatal centres that participated in the study.

- The following topics are systematically introduced/reviewed: the usefulness of a food frequency questionnaire in obtaining pertinent dietary and personal information; basics of fetal development and placental transfer; background information on POPs, namely of PCBs and prominent OC pesticides, as well as their transport routes to the Arctic; POPs in the Norwegian environment; human exposure and potential health effects of POPs; dietary sources and roles of the essential elements measured; sources of the toxic elements and their potential effects on health; and dominant pathways to the Arctic of mercury are illustrated.

Aims of the research

- Summarize the dietary intake in pregnant women in Northern Norway.
- Identify associations between dietary intake and maternal serum concentrations of PCBs and organochlorine (OC) pesticides, as well as for essential and toxic metals in maternal whole blood.
- Quantify selected OC pesticides, PCBs and phenolic metabolites of the latter in meconium, and identify factors that influence their concentrations in this medium.
- Enhance understanding of the mother-to-fetus transfer of OCs.

Experimental details in brief

- We investigated the relationship between the measured pollutants in the blood of pregnant women in Northern Norway and their food intake during the previous 12 months. For 130 different food items, we asked the mothers to record how often they ate them during the last year/month/week or day. For some food groups they were also requested to record the size of the meal. When all the data was electronically available, we converted the frequency to "grams per day" intake for all the food items identified. In addition, the women recorded personal information such as places of living, education and work, smoking and drinking habits, ethnical background and dietary supplement intake. We also asked how often they had eaten various seafood products during childhood, as teenagers and as adults. In addition, we gathered information about previous and present pregnancies. This included obtaining pregnancy health record and information from the Medical Birth Registry of Norway.
- Apart from providing dietary and pregnancy information, the women also donated blood and urine samples in the middle of the pregnancy and at 3 days and 6 weeks postpartum (their blood pressure and body weight were also measured). At delivery a hair sample was taken from the mother, as well as umbilical cord blood and a meconium sample from the newborn. Only the maternal blood taken at the first collection and the meconium samples were analysed for the work described in this thesis.

- Complicated instruments, namely a gas chromatograph and a mass spectrometer, were employed respectively to separate and determine the concentrations of the OCs in maternal serum and meconium. The analysis of the elements in whole blood involved a high resolution mass spectrometer. Maternal serum and meconium analyses of POPs were carried out at the Norwegian Institute for Air Research (NILU), Fram Centre, Tromsø, while those of the elements were conducted by the National Institute of Occupational Health (NIOH), Oslo. The statistical analyses of the data were carried out by the candidate.

- Routine statistical analysis techniques were supplemented by an approach labelled "Principal Component Analysis", which allowed the generation of new combined variables (referred to as axes) of the observed contaminant, inorganic elements (toxic and essential) concentrations and dietary consumption data to enhance interpretations of our findings.

Main results

- Brief and concise summaries are provided for the 3 publications, which summarize the findings of the research and related conclusions. Shortened versions are given below.

- *Paper I.* The estimated daily caloric intake of 8.1 MJ per day was less than recommended by the Nordic Nutritional Recommendations (NNR), but nutrient intake per MJ (nutrient density) was in good compliance with the NNR. Furthermore, the MISA database was judged suitable for investigating relationships between contaminant exposures and diet.

- *Paper II*. Although its analysis provided a technical challenge, meconium was shown to be a sensitive and informative index of fetal exposure, although gestational age and sampling time needs to be taken into consideration. Lipid adjustment of the concentrations seems essential. The evidence suggests that the biochemical modification of OCs (referred to as hydrolysis or adding water, which yields hydroxyl PCBs among other products) occurs primarily in the mother.

- *Paper III*. The statistical technique referred to as "Principal Component Analyses" not only enhanced our understanding of the inter-relationships of contaminants, but also among the food items consumed by the MISA study group. The linear combinations of variables generated by PCA identified prominent dietary sources of OC groups and of well-known toxic elements, and highlighted the importance of maternal characteristics.

Discussion

- The observed concentrations of OCs and inorganic elements are compared with values published by researchers worldwide and those provided in preliminary MISA-related publications.

- Maternal age, parity, maternal body mass index (BMI), consumption of fish and other marine products, local traditional foods, vegetables and grain & dairy products and lifestyle issues are shown to contribute to the total variation explained in the observed OC concentrations in maternal serum. It is concluded that fish and seafood products are the major contributors.

- The observed grouping of As, Hg and Se in whole blood are indicated to correspond well with other findings from Norway and elsewhere and reflects seafood intake.

- It is stated that there is no doubt that the primary source of cadmium was cigarette smoking. Women living inland were highly represented in the 4th quartile of the whole blood lead concentrations, and higher intake of local terrestrial foods is suggested as a potential source since game hunted with lead shot is a proven source of this toxic metal.

- The levels of the essential metals are judged to be in the normal range.

- The findings for OCs and the inorganic elements are discussed in the context of related data reported by other investigators, and food intake advisories and known health issues.

- The new 'fruits and vegetables' variable is considered to have a positive dependence on age, while that representing 'junk food' did not.

- Meconium is judged to be a sensitive and informative fetal exposure index for OCs when taking into account gestational age and its postpartum sampling time. Lipid adjustment of OC concentrations in meconium appears to be important.

- The study limitations and strengths are discussed in some detail.

Concluding Remarks

- Maternal serum concentrations of pesticides, PCBs and hydroxylated PCBs are discerned to be generally low compared to results from other countries, but comparable to findings from Norway (including data on pregnant women). It is concluded that they are not of clinical importance, and thus are of no heightened concern to pregnant women, the unborn, females of reproductive age and children in the study group.

- The current investigation of meconium as a biological medium for determining fetal exposure to POPs is identified to be the first to report the presence of hydroxylated PCBs in newborn stool. Although analytically challenging, a small subset of 15 meconium samples was adjusted for lipids and the latter is viewed as a crucial component for using meconium as an informative fetal exposure medium.

- The observed concentrations of cadmium, lead and mercury in whole blood are considered relatively low, but some concern remains about maternal and neonatal exposures to Cd among cigarette-smoking mothers and for the participants with Hg blood values near the maximum values observed. Since the total arsenic measured in blood primarily represents its non-toxic organic forms and was present in relatively low concentrations, toxicity concerns are not warranted. No deficiency nor excess was observed for the essential elements, which reflects adequate dietary intake.

- Generation of new variables for contaminant, inorganic elements and dietary variables by "Principle Component Analysis" facilitates the ability to identify prominent dietary sources and maternal predictors of PCBs and OC pesticides in maternal serum, and of the prominent toxic elements As, Cd, Pb and Hg and the essential element Se in maternal whole blood.

LIST OF PAPERS

The thesis is based on the following three papers, which are referred to by their Roman numerals in this dissertation.

I. The Northern Norway mother-and-child contaminant cohort study: implementation, population characteristics and summary of dietary findings.
Veyhe AS, Hansen S, Sandanger TM, Nieboer E, Odland JØ.
Int J Circumpolar Health. 2012;71:18644. doi: 10.3402/ijch.v71i0.18644

II. Is meconium useful to predict fetal exposure to organochlorines and hydroxylated PCBs?
Veyhe AS, Nøst TH, Sandanger TM, Hansen S, Odland JØ, Nieboer E.
Environ Sci Process Impacts. 2013 Aug;15(8):1490-500. doi: 10.1039/c3em00132f

III. The Northern Norway mother-and-child contaminant cohort study: PCA analyses of environmental contaminants in maternal sera and dietary intake in early pregnancy.
Veyhe AS, Hofoss D, Hansen S, Thomassen Y, Sandanger TM, Odland JØ, Nieboer E.
Int J Hyg Environ Health. 2015 Mar;218(2):254-64. doi: 10.1016/j.ijheh.2014.12.001

ABBREVIATIONS

4-OH-HpCs	4-Hydroxyheptachlorostyrene;
AGA	Appropriate for gestational age
AM	Arithmetic mean
AMAP	Arctic Monitoring and Assessment Programme
ANOVA	Analysis of variance
AR	Average requirement
As	Arsenic
BMI	Body mass index
BP	Blood pressure
BW	Body weight
Cd	Cadmium
CI	Confidence interval
cis-NC	*cis*-Nonachlor
Co	Cobalt
Cu	Copper
DDE	Dichlorodiphenyldichloroethylene
DDT	Dichlorodiphenyltrichloroethane
DHA	Docosahexaenoic acid
EOM	Extractable organic material
ESI	Electronic supplementary information
FC	Free cholesterol
FFQ	Food frequency questionnaire
Gest.	Gestational
GM	Geometric mean
HCB	Hexachlorobenzene
HCH	Hexachlorocyclohexane
Hg	Mercury
IARC	International Agency of Research on Cancer
LGA	Large for gestational age
LI	Lower level of intake
LOD	Limit of Detection
Max	Maximum
MBRN	Medical Birth Registry of Norway
MeHg	Methyl mercury
MFR	[Medisinsk fødselsregister]
Min	Minimum
MISA	[Miljøgifter i svangerskapet og i ammeperioden]
mg	Milligram
MJ	Mega joule
Mn	Manganese
Mo	Molybdenum
MW	Mann-Whitney

µg	Microgram
NC	Nonachlor
NILU	Norwegian Institute for Air Research
NIOH	National Institute of Occupational Health
NIPH	National Institute of Public Health
NNR	Nordic Nutritional Recommendations
NOWAC	The Norwegian Women and Cancer study
NS	Non-significant
n-3 PUFA	n-3 polyunsaturated fatty acid
OC(s)	Organochlorine(s)
OH-PCB(s)	Hydroxylated polychlorinated biphenyl(s)
Pb	Lead
PCA	Principal component analysis
PCB(s)	Polychlorinated biphenyl(s)
PCP	Pentachlorophenol
PKU	Phenylketonuria
PL	Phospholipids
POP(s)	Persistent organic pollutant(s)
PUFA	Polyunsaturated fatty acid
p	*p′*-DDE
p	*p′*-DDT
PP	Postpartum
QA/QC	Quality assurance and quality control
r	Pearson's correlation coefficient
RI	Recommended intake
SD	Standard deviation
Se	Selenium
TC	Total cholesterol
TG	Triglycerides
trans-NC	*trans*-Nonachlor
TL	Total lipids
T2DM	Type 2 diabetes mellitus
UL	Tolerable upper intake level
Zn	Zinc
α-HCH	Alpha-hexachlorocyclohexane
β-HCH	Beta-hexachlorocyclohexane
γ-HCH	Gamma-hexachlorocyclohexane
κ	Kappa score
ρ	Spearman's rho coefficient

1. INTRODUCTION

1.1. Rationale for and history of MISA

Persistent organic pollutants (POPs) and toxic inorganic elements are recognised to be responsible for adverse developmental and other health effects in children (Grandjean et al., 1997; Odland et al., 1999; Saint-Amour et al., 2006; Plusquellec et al., 2007). Most of these contaminants are transferred from the mother to the foetus *via* the umbilical cord, and to the child by way of the mother's breast milk (Rudge et al., 2009; Needham et al., 2011; Vizcaino et al., 2014). Contaminant concentrations in maternal blood during pregnancy can give an indication of the potential risk to the developing foetus (Odland et al., 1999; Fängström et al., 2005; Heilmann et al., 2010). Of particular concern are subtle long-term effects that might influence reproductive health, pregnancy outcomes, reduce defences against diseases, affect children's mental development, or increase the life-time risk of cancer (Grandjean et al., 1997; ATSDR, 2000; Debes et al., 2006; Heilmann et al., 2010; Halling et al., 2013).

Several multidisciplinary international projects have been conducted to determine the concentrations of POPs and toxic inorganic elements in people of different geographical regions, and to investigate if there is a possible relationship between specific body burdens of these chemicals and health. One of the most prominent is the Arctic Monitoring and Assessment Programme (AMAP), which started in 1991 and has eight arctic countries as active members (Canada, Denmark, Finland, Iceland, Norway, Russia and Sweden and the USA) (AMAP, 2003; AMAP, 2009). The early Norwegian study locations have focused on Finnmark and, by the mid-2000s, no systematic information was available about mothers and their newborn babies residing in the coastal counties of Nordland and Troms. Information from other parts of Norway had demonstrated the possibility of high levels of mercury and POPs in individuals with a high dietary intake of fish (Jenssen et al., 2012; Rylander et al., 2012; Birgisdottir et al., 2013).

Late in 2006, Professor Jon Øyvind Odland at UiT The Arctic University of Norway made plans, and subsequently obtained funding, for establishing a new study cohort. The goal was to measure concentrations of environmental contaminants in expecting mothers (and in their new babies) who lived in the three most northern counties of Norway, namely Nordland, Troms and Finnmark (see Figure 1). A primary objective was to explore exposure through food intake, as well as examining the influence of maternal anthropometric and

socioeconomic factors. During the period May 2007 to June 2009, women in early pregnancy were invited to participate in The Northern Norway Mother-and-Child Contaminant Cohort Study [in Norwegian: Miljøgifter i svangerskapet og i ammeperioden (the MISA study)]. Solrunn Hansen and I (both practising midwives) carried out and administered the project. We established contact and interacted with personnel at the various delivery units, and ensured that the project materials and equipment were available at all sampling units. Appropriate instructions about the project's procedures and protocols were provided, and ongoing project developments were shared. We were also responsible for the processing of all clerical forms and biological samples, constructing the databases, and employing and training 3 qualified individuals to conduct the data-entry. During the entire sampling period, we were we available around the clock by phone and e-mail. Research technician Bente A. Augdal was responsible for the Biobank and assisted with the project's logistics. The laboratories that conducted the analytical work were the Norwegian Institute for Air Research (NILU), Tromsø, Norway (quantification of a suite of organochlorine contaminants in maternal sera and meconium) and the National Institute of Occupational Health (NIOH), Oslo, Norway (determination of a selection of toxic and essential elements in maternal whole blood).

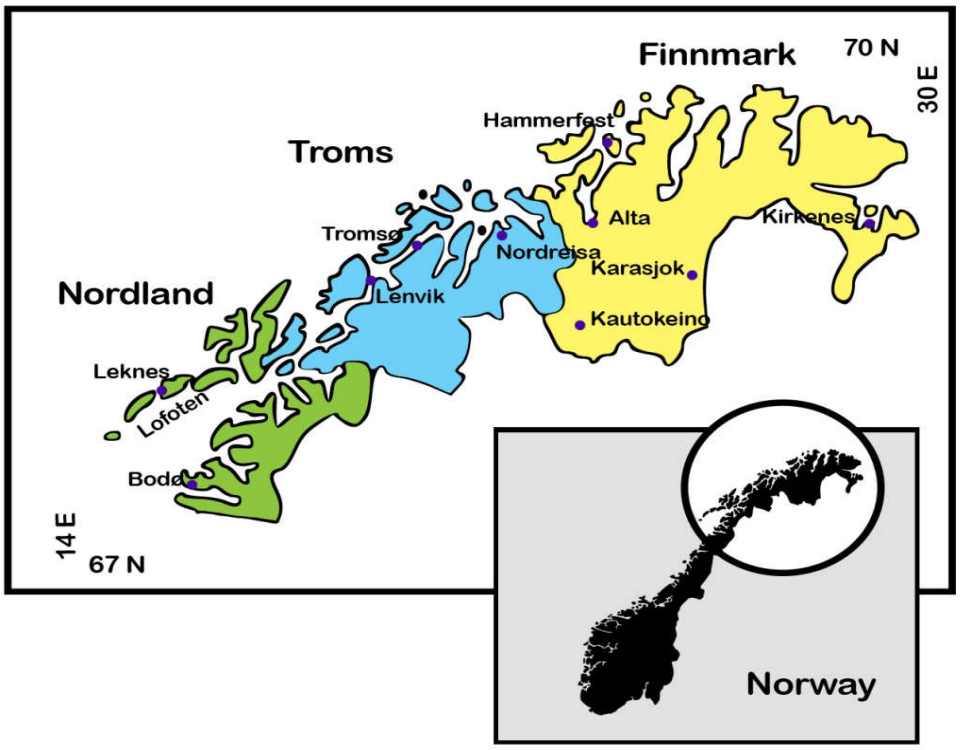

Figure 1. Location of study area, including delivering units and antenatal centres. (Reprinted with permission from Paper III)

1.2. Dietary assessment

1.2.1. Food frequency questionnaires

Diet is the most important predictor of human exposure to POPs and toxic inorganic elements (AMAP, 2009), and for this reason assessing dietary intake is essential as well as determining what dietary assessment method to employ. Methods frequently used are the 24-hour or 48-hour recall, or dietary diaries that record intake on certain days (Willett, 2013). Another research method often used is the food frequency questionnaire (FFQ). Its underlying principle is the possibility to capture information about a long-term diet that permits the calculation of average dietary intakes over a period of weeks, months or years (the duration must be determined beforehand). The food items included should be consumed reasonably often by the study group, but at the same time vary from person-to-person. In this context, frequency of use appears to be more important than portion size (Willett, 2013). Willett also recommends that the appropriate number of food items should not exceed 130. The FFQ approach allows the estimation of the respondent's usual food intake, as well as the possibility of ranking individuals according to their usual consumption of food items or groups of foods and, if portion size estimates are included, nutrient intake. Other important advantages for the participants are self-administration and reduced time requirement compared to other dietary assessment methods. In addition, this approach also keeps the research costs down compared to 24-hour recall and food diaries for example (Thompson and Byers, 1994).

However, the FFQ also has weaknesses. It only captures average intake and therefore some details of the diet may be lost for the specified study period. In addition, quantifying the intake has its challenges and this may reduce accuracy. Long FFQs tend to encourage overestimation of intake, while underestimation is more likely for short FFQs (Thompson and Byers, 1994).

1.2.2. Dietary advice for pregnant women in Norway

Pregnant women in Norway are advised to eat healthy foods and to have a varied diet, which includes details about the intake of certain vitamins and which foods to avoid. Women planning a new pregnancy are advised to take 400µg per day of folic acid until gestational week 12, and 10µg per day of vitamin D during the entire pregnancy. Minerals and micronutrients such as calcium, iron, vitamin B12 and iodine are considered to be taken in through a normal diet, and the use of supplements are only recommended after consultation

with health-care personnel. Pregnant women are urged to avoid eating more than two meals of fatty fish per week including salmon, trout, mackerel and herring (VKM, 2014), and to abstain from foods rich in toxic elements (especially mercury) and OCs. This includes fresh water fish like pike, perch > 25 cm, and trout and char > 1 kg; as well as marine products such as seal, crab meat, shark, halibut > 3 kg, fresh tuna (tinned tuna is considered safe), and fish liver (Matportalen, 2015). In January 2013, the Norwegian Food Safety Authority withdrew the recommendation that pregnant women should refrain from eating whale meat (Matportalen, 2013) in the context of the low mercury concentrations detected in Minke Whale (*Balaenoptera scutorostrata*).

In Norway, consumption of fish and fish products is high compared to other European countries (except Spain and Italy). This pertains especially to lean fish as main meals and use of fish-bread spread, as bread is a staple of the Norwegian diet (VKM, 2014). Fish intake is encouraged except for the species specifically stated earlier (Matportalen, 2015). Although still prevalent, fish consumption has declined over the last few decades. This pertains especially to young women who consume less fish compared to the general public (Brantsæter et al., 2012). Nevertheless, the Norwegian Scientific Committee for Food Safety report on fish and other seafood intake in Norway in 2006 indicates that these were higher in Northern Norway compared to the rest of the country. In the 2014 update, there was no indication that changes in individual fish consumption patterns had occurred in the interim (VKM, 2006; VMK, 2014).

The dietary advice discussed so far focuses on minimizing intake of certain food items to avoid consuming undesired components. However, declining seafood consumption can lead to insufficient intake of essential n-3 polyunsaturated fatty acids (n-3 PUFAs), as well as of nutrients essential for fetal development of the retina and brain (Cheatham et al., 2011; Harris and Baack, 2015). Furthermore, maternal plasma levels of docosahexaenoic acid (DHA) have been associated with brain maturation and cognitive development in newborn infants in the context of memory, speed of processing (which is related to sleep patterns), language and visual acuity (Cheatham et al., 2011). There are also indications of reduced risk of allergy in neonates when the mother takes omega 3 PUFA supplements (Miles and Calder, 2015). Other findings related to maternal deficiency of omega 3 fatty acids are low birth weight, risk of preterm birth and preeclampsia (Stotland et al., 2014).

1.3. Fetal development and placental transfer

1.3.1. Fetal development

A full-term pregnancy normally lasts for 280 days or 40 weeks, when calculated from the first day of the last menstrual cycle, and thus includes the pre-conceptional period until fertilization, and from fertilization to birth (Cunningham et al., 2010). Organogenesis during the prenatal period is generally divided into embryonic (gestational weeks 1-10), fetal (gestational weeks 11-28) and perinatal (gestational weeks 29-40) stages (Cunningham et al., 2010; Ross, 2011).

The neural tube and primitive vessels are the first fetal organs developed in organogenesis. Vasculogenesis begins 16 days after conception, and a functional circulatory system is present by day 21 (Rhodes et al., 2011). At this time, fetal blood vessels in the chorionic villi appear which subsequently develop into placenta. In the fourth week, the cardiovascular system has formed and circulation is established in the embryo and between the embryo and the chorionic villi (Cunningham et al., 2010).

During the fourth week, the primitive gut is formed and the development of the gastrointestinal tract is complete at approximately eight weeks of gestation (Ross, 2011). Swallowing begins at 10 to 12 weeks, coincident with the ability of the small intestine to undergo peristalsis and the development of transport capability. Much of the water in swallowed fluid is absorbed, and unabsorbed matter moves to the lower colon. About 800 mg of soluble protein is ingested daily late in pregnancy by the fetus (Cunningham et al., 2010). The first meconium appears in the fetal intestine at approximately week 12, and accumulates throughout gestation. It is composed primarily of water (72 % - 80 %), and it contains lipids, blood group substances, enzymes, salts, vernix caseosa and bile acids. Under normal circumstances, meconium is not excreted until postpartum. Large concentrations of bile pigments excreted by the biliary tract from the fourth month onward give meconium its green colour (Glantz and Woods, 2004).

Organogenesis of the liver develops from the third to fourth week of gestation on, and basic functional units are recognized during the 2nd and 3rd month. Hepatocytes perform various metabolic functions, including detoxification of drugs and toxins. However, their scope in early development is not fully understood. Assessments of plasma half-lives of drugs in newborns and adults indicate that the cytochrome P-450 activity in the fetus and newborn

remains considerably lower than that in adult liver. Based on biotransformation and elimination studies, caffeine has been shown to have a plasma half-life of 100 hours in newborns, compared to 6 hours in adults (Frank, 2011; Lobritto, 2011; Chemtob, 2011). For the toxicant dioxin, metabolic elimination does not appear to occur in infants and children while it does in adults – with respective half-lives of 0.4 y (infant) and 9.5 y in a 40-y old adult (Kreuzer et al., 1997).

1.3.2. Placental transfer

Placental development starts at the time of implantation in the uterine cavity. This occurs around 6 to 7 days after conception, and continues throughout the pregnancy with a concomitant increase in uteroplacental blood flow (up to 40-fold during the course of a normal singleton pregnancy) (Frank, 2011; Rhodes et al., 2011; Rosenfeld, 2011). In the first trimester, placental growth is more rapid than that of the fetus. Around 17 weeks of the postmenstrual cycle, the placental weight is nearly equal to that of the fetus and approximately one sixth of it at term (Cunningham et al., 2010). Concomitantly maternal placental blood flow continues to increase throughout pregnancy, which is believed to reflect vasodilation (Rosenfeld, 2011). For some compounds, the placenta functions as a barrier and thereby protects against the transfer of xenobiotics from the mother to the fetus; for others, it can facilitate their passage (Figure 2) (Syme et al., 2004).

A major function of the placenta is to transfer nutrients and oxygen from the mother to the fetus and it also assists in the removal of fetal waste products to the mother (Plonait and Nau, 2011). Fetal nutrient demands increase during pregnancy and eventually exceeds that of the placenta. Increased expression or activity of transporters likely accounts for the more efficient uptake of nutrients (Jones et al., 2011). Nearly all drugs cross the placenta, although the extent does depend on their molecular and physicochemical properties. Drug transfer is facilitated by lipid solubility and a low degree of ionization (i.e., absence of charged forms) (Chemtob, 2011). Furthermore, lipid-soluble drugs are more easily absorbed in newborns than in older children (Chemtob, 2011). Apart from lipid solubility, polarity, molecular weight, and to some degree binding to plasma proteins, the rate of placental transfer may be limiting (Syme et al., 2004; Plonait and Nau, 2011). Drugs with a molecular weight below 500 are readily transferred across the placenta (Plonait and Nau, 2011), mostly by passive diffusion (Myllynen et al., 2005); as do lipid-soluble pesticides and PCBs of comparable molecular

weights (ATSDR, 2000; ATSDR, 2002; ATSDR, 2013). Vizcaino et al. (2014) suggests that active transfer can occur as well.

Since the human placenta contains multiple enzyme systems, the transfer of foreign chemicals can be modified by metabolism in the placenta. However, such enzymatic activities are usually relatively low compared with those of the maternal or fetal liver (see Figure 2) (Syme et al., 2004).

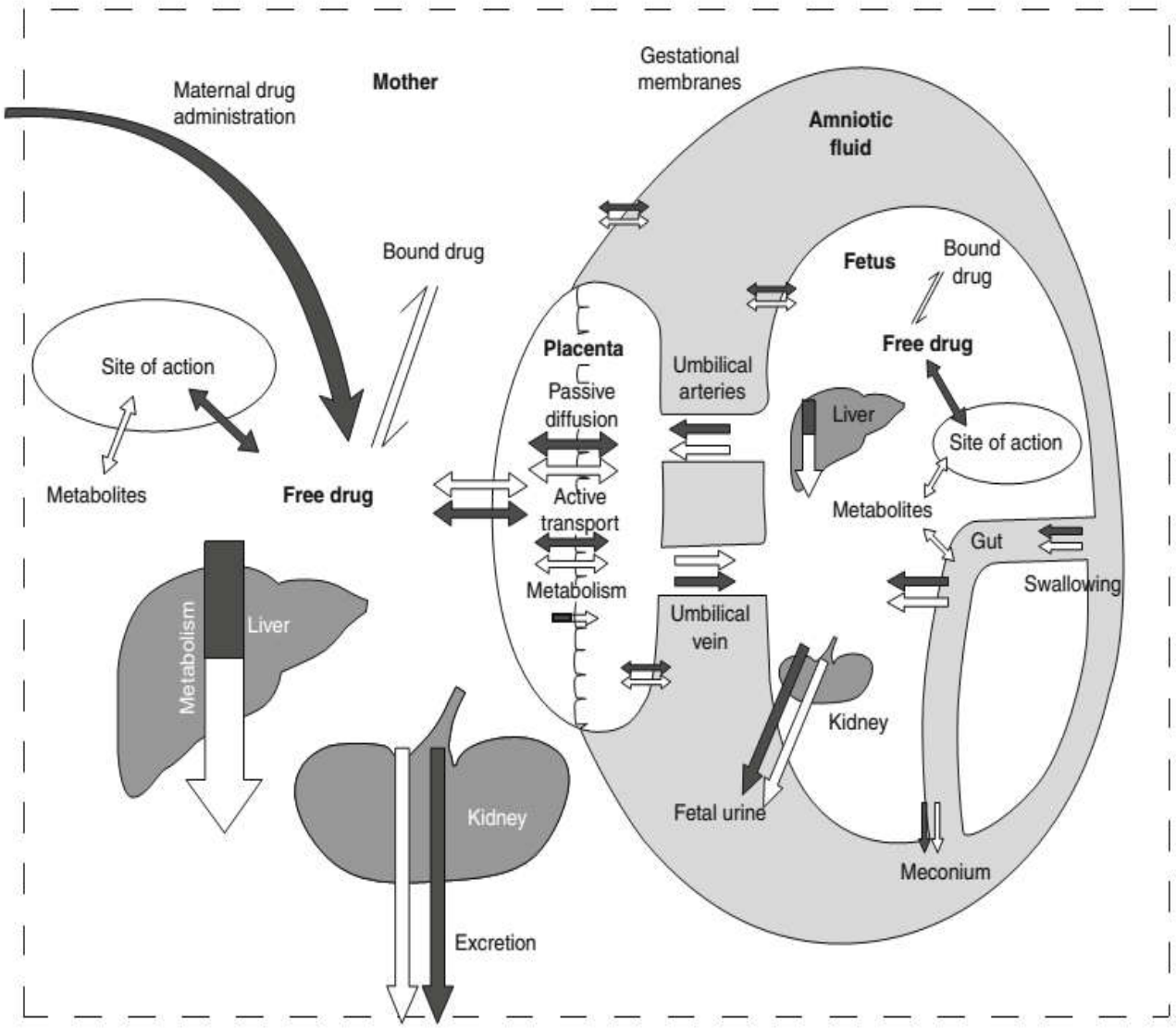

Figure 2. Drug disposition in mother and foetus after maternal drug administration. A variety of pharmacokinetic variables, including transplacental transport and metabolism, determine the degree of maternal-to-fetal drug transfer and fetal drug exposure. Black arrows represent parent the drug and white arrows represent its metabolites. The size of the arrows approximates relative importance, although this is drug-dependent and will vary during pregnancy with fetal and placental maturation. (Reprinted with permission from Syme et al., 2004)

1.4. Persistent organic chemicals

POPs are man-made chemicals including pesticides have been released into the environment during the 20th century. Generally speaking (e.g., ATSDR, 2000/addendum 2011; ATSDR, 2008), these compounds are inert (i.e., resistant to degradation, including thermal stability), have low volatility, and are relatively insoluble in water but freely soluble in nonpolar organic solvents (i.e., are lipophilic). Because of their toxicity and environmental bioaccumulation properties, the production and use of POPs were regulated under the Stockholm Convention in 2004 (European Union, 2004).

1.4.1. Polychlorinated biphenyls

Polychlorinated biphenyls (PCBs) belong to a broad family of man-made organic chemicals known as chlorinated hydrocarbons, and consists of two benzene rings with the chemical formula $C_{12}H_{(10-n)}Cl_n$ (n is the number of chlorine atoms, usually 1-10). Around 200 PCB congeners are possible, but only about 130 of these were likely to have been present in commercial products (UNEP, 1999; EFSA, 2010; EPA, 2013). Due to their non-flammability, chemical stability and high boiling points, PCBs were used in industrial and commercial applications including: electrical and heat transfer and hydraulic equipment, plasticizers, paints, plastics, and rubber products (ATSDR, 2000). Although the manufacture of PCB was banned in 1979 (EPA, 2013), due to their environmental persistence these compounds biomagnify and bioaccumulate in the animal (and of course human) food chain as illustrated in Figure 3.

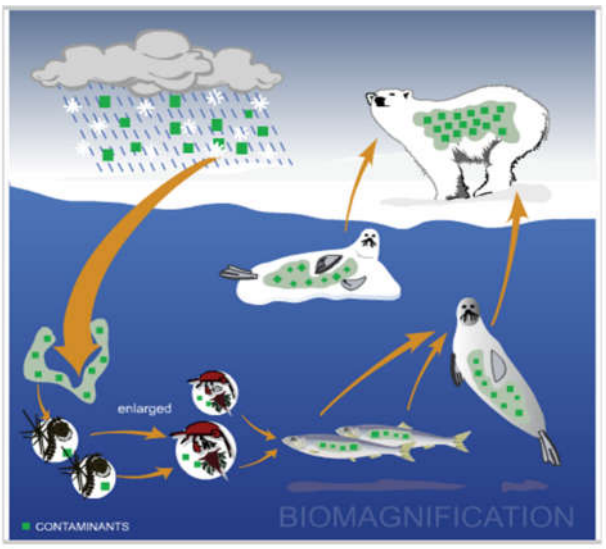

Figure 3. Animals in higher levels of the food chain consume large quantities from the lower levels.

If lower levels have accumulated contaminants, the contaminants will become more concentrated in higher levels.

(Reprinted with permission from Inuit Tapiriit Kanatami; https://www.itk.ca/)

The Stockholm convention has listed the PCBs in Annex A (which aims to eliminate production and use of chemicals) and Annex C ("parties must take measures to reduce the *unintentional releases* of chemicals"; Stockholm Convention, 2004). The consequence of banning PCB production has been a decline in human tissues levels (AMAP, 2009). In Norway ongoing monitoring of sediments, fish and zooplankton have demonstrated decreasing levels prior to 2000, although during the last ten years this decline has levelled off (Miljøstatus, 2014b). As demonstrated in cross-sectional studies, PCB concentrations increase with age in humans due to bioaccumulation. However, a Norwegian birth cohort study of males has demonstrated that serum concentrations across the 1979-2007 sampling period declined (Nøst et al., 2013). This reflects the impact of the Stockholm Convention ban.

In humans, PCBs are biotransformed to hydroxylated forms (OH-PCB) *via* cytochrome P450-mediated oxidation processes (Fängström et al., 2002; Dirtu et al., 2010). Even the most persistent PCBs in the environment, such as PCB 153, are biotransformed *in vitro* and *in vivo* into such metabolites (Dirtu et al., 2010). The OH-PCB metabolites are generally more hydrophilic than the parent compounds, and therefore are more easily eliminated from the body by way of the faeces and/or urine (AMAP, 2009).

1.4.2. Organochlorine pesticides

These chemicals include insecticides, herbicides, fungicides and disinfectants and have the features of being environmentally persistent and accumulation in human tissues.

p,p'-Dichlorodiphenyldichloroethylene (p,p'-DDE)

p,p'-DDE is the primary metabolite of dichlorodiphenyltrichloroethane (DDT). Compared to its parent compound this metabolite is more stable, and it too is considered toxic. DDT was widely used during World War II to protect soldiers and civilians from malaria, typhus and other diseases spread by insects (Stockholm Convention, 2009). Its use continued after the war in controlling agricultural insects that cause diseases such as malaria (ATSDR, 2002). DDT was banned in the United States in 1972 because of its potential harm to wildlife and humans (ATSDR, 2002). In 2007, 147 countries worldwide committed to follow the recommendations of the Stockholm Convention regarding the use of DDT, which according to Annex B now allows restricted production and use in disease vector control (Stockholm Convention, 2004; WHO, 2011). DDT protects against malaria and, not surprisingly, 11

countries in the WHO African and South-East Asian regions in 2013 reported the use of DDT as an indoor residential spray (WHO, 2014).

Hexachlorobenzene (HCB)

HCB is a fungicide used in seed treatment and is a by-product of the manufacture of industrial chemicals. In the Stockholm Convention (2004), this compound is listed under both Annex A and Annex C. Although commercial production ended in the late 1970s, some HCB continues to be produced as a by-product in the manufacture of or impurity in chlorinated solvents and other chlorinated compounds (ATSDR, 2013). HCB is one of the most persistent environmental pollutants. It is practically insoluble in water, but is soluble in fat, oils, and organic solvents (ATSDR, 2013).

Chlordane

Chlordane is a broad-spectrum insecticide. Technical chlordane is a mixture of compounds of which the *cis* and *trans* chlordane forms (i.e., stereoisomers that have different spatial orientation of its chlorine atoms) predominate. It is very resistant to degradation and has high bioaccumulation potential (ATSDR, 1994). These pesticides have been listed under Annex A of the Stockholm Convention (Stockholm Convention, 2004).

1.5. Global transport

Analyses of sediments, animal and human tissues have detected levels of OCs far from their manufacturing and primary use sites. This implies transport of these compounds to distant locations, as documented in the vast monitoring programme carried out in the Arctic area (AMAP, 2004). Figure 4 depicts how oceanic currents, river flows and winds move towards the Arctic area and illustrates that these contaminants can be delivered to remote places by air, river and ocean currents.

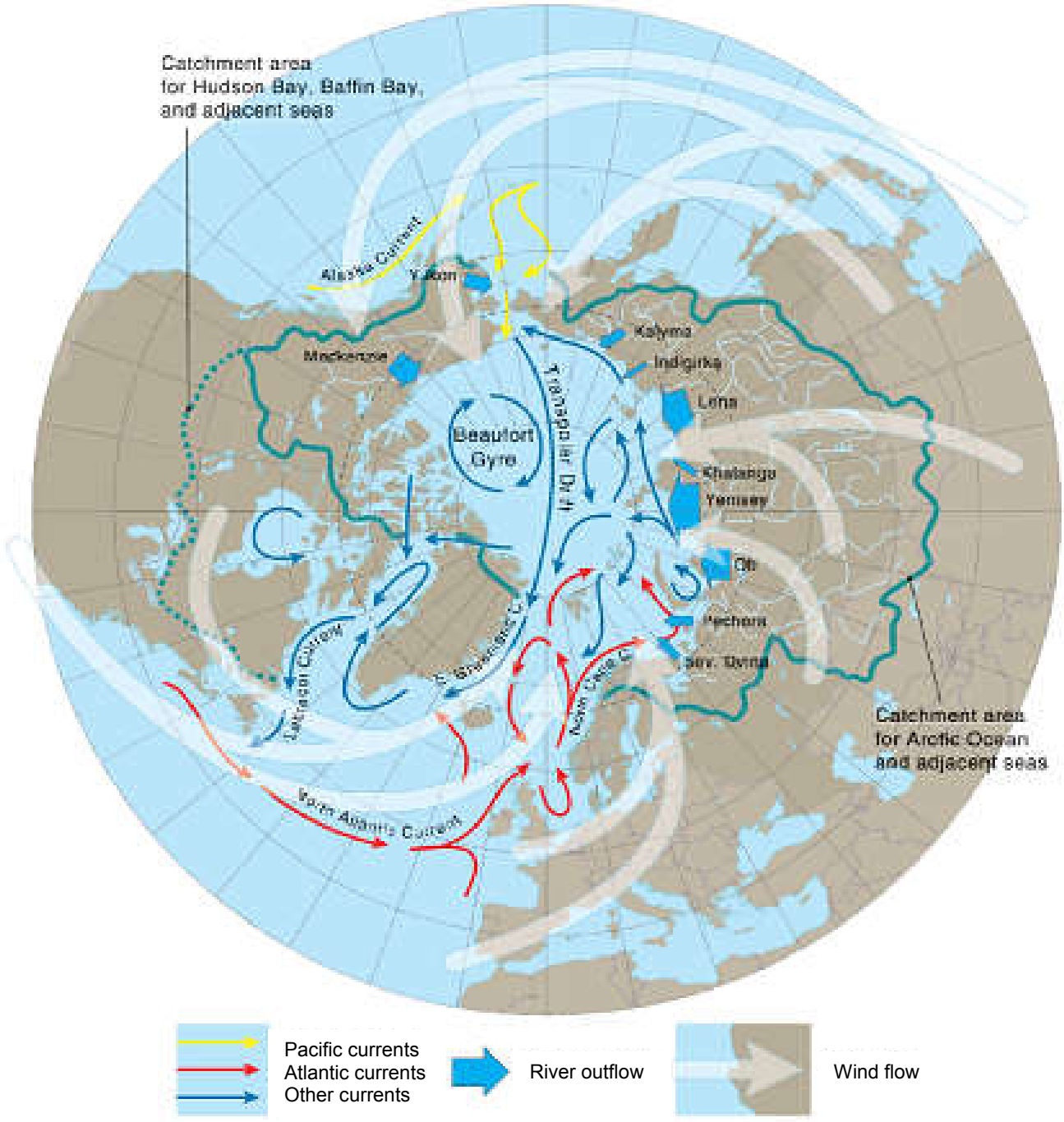

Figure 4. Transport routes for pollutants from distant places towards the Arctic region. (Reprinted with permission from AMAP, 2004)

Once in the Arctic, contaminants can either remain unchanged, or can undergo chemical or physical state changes. Their transport, uptake and metabolic degradation are all influenced by the physical, chemical and biotransformation processes mentioned above (AMAP, 2009). How climate change influences these processes and impacts the environment (including humans) is not fully understood.

1.6. POPs detected in the Norwegian environment

Organochlorines, like PCB, DDT and dioxins have been and continue to be detected in Norwegian lakes, although their concentrations are generally low. Long-distant transport appears to be their primary source. Due to their long half-lives in detritus, the highest concentrations detected do reflect local past emissions (Miljøstatus, 2014a). PCBs were banned for use in Norway in 1980, and subsequently levels remaining in soils, structures and equipment have declined by 90 % between 1980 and 2010 (see Figure 5).

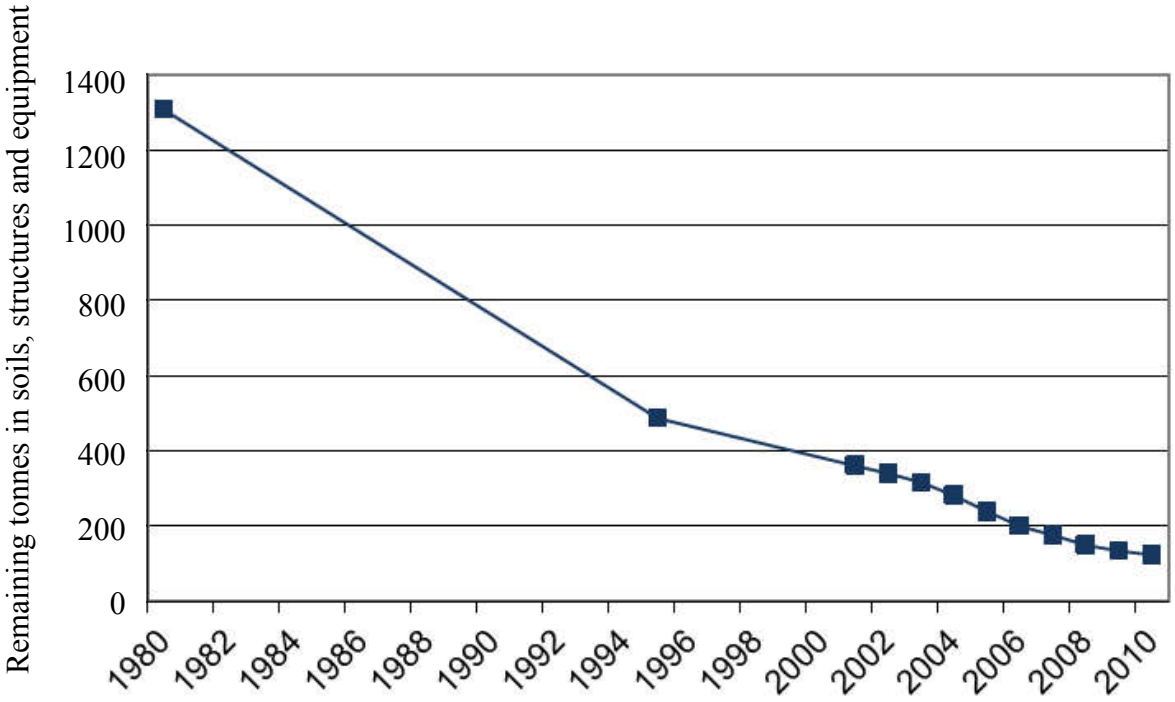

Figure 5. Declining levels of PCB in Norway. (Reprinted with permission from KLIF, 2012)

Analyses of fish and zooplankton in freshwater lakes reflect a similar decline in PCB concentrations during the 1990s, although after 2000 it has levelled off (KLIF, 2013). A directive from the European Union (EU) in 2012 states that PCB concentrations in fish-oil

products for domestic use must not exceed 200 µg/kg. Recent analyses of such products have shown that none exceeded this concentration (NIFES, 2012).

A national ban on the use of HCB was implemented in 1995, and since then emissions have been reduced by 90 %, as illustrated in Figure 6; in 2010, it was estimated to be a total of 9 kg (KLIF, 2012). The same declining trend was observed for DDT during the 1998-2012 period in herring and trout samples from Lake Mjøsa, the largest fresh water lake in Norway (KLIF, 2013).

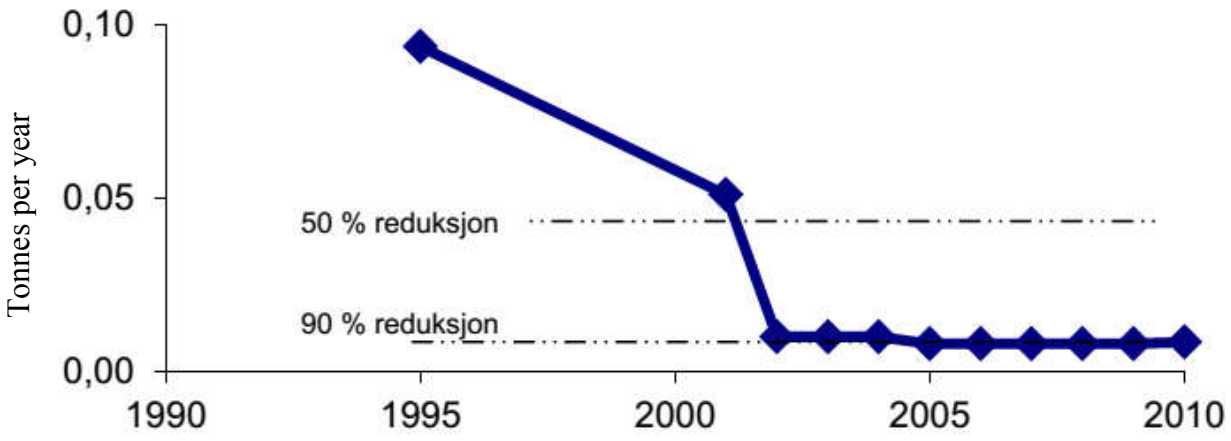

Figure 6. National emissions of HCB. (Reprinted with permission from KLIF, 2012)

1.7. POPs in humans and related health effects

1.7.1. Human exposure

The main exposure by humans to contaminants is through food and breast milk, and to a lesser extent by way of inhalation or dermal contact (AMAP, 2003). In Norway, there are no large-scale industrial areas with local emissions, and it has been estimated that food accounts for more than 90 % of the exposure to PCBs and dioxins (Kvalem et al., 2009). Generally speaking, the most important sources are animal fats, especially marine fats from fish and shell fish, as well as seabird meat and eggs (Kvalem et al., 2009). Although the primary exposure route of POPs for Norwegians is through food consumption, inhalation and dermal

contact remain relevant in places where people live in industrial areas with current emissions such as in Slovakia (Chovancová et al., 2014).

Fetal exposure *via* the placenta during pregnancy seems less of a source than breast milk post-birth. It is well documented that POPs are transferred by breast milk from mother to child because of its high lipid content (AMAP, 2009). Nevertheless, good correlations are observed between maternal and umbilical cord sera concentrations or with those in meconium, and thereby indicate significant transfer during pregnancy (Zhao et al., 2007; Park et al., 2008; Needham et al., 2011). Aylward et al. (2014) examined the concentration ratios for paired cord blood/maternal blood samples of PCBs, pesticides and selected elements. The lipid-adjusted ratios reported for PCBs, hydroxylated PCBs, HCB, nonachlor and DDE were mostly 1.0 or lower. Consequently, and speaking generally, one may conclude that PCBs and OC pesticides are subject to transplacental transfer and thus maternal concentrations constitute reasonable predictors of fetal exposure.

The downward trends depicted in Figures 5 and 6 are also reflected in breast milk from Norwegian mothers (see Figure 7) (VKM, 2013), as well as in Sweden and Canada (Norén et al., 2000; Ryan et al., 2014). For selective OCs in breast milk, the plots in Figure 7 suggest that the implementation of regulations by countries in conjunction with the Stockholm Convention has resulted in a reduction in emissions and exposure to POPs during the new millennium (KLIF, 2012) in Norway and other countries (e.g., Nøst et al., 2013; Parera et al., 2013; Bonita et al., 2013). This downward trend is consistent with a lowering of the concentrations in food, but likely has also been enhanced by a reduction in fish consumption especially among younger women (VKM, 2014). On the other hand, Leckmann (2006) has shown that extending breastfeeding from six weeks to six months increases the transfer of POPs to the neonate nearly 2-fold for PCB 138, 153 and 180 and *p,p′*-DDE and 3-fold for HCB. This potential increase in neonatal exposure indicates that the duration of breastfeeding should be considered in the context of its benefits.

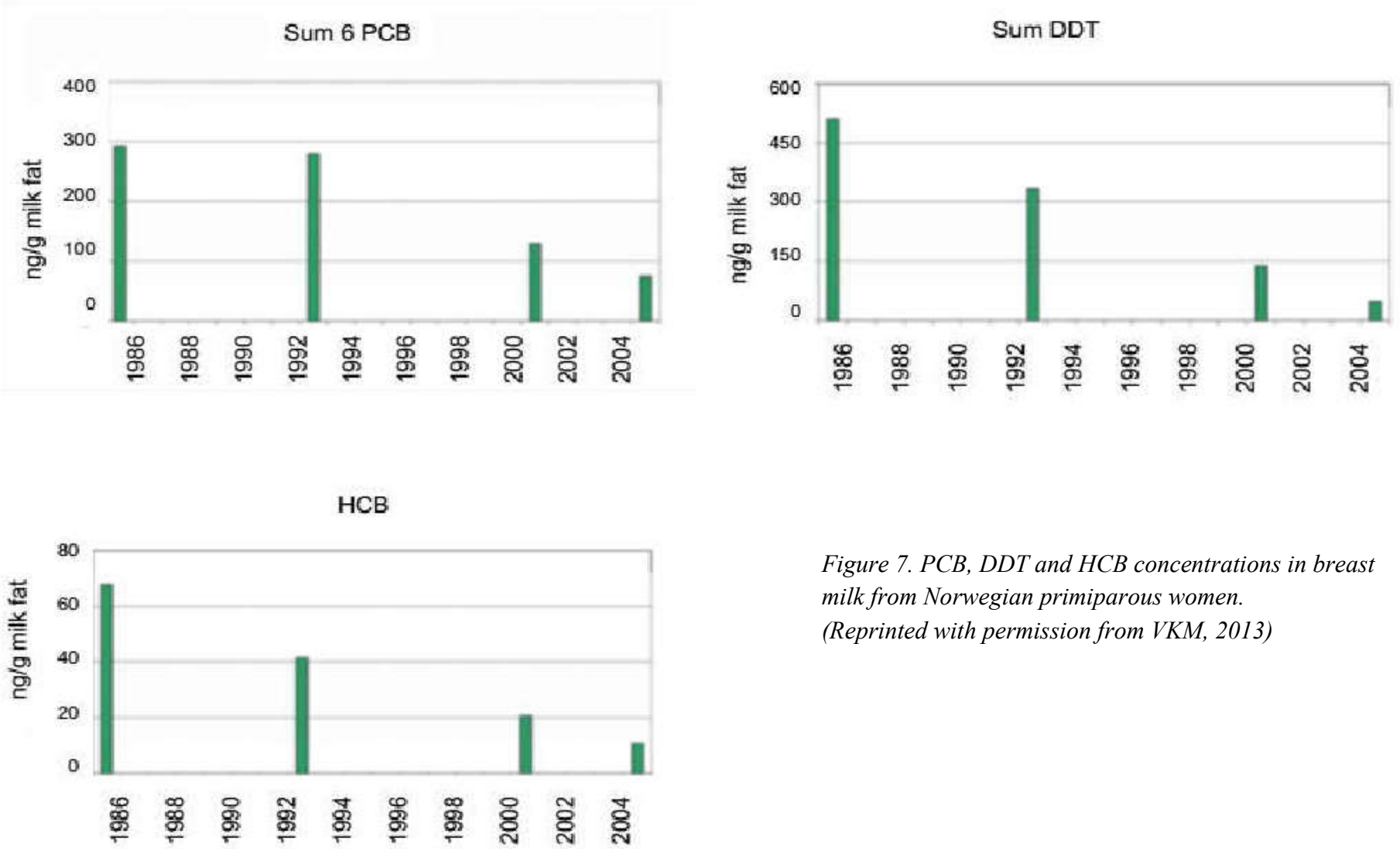

Figure 7. PCB, DDT and HCB concentrations in breast milk from Norwegian primiparous women.
(Reprinted with permission from VKM, 2013)

1.7.2. Health effects

In terms of potential health impacts and generally speaking, the International Agency of Research on Cancer (IARC) designates chlorinated POPs, such as HCB, DDT and chlordane (its technical grade contains nonachlor), as Group 2B carcinogens (the agent *is possibly carcinogenic* to humans; IARC, 2015). The cancer risk of PCBs have recently been re-evaluated (Lauby-Secretan et al., 2013) and are now designated as Group 1 carcinogens (the agent *is carcinogenic* to humans) because a number of epidemiological studies in occupational settings indicate excess risks of melanoma, non-Hodgkin lymphoma and breast cancer. Furthermore, Taylor et al. (2013b) critically reviewed and summarized studies that examined the association between plasma concentrations of chlorinated POPs and Type 2 diabetes mellitus (T2DM). Although an overall positive relationship does appear to exist, its exact nature seems to be complex. Hansen et al. (2010) suspected that it may simply reflect lipidemia, which is a hallmark of T2DM. Similarly, Magliano et al. (2013) indicate that this observed association may constitute confounding, since OCs are stored in body fats. In an innovative approach, Rylander et al. (2015) illustrate that the robust positive associations observed between the rank sum of a range of OCs in plasma and T2DM were not supported by predicted concentrations of early-life exposures to PCB-153, or its accumulated concentrations until the time of diagnosis.

The evidence for other adverse health effects of POPs for the general adult population, as opposed to exposed workers, is mostly inconclusive in terms of impact on reproductive health and hypertension. The association with the latter can perhaps again reflect lipidemia and metabolic issues related to fat turnover (Singh et al., 2014; Peters et al., 2014; Donat-Vargas et al., 2015). The 67 % increased risk of stroke among middle-aged women assigned to individual dietary PCB intake in a prospective study by Bergkvist et al. (2014) may need to be re-visited in the context of the Rylander et al. (2015) analyses.

Prenatal exposure to OCs has been linked to a decline in birth weight (Halldorsson et al., 2008; Govarts et al., 2012; Papadopoulou et al., 2013; Guo et al., 2014; Casas et al., 2015), while an attenuation of fetal growth linked to the dietary intake of dioxins and PCBs decreased with seafood intake (Papadopoulou et al., 2013). There is also considerable concern that PCBs and other OCs can have an impact on neurodevelopment, with disruption of thyroid hormone homeostasis as the underlying mechanism (see Park et al., 2009). In an occupational setting, an excess of neurodegenerative mortality in females has also been reported (Steenland

et al., 2006). Grandjean and colleagues (2012) investigated possible neurotoxic effects from prenatal PCB exposure in seven-year-old children. The statistical analyses showed only a weak negative association of total PCBs in cord blood with the Boston Naming test; by contrast, neither HCB nor *p,p'*-DDE showed any clear link to the neurobehavioral deficit tests conducted. Adjustments for cord mercury mostly attenuated the influence of the PCBs. By contrast, a comparison of the effects on the brain of prenatal exposure to methyl mercury (MeHg) at ages 7 and 14 appear to be multifocal and more permanent in the same cohort (Debes et al., 2006).

1.8. Essential and toxic elements

Maternal whole blood was analysed for 10 different elements that comprise the most common essential and toxic elements. The essential elements included copper (Cu), manganese (Mn), molybdenum (Mo), selenium (Se) and zinc (Zn), while those recognized as non-essential and toxic were arsenic (As), cadmium (Cd), cobalt (Co), lead (Pb) and mercury (Hg).
This suite of elements is comparable to that used internationally in multiple publications, and represent common essential and toxic elements (Osman et al., 2000; Odland et al., 2004; Röllin et al., 2009; Rudge et al., 2011; Needham et al., 2011).

1.8.1. Sources of essential elements and their roles

Opposite to what is generally believed, there is not a general consensus about which micronutrients should be classified as essential (NNR, 2004). According to the International Food Standards Codex Alimentarius essential elements are defined as: "*Essential nutrient means any substance normally consumed as a constituent of food which is needed for growth and development and the maintenance of healthy life and which cannot be synthesized in adequate amounts by the body*" (CODEX, 2014). In terms of the elements in the present study, the evidence for the essentiality of those identified as such above is beyond doubt (Shenkin and Roberts, 2012).

Reference values of nutrients include: (i) *lower level of intake* (LI), which refers to the level below which an intake can lead to deficiency symptoms in some individuals; (ii) *average requirement* (AR) defines the intake of a nutrient that represents the average requirement for a defined group of individuals; (iii) *recommended intake* (RI) refers to the amount of a nutrient that according to present knowledge can meet the known requirement and maintain good

nutritional status among practically all healthy individuals; and (iv) *tolerable upper intake level* (UL), which is defined as the maximum level of total chronic intake of a nutrient, is judged to unlikely pose a risk of adverse health effects in humans (NNR, 2004). In the new edition of the NNR document, these definitions of reference values remain unchanged (NNR 2012). The Nordic Countries share common advisories for adequate daily intake adjusted for gender and age with specific recommendations for pregnant and lactating women (NNR, 2012).

Copper

Cu is an important trace element and absorption occurs mainly in the small intestine (Barceloux, 1999b). Absorbed Cu is transported to the liver via portal blood bound to albumin. Two thirds of the total body Cu content is located in the skeleton and muscle, and the liver is the key in Cu homeostasis (Turnlund, 1998). Its absorption is reduced by competition with other dietary components, such as Zn, Mn and iron (Fe), and increased by amino acids and by dietary sodium. Nevertheless, uptake an excretion of Cu is tightly controlled (Nieboer et al., 2007).

Cu is an essential metal that constitutes an important cofactor in oxidative proteins or enzymes (IOM, 2001; Shenkin and Roberts, 2012). For example, cytochrome-c oxidase is critical to respiration and tyrosinase is a Cu-based enzyme involved in the oxidative catabolism of the amino acid tyrosine. Ceruloplasmin is the most important serum Cu-transport protein.

Sources are organ meats and shellfish, especially oysters. Nuts, whole grain cereals, and cocoa-containing products, legumes and dried fruits are selected plant food rich in Cu, and it is present in lesser amounts in dairy products, especially cow's milk (Shenkin and Roberts, 2012). Cu deficiency is rare in healthy adults. When it occurs symptoms include hypochromic anaemia, de-pigmentations of skin and hair, impaired immune function, bone abnormalities, especially demineralization. Symptoms are reversible by Cu supplementation (Groff and Gropper, 2000). Toxicity is fairly rare but includes symptoms of nausea, vomiting and diarrhoea; in severe poisoning, haematuria, jaundice, oliguria or anuria can occur. *Wilson's disease* is a genetic disorder of Cu metabolism that causes an increase in Cu to toxic concentrations throughout the body, while genetically-based impaired absorption is the basis for *Menkes disease* (Bandmann et al., 2015).

Manganese

Mn like Zn is incorporated in certain proteins and acts as an enzyme activator; it competes with Fe absorption. Mn is associated with the formation of connective and bony tissue, with growth and reproductive functions, and with carbohydrate and lipid metabolism (Shenkin and Roberts, 2012). Dietary sources rich in Mn include whole grain food, nuts, leafy vegetables and soy products. Tea is also rich in Mn, but is not well absorbed from it (Groff and Gropper, 2000). Mn deficiency has not been documented in humans with a balanced diet, and toxicity is documented from prolonged exposure to Mn-containing dust or fumes (ATSDR, 2012). Its symptoms resemble Parkinson's disease and include prolonged reaction time, tremor and diminished memory capacity (Groff and Gropper, 2000; Michalke et al., 2007; Shenkin and Roberts, 2012).

Molybdenum

Mo is necessary as a cofactor for three metalloenzymes, all of which catalyse important oxidation-reduction reactions; it is eliminated from the body by way of the kidney (Barceloux, 1999c; Groff and Gropper, 2000). Dietary sources include legumes, such as peas, lentils, beans, grains and nuts. Meat, fruit and many vegetables are poor in Mo. Neither deficiency nor toxicity has been observed in healthy humans consuming a varied diet. Nevertheless, excess Mo can induce Cu deficiency by blocking Cu absorption (Shenkin and Roberts, 2012).

Selenium

Se-containing proteins (selenoenzymes) constitute an antioxidant defence system such as in thyroid hormone metabolism, and resemble/complement the role played by vitamin E (El-Shenawy et al., 2015). Se is present in all proteins non-specifically to some extent, as it can substitute for sulphur in the amino acids methionine and cysteine (Fairweather-Tait et al., 2011). Se occurs naturally in foods almost exclusively in the form of organic compounds. Inorganic forms of Se may be found in some vegetables. Both organic and inorganic forms are absorbed from the gastrointestinal tract, are incorporated into proteins, can interconvert, and subsequently are transported to the liver, kidney, heart, pancreas and muscle, with all organs containing significant concentrations of Se (Groff and Gropper, 2000; Fairweather-Tait et al., 2011; NNR, 2012; Shenkin and Roberts, 2012).

Perhaps more than any other trace element, Se varies greatly in soil concentrations throughout different regions worldwide and thereby related concentrations in food plants. This makes intake from food difficult to assess. Apart from plants, fish and other seafood, eggs and offal are relatively rich in Se (Shenkin and Roberts, 2012; NNR, 2012).

Marginal deficiencies are thought to impact thyroid and immune function, reproductive disorders, inflammatory conditions, and cardiovascular disease. Severe deficiencies in humans have been identified in areas where the soil is particularly low in Se. Indeed, in China people have been diagnosed with *Keshan disease* causing cardiomyopathy and *Kashin-Beck disease* causing severe arthritis. Selenium toxicity (selenosis) from inorganic forms (i.e., selenite or selenate) includes symptoms of significant hair loss, muscle cramps, nausea, vomiting, diarrhoea, joint pain, fatigue, fingernail changes and blistering skin. Outbreaks of selenosis related to the consumption of crops grown in contaminated soils are known (ATSDR, 2003; Fairweather–Tait et al., 2011; Shenkin and Roberts, 2012).

Zinc

Zn is found in all organs and tissues and in body fluids. Most of the Zn in humans is found in bone, liver, kidney, muscle and skin (Groff and Gropper, 2000). Zn is distributed in food mainly bound to proteins, and its most available dietary sources are red meat and fish. Whole grains and vegetables are good plant sources but their Zn content is reduced my milling and food processing (Groff and Gropper, 2000; Shenkin and Roberts, 2012). Because of its multiple biochemical functions, clinical presentations of Zn deficiency vary; they are nonspecific and relate to the degree and duration of the depletion. Symptoms include growth restriction with stunting, increased risk of infection and diarrhoea, defects in carbohydrate use, reproductive teratogenesis and skin lesions to mention some (Cummings and Kovacic, 2009). Excessive intake of Zn-contaminated diets can induce symptoms like abdominal pain, diarrhoea, nausea, and vomiting. In the occupational setting, exposure to Zn oxide fumes induces a reversible effect referred to as fume fever (Barceloux, 1999d).

1.8.2. Fetal exposure

Se, Zn and Cu pass through the placenta bound to proteins (Sakamoto et al., 2013) and, in a recent study based on *in vitro* studies, it is hypothesized that Mn is actively transported across the placenta (Nandakumaran et al., 2016). For the essential elements, Aylward et al., (2014) report that the concentration ratios for paired cord blood and maternal blood samples were: 2-

3 (Mn), 1-2 (Zn), ≤ 1 (Se), and well below 1 for Cu; that for Mo appears to be 1 (Krachler, 1999).

1.8.3. Sources of toxic elements and their health effects

Some metals and non-metals have been recognized as toxins for centuries and, in more recent times, two examples with devastating effects on human health are of As in drinking water in Bangladesh (Edmunds et al., 2015) and MeHg-contaminated fish in Minimata, Japan (Tsuda et al., 2009). Of the five toxic elements included in the present study, four are listed in the top 20 of the 2007 CERCLA (Comprehensive Environmental Response, Compensation, and Liability ACT) Priority List of Hazardous Substances, namely: As, (No.1), Pb (No. 2), Hg (No. 3), and Cd (No. 7) (Moyer, 2012).

Arsenic

As is the 20th most common element in the earth's crust. As-containing pesticides were used in the past. The primary route of exposure is the normal diet, or by consumption of contaminated food or drinking water as implied above. Inadvertent hand-to-mouth activity of contaminated soil is another established route (especially by children) (ATSDR, 2007a). The highest concentrations have been found in seafood, followed by meats, cereals, vegetables, fruit and dairy products (Molin et al., 2015). The non-toxic organic forms of As are mostly found in seafood, fruit and vegetables, whereas toxic inorganic As forms are present in meat, poultry, dairy products, cereals and some seafoods. It is estimated that on average approximately 25 % of daily dietary As intake is in the form of inorganic species (Schoof et al., 1999; IARC, 2012).

As is widely distributed within the body (ATSDR, 2007a; CDC, 2009). Placenta transfer through passive diffusion appears to occur (Rudge et al., 2009; Sakamoto et al., 2012; Chen et al., 2014), with paired cord blood/maternal blood ratios of ≤ 1 (total As) (Guan et al., 2010; Aylward et al., 2014). Its detoxification occurs in the liver and excretion is by way of the kidney (Moyer, 2012; IARC, 2012; Molin et al., 2015). The half-life of inorganic As in blood is 4 to 6 hours (h) and 20 to 30 h for its methylated metabolites (Moyer, 2012). Consequently the excretion into urine of inorganic As and its metabolites, as well as of organic As (mostly in the arsenobetaine form), is relatively short (hours to 1 day; Lauwerys and Hoet, 2001).

The toxicity of inorganic As is primarily due to its interference with energy transfer in cells. High exposures to inorganic As occur in the workplace by inhalation or in regions of the world through drinking water that is naturally contaminated with this element. Adverse outcomes include dermal effects (e.g., hyperkeratosis, hyperpigmentation and skin cancer), internal cancers (IARC, 2012), neurological impairment (e.g., sensorimotor and peripheral neuropathy), vascular diseases, gastrointestinal/hepatic disorders, and detrimental reproductive/developmental issues (Mohammed Abdul et al., 2015). In terms of the latter, Laine et al. (2015) observed significant negative associations between urinary inorganic metabolites of As and birth weight, birth length and gestational age. Its ability to target the brain can affect learning skills in childhood (Mohammed Abdul et al., 2015).

Cadmium

Cd occurs naturally in the earth's crust. Industrialized release includes mining and smelting of Zn, battery manufacturing, pigment production for paints, and occurs in tobacco products (CDC, 2009; Moyer, 2012; IARC, 2012). Cd is absorbed *via* inhalation and ingestion. The primary non-occupational source is cigarette smoking, and for non-smokers with no occupational exposure the main source is ingestion of foods that include cereals, rice, potatoes and various seeds grown in Cd-contaminated soils (CDC, 2009; Charania et al., 2014). The gastrointestinal absorption of dietary Cd is about 10 % higher in women than in men, and Cd uptake is inversely related to Fe status (CDC, 2009; Meltzer et al., 2010). Cd in blood is bound to the protein metallothionein and represents mostly recent exposure with a half-life of 40-90 d by contrast, Cd accumulated in the kidney and liver has a half-live of 10 y or more, and this is reflected in its excretion rate into urine primarily as metallothionein (Nieboer et al., 1999; Lauwerys and Hoet, 2001). Sakamoto et al. (2012) report the fetal Cd concentration to be about 20 % of that in maternal whole blood, and indicate that the protein metallothionein in the placenta plays a role in restricting the transfer of this metal (also see Aylward et al., 2014).

Renal damage is the primary target of Cd, although breathing of Cd-containing fumes/dust such as in occupational settings can lead to nasal and pulmonary damage, as well to lung and other cancers (IARC, 2012; Moyer, 2012). Cd in non-smoking women has been observed to be inversely related to birth weight of their neonates (Lin et al., 2011; Johnston et al., 2014), although Zhang et al. (2004) could not observe this association. Few studies have investigated the effects of Cd in non-smokers and related neonatal outcomes.

Cobalt

Co is a magnetic element that occurs naturally in nature. It is emitted into the environment from burning coal and oil, and automobile exhaust, although diet is the main source of Co in the general population (Barceloux, 1999a; ATSDR, 2004; CDC, 2009). Co is an essential cofactor in vitamin B_{12} (nutritional Co deficiency occurs with a total abstinence of B_{12} containing foods; Reinhold, 1975), is not highly toxic generally speaking, and can be absorbed *via* the oral and pulmonary routes (CDC, 2009; Moyer, 2012). Individuals suffering with nickel dermatitis on occasion are also sensitive to Co and, by analogy to nickel (Dolovich et al., 1984), cases of Co-induced asthma are rare. Occupational exposure to Co-containing dust has been associated with an interstitial lung disorder known as "hard metal disease" (CDC, 2009). Fish and vegetables, such as green leafy vegetables and fresh cereals are rich sources of Co, while animal products are the best sources of vitamin B_{12}. Animal livers also contain high Co concentrations and tobacco does as well (Barceloux, 1999a), but not cigarette smoke (Pappas et al., 2014). Gastrointestinal absorption of Co varies between 5 to > 20 % (Barceloux, 1999a). It accumulates mostly in the liver followed by the kidney, although most is excreted through urine and to lesser extent in the faeces (with a half-life of about 24 h, along with a minor fraction exhibiting longer times (Lauwerys and Hoet, 2001). Paired cord blood/maternal blood ratios of ≤ 1 (Co) have been observed (Aylward et al., 2014).

Lead

Pb is present naturally in soils and rocks. In some mineral deposits, it occurs with other elements such as As, bismuth (Bi), Cd, Cu and Zn. Pb is recovered by recycling scrap metal, including batteries, Pb pipes and ammunition. Pb compounds were extensively used as gasoline additives, but this practice was phased out in the 1980s ─ it was banned in the USA on January 1, 1996 and in 1997 in Norway (ATSDR, 2007b; Miljøstatus, 2015). Concurrently, a continuous decline has been observed in its concentration in humans (Nieboer et al., 2013). Leaded gasoline emission constituted a major environmental problem (CDC, 2009). Today, contact with contaminated soils and consumption of vegetables grown on them remain sources for the general population, as well as drinking water in older homes with Pb-plumbing (Nieboer et al., 2013). Cigarette smoking makes a minor contribution to Pb exposure (Chelchowska et al., 2013; Taylor et al., 2013a). Exposures can also occur during gun use (fumes given off during gun firing contain Pb that originates from the gunpowder) as

can the consumption of hunted game such as waterfowl (tissue-embedded Pb pellets and/or fragments are sources; Meltzer et al., 2013; Nieboer et al., 2013).

Pb, like most inorganic substances, is poorly absorbed through the skin (ATSDR, 2007b). When inhaled, 10-60 % of Pb-containing micro-sized particles (0.01-5.0 µm diameter) are deposited in the respiratory tract, and most of the PB is absorbed within 24-h of inhalation unless the substance has low solubility (Skerfving, 1995). About 10 % of ingested Pb is absorbed in the gastrointestinal tract (Moyer, 2012), and its uptake increases when Fe-deficiency and/or low calcium intake occur (Mahaffey, 1990). Once in the blood, Pb is bound primarily to erythrocytes and is distributed by way of plasma to other organs such as liver, kidney, lung, brain, muscle and heart; it accumulates in bones (including teeth) because Pb can substitute for calcium. About 94 % of the total amount of Pb in the body is stored in the skeleton (ATSDR, 2007b). The half-life of Pb in the peripheral blood and soft tissue compartments is around one month, while in the skeleton it is 9-12 y (Skerfving, 1995). Consequently, bone constitutes an ongoing source of Pb for the blood compartment. Approximately 70 % of Pb is excreted into urine, with a lesser amount eliminated *via* the faeces.

Pb readily passes the placenta (Odland et al. 1999; Needham et al., 2011; Chen et al., 2014) with paired cord blood/maternal blood ratios of < 1 (Aylward et al., 2014). Pb is a systematic poison with no apparent toxicological threshold (Rogan and Ware, 2003; Flora et al., 2015). It exhibits universal adverse effects, including impairment of the nervous system and development, an increase in blood pressure, renal perturbations (ATSDR, 2007b), and reproductive effects. Maternal blood concentrations of Pb have been associated negatively with birth weight, birth length and head circumference, as well as gestational length (Ettinger et al., 2010; Moyer, 2012; Nieboer et al., 2013). High levels have also been associated with miscarriages (ATSDR, 2007b). Blood Pb levels > 5 µg/dL (50 µg/L or 0.24 µmol/L, the concentration currently recommended in the USA to identify children with elevated levels; CDC, 2012) have been negatively correlated to adaptive behaviour (social withdrawal, sleep problems, atypical body movements, previous medical diagnoses, aggression and destruction), gross and fine motor, language and individual social behaviour (Hou et al., 2013). Interestingly, the negative effects of Pb on mental and psychomotor development as measured by the Bayley Scales of Infant Development-II Assessment appear to be enhanced by co-exposure to Mn (Claus Henn et al., 2012).

Mercury

Hg is widely found in the environment and occurs both naturally and as results of industrial processes. At room temperature it is a liquid that is volatile, it is toxic in both its elemental (Hg^o) and ionized forms. Elemental Hg is bio-converted to MeHg (CH_3Hg^+) by microorganisms that exist in the sediments of lakes and rivers. CH_3Hg^+ has both hydrophobic and hydrophilic properties, strongly binds to proteins especially *via* sulphur atoms, and the central nervous system is a primary target (Costa et al., 2004). Elemental Hg is released to the air from the combustion of fossil fuels, mining and smelting operations, and direct release of elemental and inorganic Hg in industrial discharges are also important. MeHg has the ability to bio-accumulate in aquatic and terrestrial food chains, and this constitutes the main route of human exposure. Intake of fish and some other marine foods (CDC, 2009) correlate with blood Hg (Brantsæter et al., 2010; Rice et al, 2014). Elemental Hg is poorly absorbed from the gastrointestinal tract (less than 0.1 %), whereas 7 % and 95 % of inorganic and $CH_3Hg^+$is absorbed respectively (Nieboer et al. 1999; ATSDR, 1999). After entering the blood, Hg is distributed to all tissues including secretion into hair. MeHg is excreted via the faeces, while inorganic Hg forms are eliminated primarily by the urinary pathway (ATSDR, 1999) with a half-life of 45-70 d. MeHg appears to pass easily through the placenta *via* active transport by amino acid carriers, with cord blood concentrations approximately 1.5 to 2 times those in maternal whole blood; this ratio was comparable for total Hg, namely 1-2 (Aylward et al., 2014).

The toxicological impacts of Hg include cardiovascular, haematological, pulmonary, renal, immunological, neurological, endocrine, reproductive, and embryonic effects (Rice et al., 2014). As a known neurotoxicant, MeHg is particularly harmful to fetal brain development (Mahaffey 2011). As mentioned earlier, Grandjean et al. (2012) observed weak associations between OCs and neurobehavioral deficits in children at age 7, which became weak or disappeared after adjusting for Hg concentrations (observed mean of 42 nmol/L or 8.4 µg/L). Chen et al. (2014) found significantly higher Hg concentrations in maternal and cord plasma and red blood cells [mean of 11.7 nmol/L (2.3 µg/L) for mothers and 17.8 nmol/L (3.6 µg/L) in cord blood] in preterm (gestational age < 37 weeks) or babies with birthweights below 2500 g. These associations were weaker for Pb. Similarly Ramón et al. (2009) observed a reduction in birth weight of 144 g in the highest Hg quartile measured in cord blood (range of 30-64 nmol/L or 6.0-12.8 µg/L). Vejrup et al. (2013) investigated possible association between birth weight and estimated Hg intake based on dietary information from a FFQ in the

Norwegian Mother and Child Cohort study (MoBa). Newborns of mothers in the highest quintile compared to the lowest quintile of Hg exposure had an increased risk (adjusted) of a reduction in birth weight of 34 g and a 9 % increased risk of being born small for gestational age. By contrast, a similar investigation in Greenland found only a weak or no association between MeHg exposure and birth weight (AMAP, 2011), as have others (EFSA, 2012; Taylor et al., 2014).

1.9. Global transport and time-dependent patterns of toxic elements

The transport of contaminants (including toxic metals) to the Arctic has been studied extensively (Macdonald et al., 2005). Cd- and Pb-containing aerosols appear to be poorly captured within the Arctic regions (the proportion is estimated to be < 15 %), but changes in precipitation patterns are believed to be able to alter this (Macdonald et al., 2005). Hg is transported to the Arctic by air currents (within a matter of days), ocean currents (that may take decades) and rivers (AMAP, 2011). This is illustrated in Figure 8, which depicts the dominant air transport pathways for Hg into the Arctic. The global emissions shown in Figure 9 indicate that Asia and central Europe, and to lesser extent the US, Central America and South America, have been major sources.

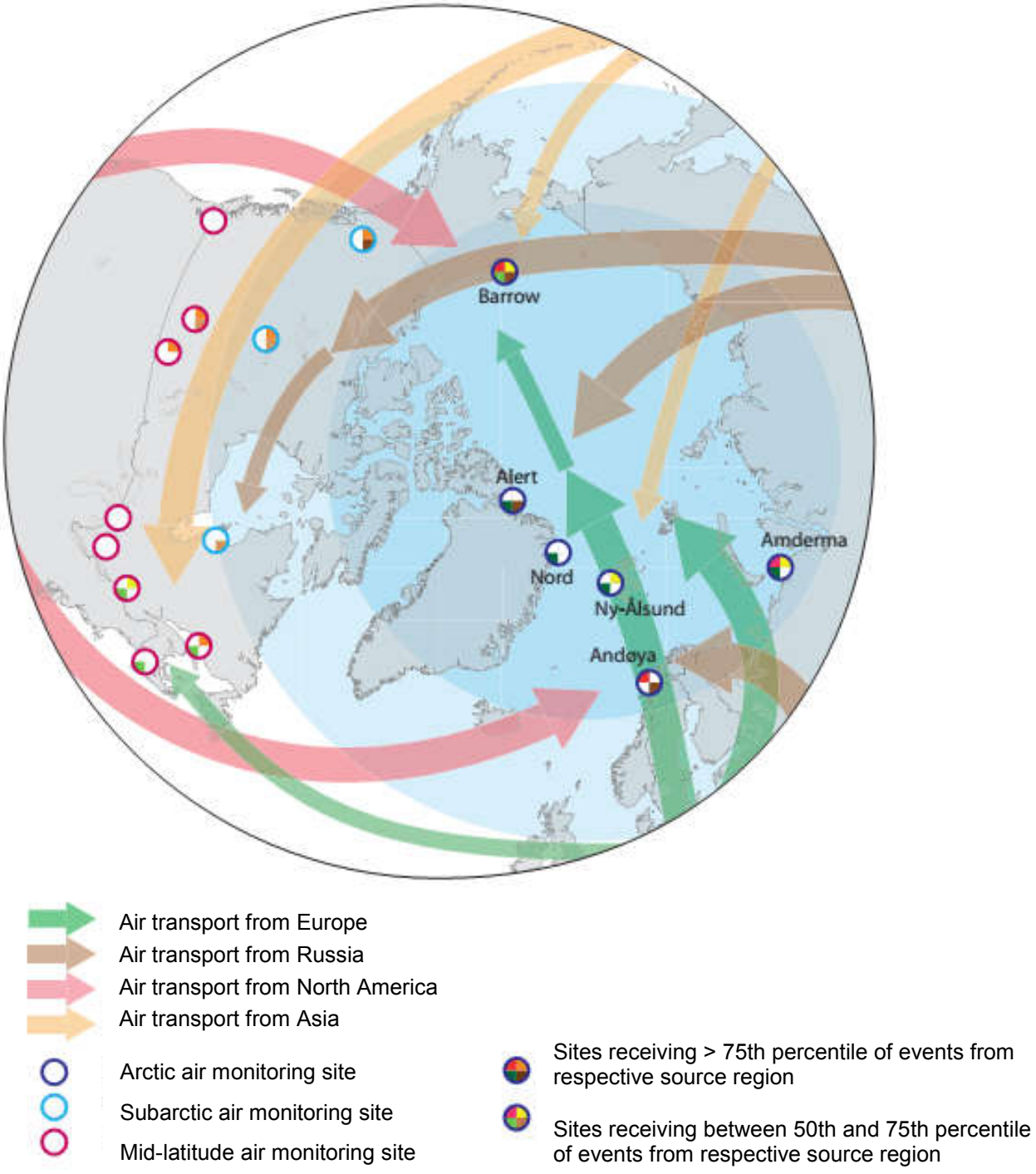

Figure 8. Dominant air transport pathways for Hg into the Arctic from major source regions, with an indication of the contribution by them at specific monitoring locations. (Reprinted with permission from AMAP, 2011)

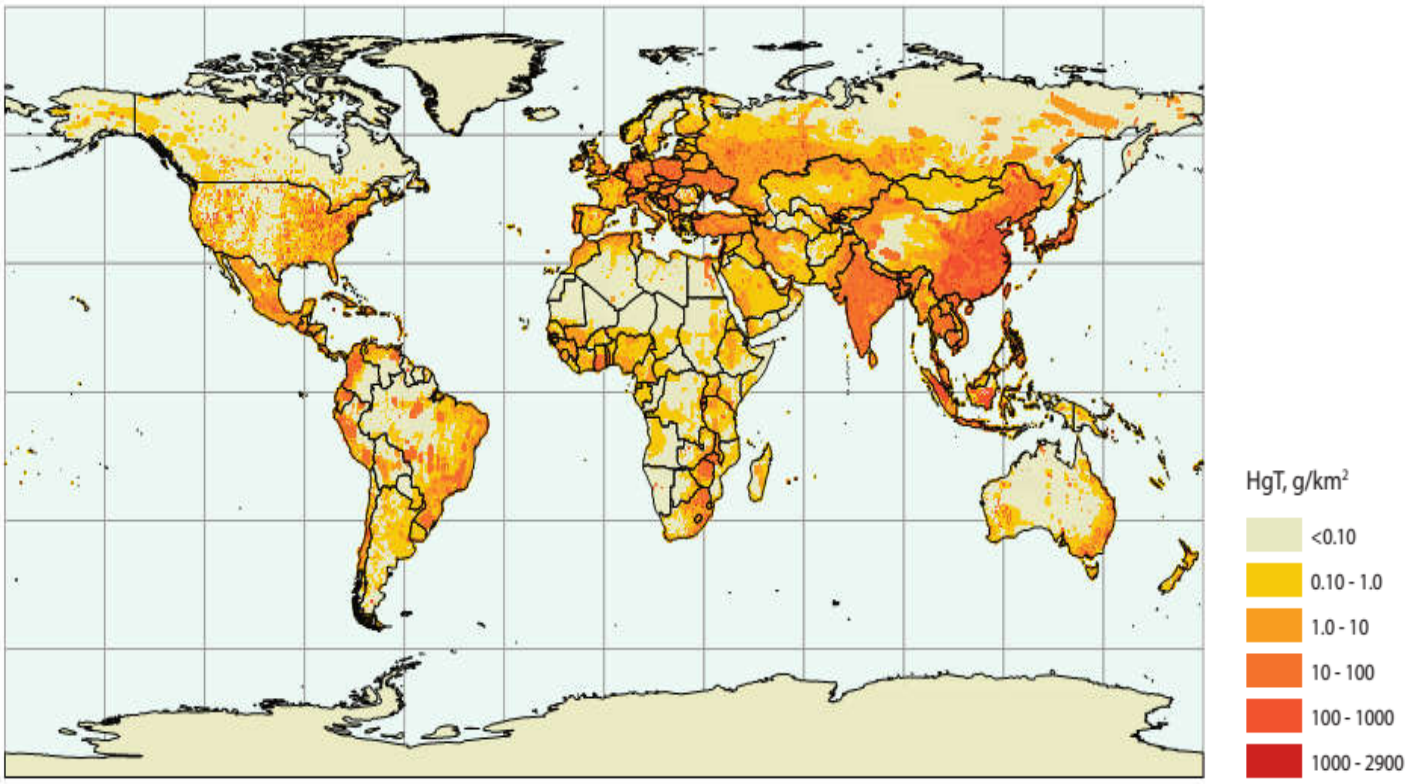

Figure 9. Global distribution of anthropogenic atmospheric emission of mercury in 2005 at a 0.5° x 0.5° latitude/longitude grid. Source: AMAP/UNEP (2008). (Reprinted with permission from AMAP, 2011)

As, Co, Cd, Ni, Pb and Zn are also transported through air and ocean currents and rivers. Interestingly, As and Co were detected in rainwater samples from eight Arctic catchments in Russia, Norway and Finland and were linked to emissions from the nickel mining and refining industries located in the Kola Peninsula (North West Russia) (Macdonald et al., 2005; ATSDR, 2004 and 2007a). Such emission patterns have been documented for other areas with nickel mining/refining activities (Nriagu and Rao, 1982; Rose and Parker, 1982).

Continued monitoring of Hg and Pb in maternal blood samples indicate decreasing trends during the period 1990-2007, as illustrated in Figures 10 (a) and 10 (b) (AMAP, 2009), although rather high Hg levels are still evident in Northern Canada and Greenland. Since these areas have minor local sources and traditional foods remain a staple (see Figure 9), the potential detrimental influence of global Hg transport on local Arctic inhabitants remains.

However, a recent study of the temporal trend from 1970s to 2012 of Hg concentration in fresh water fish from Ontario, Canada observed a reversal of the decreasing tendency from 1995 onwards. Although Hg emissions have declined in North America, other factors such as global emission and climate change are considered likely causes (Gandhi et al., 2014). By comparison, a study in Sweden measuring Hg levels in freshwater fish consumed from 1965-2012 indicated an overall long-term decline of 20 % or more, but consistent regional patterns were absent (Åkerblom et al., 2014).

Subsequent to the phasing out of leaded gasoline, Pb concentrations in humans have been steadily declining. However, continued use of Pb-containing gun powder/ammunition by indigenous people and other hunters remains a source, as does living in older homes with Pb plumbing and residing on/near contaminated soils (Nieboer et al. 2013). Reduced emissions of As, Co and Ni have accompanied the general lowering of emissions from metal refineries such as in Norway, Russia and Canada (Keller et al., 1999; Schindler et al., 2013). Reduction in cigarette smoking has also mitigated exposure to Cd (Tellez-Plaza et al., 2012).

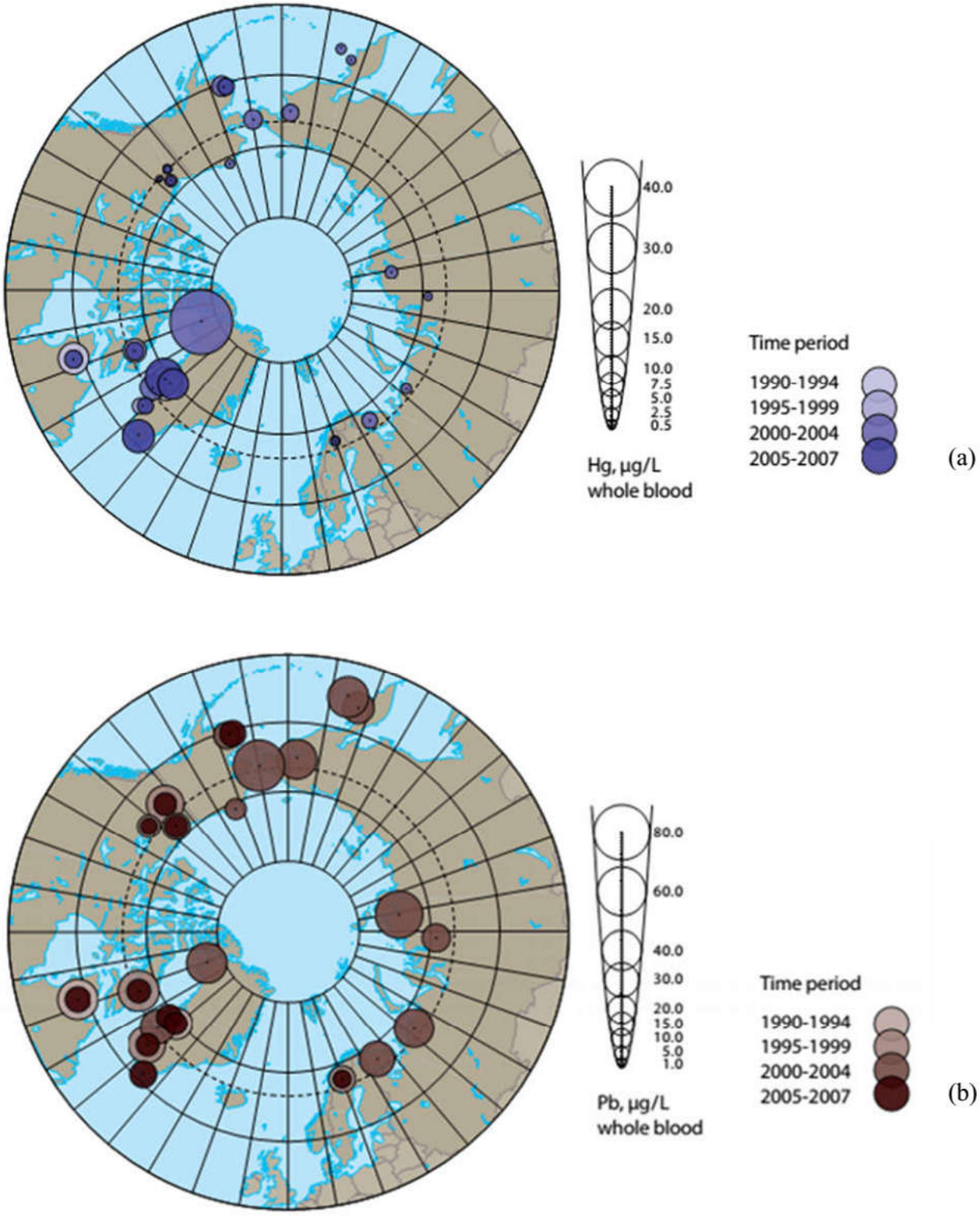

Figure 10. Total Hg (a) and Pb (b) concentrations in blood of mothers, pregnant women and women of childbearing age in the circumpolar countries. (Reprinted with permission from AMAP, 2009)

1.10. Toxic elements detected in the environment in Norway

The emission of none-essential elements reported in the Norwegian national priority list has decreased consistently during the period 1995-2010. Release of Hg, Cd and Pb were reduced between 67 to 80 % (KLIF, 2012), although there are indications that Hg detected in freshwater fish increased during the 2010- 2012 observation period (Braaten et al., 2014), which reflects the trend mentioned above for Ontario, Canada. Those for As were only reduced by 15 % during 1995-2010, likely because it is/was released from pressure-treated (impregnated) wood by leaching (KLIF, 2012). Other sources for local emissions of these toxic elements involve industries including oil and gas production, and sewage treatment and sediments (KLIF, 2012).

2. AIMS OF THE THESIS

This thesis is based on the Northern Norway Mother-and-Child Contaminant Cohort Study (The MISA study).
The study objectives were:

- Summarize the dietary intake in pregnant women in Northern Norway;
- Identify associations between dietary intake and maternal serum concentrations of PCBs and organochlorine (OC) pesticides, as well as for essential and toxic metals in maternal whole blood;
- Quantify selected OC pesticides, PCBs and phenolic metabolites of the latter in meconium, and identify factors that influence their concentrations in this medium; and
- Enhance understanding of the mother-to-fetus transfer of OCs.

3. MATERIAL AND METHODS

3.1. Study population

Pregnant women were recruited in early pregnancy (preferably before gestational week 20) when making their pregnancy ultrasound appointment or at antenatal centres. As summarized in Figure 11, a total of 2600 women were invited to participate in the project with a response rate of 23.4 % and an enrolment of 515 (19.8 % of invited subjects). Paper I included 391 women who completed all study aspects, although selected personal and obstetrical data available in the Medical Birth Registry of Norway (MBRN) were compared for the study subjects and the dropouts (n = 113), as well as the questionnaire dietary information provided at enrolment by both groups. Paper II included 39 women and their matched 40 newborns (including one pair of twins) randomly selected from the cohort, and the Paper III dataset was based on the entire group of eligible study subjects (n = 515). However, the exact number of participants depended on the available number of maternal serum and/or whole blood specimens, the specific substances analysed for, the completeness of the FFQs, and the model adopted in the statistical analyses.

3.2. Information, measurements and sample collection

Collection of personal information and biological samples and the administration of selective anthropometric and clinical measurements were carried out at enrolment, delivery, and three days and six weeks postpartum (PP) (see flow chart in Figure 12). At the first meeting the women donated blood and urine samples, their blood pressure (BP) and body weight (BW) were measured and the women completed a self-administrated questionnaire pertaining their education, lifetime residency, self-perceived health, smoking habits and alcohol intake, and a semi-quantitative FFQ. At delivery the women's BP and BW was measured again. In addition a maternal scalp-hair sample was taken, and umbilical cord blood and meconium samples were collected. Three days PP and six weeks PP maternal blood and urine specimens were taken and both the BP and BW were measured. When handing in the written consent, the women agreed for the researchers to access their current and former birth registry data from the MBRN.

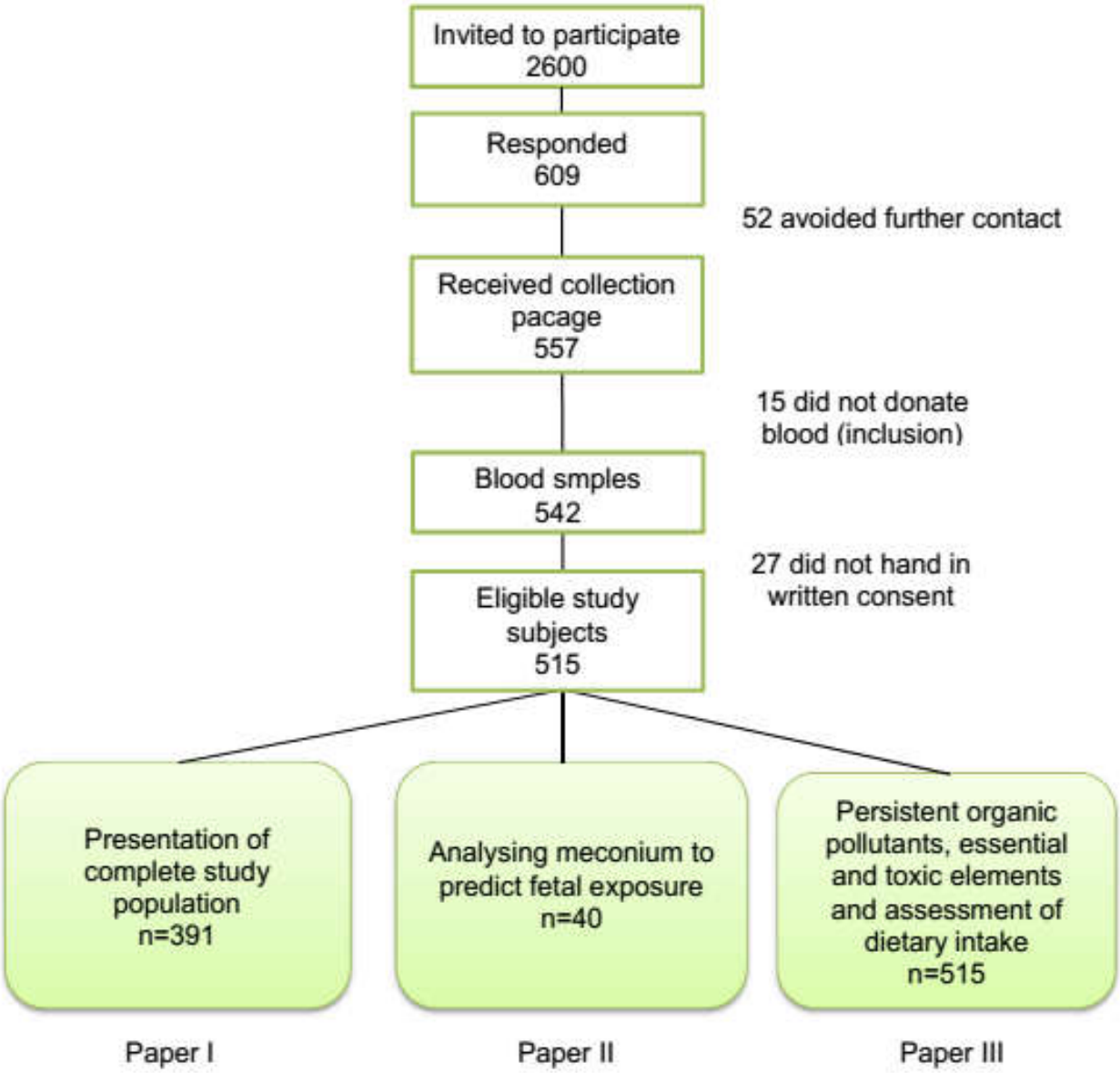

Figure 11. Study population and Papers I, II and III participants.

Paper I was based on the personal, social and dietary information obtained through the FFQ. Obstetrical data were obtained from the MBRN. In Paper II, the measured concentrations in sera samples (collected in early pregnancy) and in matched newborn meconium samples of POPs (specifically OC pesticides, PCBs and hydroxylated PCBs) were compared. Paper III examined the complete early pregnancy serum POPs dataset (n = 515) and the concentrations of essential & toxic elements in a subset of 282 whole blood samples, with personal, lifestyle and dietary factors as predictors of the observed concentrations the primary focus.

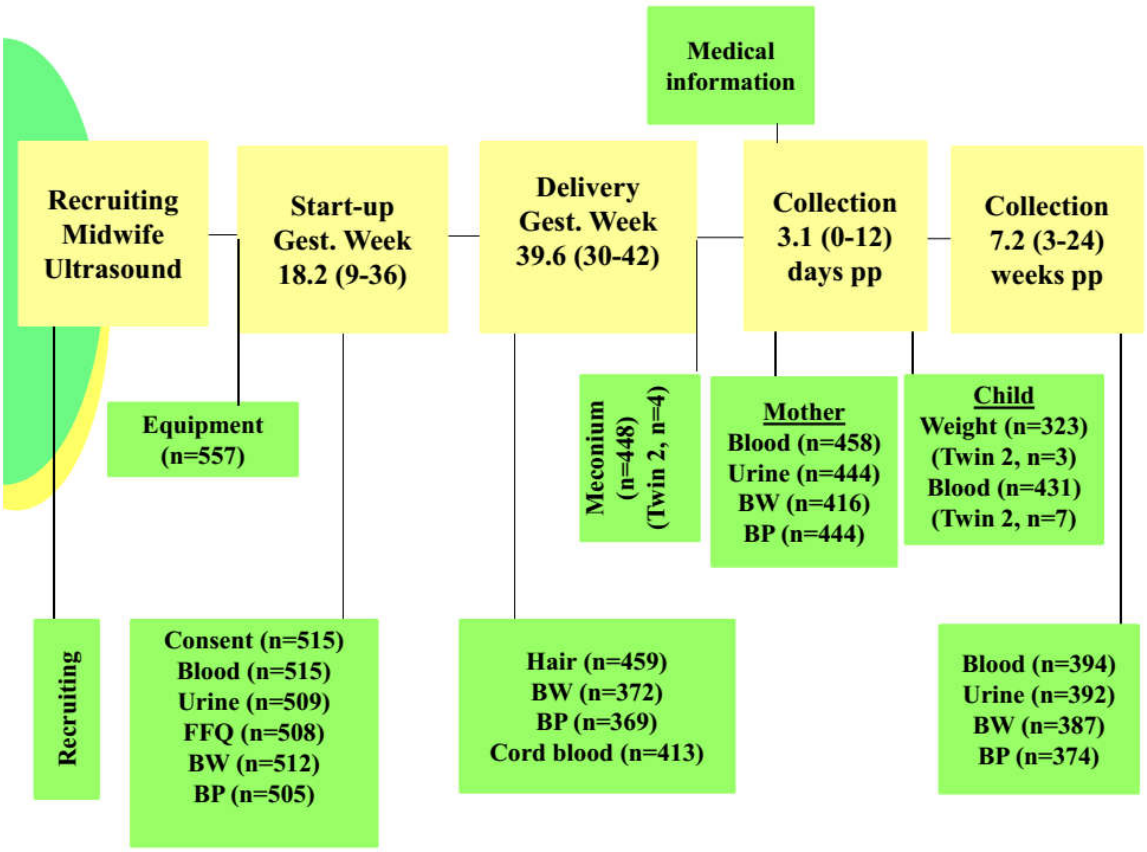

Figure 12. Protocol flow chart of the MISA study. (Reprinted with permission from Paper I, with adjustment to the start-up period to include the entire study group)

3.3. Dietary assessment

The MISA dietary questionnaire was based on that used in the Norwegian Women and Cancer study (NOWAC) (Engeset et al., 2005; Parr et al., 2006; Hjartåker et al., 2007). It included an expanded section for maternal intake of fish, whale/seal, sea gull eggs, reindeer, moose, grouse and local berries. Recorded consumption was converted to daily intake in grams (Blaker and Aarsland, 1995) based on the Norwegian Weight and Measurement Table (Matvaretabellen, 2014). The MISA FFQ was designed to assess primarily the habitual diets over the past year, and included questions about 137 food items. All questions had 4 to 7 fixed options, ranging from never/seldom to either 5-7 times per week, or 2+ times per day. Details were also sought about the amount consumed, as well as seasonal variation of fish intake. The women were also asked about past seafood intake during childhood, youth and adult life stages. Consumption of fatty fish, fresh water fish, fish liver, whale and seal, crab meat, sea birds and sea bird eggs were emphasized.

3.4. Blood and meconium sampling and chemical analyses

The maternal serum and whole blood samples considered in this thesis were drawn during the 2nd trimester (mean of 18.2 weeks and range 9.0 – 36.0), and the meconium samples at the earliest possible time postpartum (mean of 13.8 and range 1– 61 hours postpartum). All biological samples were stored at -20°C in a biobank at the UiT The Arctic University of Norway until analysed further.

Maternal serum and meconium analyses were carried out at the Norwegian Institute for Air Research (NILU), Fram Centre, Tromsø, Norway. PCBs, OC pesticides (including, *p,p′*-DDT *p,p′*-DDE, nonachlors and hexachlorobenzene) and PCB phenolic metabolites in both serum and meconium extracts were analysed according to Rylander et al. (2012). All were quantified employing an Agilent 7890A gas chromatograph, equipped with a series 5975C mass spectrometer (Agilent Technologies, Böblingen, Germany).

Maternal whole blood analyses were carried out at the National Institute of Occupational Health (NIOH), Oslo. In brief, maternal whole blood was analysed for As, Cd, Co, Cu, Hg, Mn, Mo, Pb, Se, and Zn by inductively plasma-mass spectrometry (ICPMS), employing a high resolution magnetic sector field Element 2 mass spectrometer (Thermo Electron, Bremen, Germany) calibrated with whole-blood matched standard solutions. Further details are provided by Hansen et al. (2011).

Lipid determination in meconium was determined as % extractable organic material (EOM) according to Folch et al. (1957), and serum lipids were determined enzymatically using the following summation formula to calculate the amounts of lipids in each plasma sample: TL = 1.677 (TC – FC) + FC + TG + PL, where TL = total lipids, TC = Total cholesterol, FC = free cholesterol, TG = Triglycerides and PL = phospholipids (Akins et al., 1989; Hansen et al., 2010).

3.5. QA/QC

The NILU Laboratory has participated in the AMAP Human Health ring test (Eik Anda et al., 2007). Uncertainties associated with the calculated serum concentrations were within ± 15 %, which is considered “best” performance; for meconium, the uncertainties were somewhat larger (within ± 25 % for the majority of the compounds).

The NIOH laboratory participates in the Wadsworth Center, New York State (USA) Department of Health Proficiency Testing Schedules for trace elements in whole blood and urine, with acceptable results (typically within ± 2–10 % deviation from the target values) and no indication of systematic bias.

Additional details are provided in Papers II and III.

3.6. Statistical analysis

All concentrations below the limit of detection (LOD) were replaced with LOD/√2 as recommended by Eik Anda et al. (2007). All data were entered in a constructed Microsoft Office Access database and eventually converted to IBM SPSS Statistics for Windows (version 19.0 and 21.0; SPSS Inc., Chicago, IL, USA) when statistical analysis were carried out. Data was assessed for normal distribution by the Kolmogorov-Smirnov test and found to be positively skewed. These variables were either log-transformed [base 10 logarithm ($\log_{10} x$)] before entering them in the statistical analyses where this was required or, when not, the appropriate non-parametric analysis was applied. T-tests, Pearson correlation and Spearman's rho rank statistics were employed, as well as the chi-squared test for categorical variables, kappa (κ) to determine the strength of agreement, and principal component analysis (PCA) to group variables to enhance interpretations. ANOVA and/or the *Post Hoc* Bonferroni Test were employed for comparisons involving PCA-generated variables.

3.7. Ethical considerations

The MISA project was approved be the Regional Committee for Medical and Health Research Ethics (REC North) and the Norwegian Data Inspectorate. The women were informed in the written consent form that their participation was on a voluntary basis, and that they could withdraw at any time. All results are presented anonymously.

4. MAIN RESULTS

4.1. Paper I

Presentation of population characteristics and summary of dietary findings in The MISA study

Among the 515 women who donated blood in early pregnancy and provided written consent (criteria for participation), 391 completed the study protocol that included a comprehensive self-administrated FFQ, donating blood and other biological materials post-partum, as well as acquiescing to anthropometric measures at the three time points. The participants were compared to the drop-out group based on data obtained through the study questionnaire and the MBRN; and using the latter, to all Norwegian mothers for the 2004-2006 period. Compared to the MBRN women, those in the study cohort on average were about 2 years older and smoked less. Parity, gestational age and birth weight of the newborn were comparable. Compared to the drop-out group, the study group was approximately 2 years older, attended school one more year (15.9 compared to 14.7, respectively), smoked less and had fewer instrumental deliveries. Estimated daily intake of 8.1 MJ per day was less than recommended by the Nordic Nutritional Recommendations (NNR), but nutrient intake per MJ (nutrient density) was in good compliance with NNR. It was concluded that the occurrence of bias was minimal and that an acceptable external validity prevailed. The MISA database was considered suitable for exploring associations between contaminant exposures and diet, enhancing our knowledge of the interplay of physiological changes that occur in mothers with contaminant pharmacokinetics (including transfer to the infant before and after birth), and conducting prospective health studies of the neonates.

4.2. Paper II

Is meconium useful to predict fetal exposure of organochlorines (OCs) and hydroxylated PCBs?

The objective was to investigate if it was possible to detect OCs and their metabolites in meconium, and if the quantified contaminants would reflect the corresponding maternal serum levels. A subset of 40 meconium samples and complementary maternal sera were selected from the MISA Cohort Study and analysed for the AMAP suite of PCBs and OCs. Meconium was collected at the earliest opportunity (median 9.0 hours postpartum, range 0-

61hours) and maternal serum in the 2nd trimester (median 19.0 gestational weeks, range 13-34 weeks). Eight compounds had detection frequencies greater or equal to 70 % in both media and were included in the statistical analyses. The pesticide concentrations favoured meconium, whereas the PCBs did so in maternal serum. All inter-media correlations (Spearman's rho) were significant for wet-weight concentrations and improved for the subset of 15 samples for which lipid lipids were quantified in both media. Multivariable linear regression models confirmed that maternal serum was the most consistent predictor of meconium OC concentrations. When collection time and gestational age were included in the model as predictors, the overall variation explained improved. This was supported by the observed magnitude of the standardized β-coefficient for the multivariable regression models. Respectively for *p,p'*-DDE and HCB, maternal serum concentration accounted for 54 % and 36 % of the variation, hour of sampling for 26 and 33 %, and gestational age for 20 % and 19 %. Similarly for PCBs 138 and 153, these relative contributions were: 54 and 50 % (maternal serum), 26 and 26 % (sampling time), and 23 and 27 % (gestational age) respectively. Although its analysis is challenging, meconium has proved to be a sensitive and informative fetal exposure index when gestational age and sampling time are taken into account. Lipid adjustment also appears to be important.

4.3. Paper III

Principal Component Analysis (PCA) of environmental contaminants in maternal sera and dietary intake in early pregnancy in the MISA population.

This study had two primary objectives: (i) using PCA to generate new variables for suites of organochlorines [8 PCBs and 4 organochlorine (OC) pesticides], of 10 inorganic elements in whole blood (5 essential and 5 toxic), of all the OCs and elements mentioned, and of 20 food groups in sera of pregnant women collected in the 2nd trimester (mean of 18.2 weeks, range 9.0 – 36.0); and (ii), to determine the influence of personal and social characteristics on contaminant, elemental and dietary PCA factors.

When all POPs and elements were included the PCA analysis, 3 axes stood out in the multivariate analysis with robust loadings of: all POP compounds; the elements As, Se and Hg; and the toxic metals Pb and Cd. For these 3 axes, the respective predictors were: maternal age, parity and consumption of freshwater fish and land-based wild animals; marine fish; cigarette smoking, dietary PCA axes reflecting consumption of grains & cereals, and food

items involving hunting. PCA of only the POPs separated them into two axes that, in terms of the recently published results, could be understood to reflect longitudinal trends and their relative contributions to summed POPs.

The dietary PCA axes reflected patterns of healthy foods, junk food, fish consumption, cereal & grains, and local traditional foods. Predictors in the multivariate analysis involving the dietary PCA axes denoting fruit/vegetable intake, junk food consumption and marine diet were age, education, BMI and physical activity.

The PCA has not only enhanced our understanding of the inter-relationships between contaminants, but also among food items consumed by the MISA study group. The linear combinations of variables generated by PCA identified prominent dietary sources of OC groups and of well-known toxic elements, and highlighted the importance of maternal characteristics.

5. DISCUSSION

5.1. Overall main findings

5.1.1. Paper I.

The MISA database is considered suitable for exploring associations between contaminant exposure and diet, enhancing our knowledge of the interplay of the physiological changes that occur in mothers with contaminant pharmacokinetics (with emphasis on the transfer to the infant before and after birth), and conducting prospective health studies of the children.

5.1.2. Paper II.

Although more challenging to collect and analyse than maternal serum and cord blood, meconium may be viewed as a helpful complementary biomonitoring medium. The current study suggests it to be a sensitive and informative fetal exposure index for OCs when taking into account gestational age and its postpartum sampling time. Lipid adjustment of OC concentrations in meconium is recommended. An important role is anticipated for its use in investigating the placental transfer of contaminants, and of their subsequent metabolism and toxicity.

5.1.3. Paper III.

Combinations of variables generated by PCA facilitated our ability to identify prominent dietary sources of OC groups and of the prominent toxic metals Cd, Pb and Hg, as well as highlighting the importance of maternal characteristics (including pregnancy histories and smoking habits). Although the maternal concentrations of the toxic contaminants observed were relatively low, more substantial exposures would be a concern. This is especially worrisome in case of Cd for mothers who smoke cigarettes during pregnancy.

5.2. The context of the observed concentrations of OCs and elements

5.2.1. OCs

When considering sampling year and total fish consumption, the observed concentrations of PCBs and pesticides in maternal sera were comparable in magnitude to those reported for other pregnant women in the Nordic countries (Glynn et al., 2007, 2011; Halldorsson et al.,

2008). They were substantially higher elsewhere in Europe. Soechitram et al. (2004) report 3 to 8 times higher concentrations of POPs in Dutch mothers, while for Slovakian women the factor was 5- to 13-fold (Park et al., 2008). Even higher values (e.g., 10-20 fold for *p,p′*-DDE and the sum of PCBs) have been observed for women of reproductive age in indigenous communities in Northern Canada (Butler Walker et al., 2003; Liberda et al., 2014). In a recent paper from Spain, concentrations in adult women (28 years older than the MISA women) were somewhat higher compared to our subjects ─ specifically, 2.5, 3.9, 6.5 and 3.3 times for *p,p′*-DDE, HCB, PCB 138 and 153, respectively (Fernández-Rodríguez et al., 2015). In 2004/06, pregnant women living on the Mediterranean coast of Spain had comparable PCB concentrations to the MISA participants but were 3-4 times higher for HCB and *p,p′*-DDE. By comparison, those living in the Atlantic coastal areas of the Basque region were about 2-fold higher for the PCBs and fourfold for *p,p′*-DDE than found for the women in our study (Fernández-Rodríguez et al., 2015). A Swedish study conducted in 2010/2011 of women 17 years older than the MISA women reports concentrations for PCBs, HBC, *p,p′*-DDE and trans-Nonachlor twice those reported in Paper III (Bjermo et al., 2013). The prominence of 4-OH-PCB 146 and 187 in maternal sera among the PCBs metabolites in the current study has also been noted by others. Results from the Faroe Islands and Slovakia disclosed higher concentrations [~35-fold (Fängström et al., 2002) and ~ 5.5-fold (Park et al., 2008), respectively] than those presented in Table 3 of Paper II; while those for Dutch mothers (Soechitram et al., 2004) were 2-fold higher (4-OH-PCB 146) and 2-fold lower (4-OH-PCB 187). In this Dutch study, the concentration of 4-OH-PCB 146 was about 3 times that of 4-OH-PCB 187, as opposed to being comparable in our data set.

The first report of OCs for the MISA project was based on a subset of 50 maternal serum samples (Hansen et al., 2010). Despite its limited sample size, the observed concentrations presented as geometric means (GMs) with their range for the 2nd trimester collection deviated only slightly from those summarized in Paper III for the full set (both wet-weight and lipid-adjusted values). Note that the preliminary study did not include mothers from coastal communities. The highest average concentrations were observed for *p,p′*-DDE and, relative to it, the decreasing concentration sequence was comparable to that reported in Hansen et al. (2010) (for both wet-weight and lipid-adjusted values) was seen for the most prominent POPs: *p,p′*-DDE >> PCB 153 > 180 > 138 > HCB > PCB 170. The remaining OCs occurred at lower concentrations with the sequence: PCB 187 > 118 > 163 > *trans*-Nonachlor > PCB 156 > 99 > 183 > *cis*-Nonachlor. The 40 meconium samples had a similar relative

concentration pattern (wet-weight): *p,p'*-DDE>> PCB 153 ≥ HCB > PCB 138 > PCB 118 ~ *trans*-Nonachlor ~ PCB 52 > *cis*-Nonachlor ~ γ-HCH > α-HCH.

As for maternal serum, meconium concentrations appeared to be low, although only few studies employing the more recent analytical methods were available for comparison (Whyatt et al., 2001; Hong et al., 2002; Zhao et al., 2007). Interestingly, the highly chlorinated hepta PCBs (PCB 170, 180, 183 and 187) were all below their limit of detection (LOD) in meconium, which were relatively high. Even though lipid adjustment of meconium concentrations had been suggested by Tuomisto, (2006), it does not appear to have been investigated previously. Our study also appears to be the first to identify hydroxylated PCBs in this medium. Meconium seems poorly investigated for its content of environmental contaminants, although historically it has been employed to assess fetal exposure to nicotine, drugs and alcohol (Gareri et al 2006; Bakdash et al., 2010; Gray et al., 2010).

5.2.2. Elements

The elements were measured in two rounds, with the first set consisting of 211 samples as reported in Hansen et al. (2011). A second batch of 71 was analysed subsequently. The LODs from the first round were somewhat more conservative (slightly higher values) for all ten elements and therefore were used in the current (complete) study. Although some differences in mean concentrations were evident for Cu, Mo and Zn, the relative concentration patterns remained as presented earlier (Hansen et al., 2011). For the toxic elements, the sequence was Pb >> As > Hg > Cd (smokers) > Cd (non-smoker) > Co, with the relative concentrations of the essential elements exhibiting the pattern Zn >> Cu >>> Se >> Mn >> Mo.

The observed concentrations of the toxic elements (As, Cd, Hg and Pb) seem relatively low, but of comparable magnitude to those reported for other pregnant women in Norway (Brantsæter et al., 2010) and Sweden (Gerhardsson and Lundh, 2010). In the Curren et al. (2014) study, which included first time mothers from southern and northern Canada, the lowest concentrations were seen among Canadian-born women from southern Canada and non-Aboriginals from Inuvik; the highest occurred among the Inuit and reflected their lifestyle and local dietary habits. Participants from the Norwegian Fish and Game study, which included males and females and were approximately 20 years older than the MISA women, exhibited somewhat higher levels for As, Cd, Hg and Pb (Birgisdottir et al., 2013). Se whole blood concentrations were also somewhat lower when compared to participants in the

MoBa study (Brantsæter et al., 2010), as well as in the Canadian study referred to (Curren et al., 2014). Although few publications provide concentrations of the essential elements (Cu, Mn, Mo and Zn) in pregnant women, the results from Brazil and South Africa indicate comparable values to the our data set (Rudge et al., 2009, 2011; Röllin et al., 2014). Additional details about established sources are provided in the next section.

On the whole, the observed concentrations of essential elements in blood may be considered normal in the clinical chemistry context, while those for the toxic elements may be deemed relatively low and of no clinical importance (Hansen et al., 2011; Shenkin et al., 2012; Moyer, 2012; Paper III). Nevertheless, some concern remains about maternal and neonatal exposure to Cd among cigarette-smoking mothers, and for the participants with Hg blood concentrations near the maximum values observed. Since the total arsenic measured in blood primarily represents its non-toxic organic forms and was also present in relatively low concentrations, a comment on its risk is not necessary.

5.3. Predictors of sources

5.3.1. OCs in maternal serum

In the multivariable linear-regression models described in Paper III, maternal age, parity, maternal BMI, consumption of fish and other marine products, local traditional foods, vegetables and grain & dairy products and lifestyle issues were shown to contribute to the total variation explained. Fish and seafood products were the major contributors to OCs intake.

It is well documented that the main source of OCs derives from specific dietary items (AMAP, 2003; Long et al., 2015). Due to the persistency, biomagnification and bioaccumulation of OCs, the aquatic food chain constitutes an important source. Previous studies have demonstrated relatively high seafood intake in Northern Norway (VKM, 2006). Relative to the May 2007–June 2009 recruitment period of our MISA study, there are no indications in more recent reports of substantial changes in this consumption pattern (Rylander et al., 2009; VKM, 2014). Our study endorses these observations as fewer than 3 % of the participants reported eating seafood never or seldom, whereas 64 % of this group report an intake of at least one time per week. It also supports the interpretation that marine and freshwater fish constitute important sources of OCs and that the latter accumulate with maternal age, while parity reduces the body burden due to breastfeeding. Avoidance of

seafood constitutes a dilemma, especially during pregnancy, as it is not only rich in essential elements (e.g., Se and Zn) and n-3 PUFA fatty acids but also is a source of toxic substances.

Based on our data, parity seems to be a more consistent predictor than breastfeeding, even though the OC transfer is believed to occur primarily by way of breast milk compared to placental transfer (Needham et al., 2011). The parity data collected was likely more reliable than for breastfeeding. The negative dependence of OC concentrations on BMI observed has been reported previously, as have positive relationships (Wolff et al., 2005, 2007). A negative association between OCs and BMI likely suggests a 'dilution' effect as OCs reside primarily in the lipid tissues. The clear separation of the loadings of POPs on the PC-1 and PC-2 axes in the 'POPs-only' PCA analysis of Paper III is interesting. Hansen et al. (2010) showed that serum concentrations of OCs in our study subjects increased in parallel with circulation lipid concentrations, which are known to be mobilized during pregnancy from fat tissues. Robust loadings of PCBs 180, 153 and 138/163, and *p,p'*-DDE define PC-1, while PC-2 featured HBC, *trans*-NC, *cis*-NC and PCB 118. This grouping is consistent with the findings of Nøst et al. (2013) who demonstrated that, relatively speaking, the latter group contributed considerably less to the total OCs body burden. In addition, the contributions of the PC-2 group decreased during the 1979–2007 period in the Nøst et al. (2013) investigation, while those for the PC-1 group increased. Our multivariate modelling (Paper III) also suggests a greater dependence on marine and local traditional foods of the PC-2 members.

Other than consumption of marine and fresh water foods, wild animals (mainly reindeer, moose and grouse) and local traditional items, other provisions were not as important in understanding the variation in serum POP concentrations. This is born out in other studies. Fish and seafood products as sources for PCBs were estimated to contribute 64 % in a Swedish study (Törnkvist et al., 2011) and 46 % in Belgium and Russia (Voorspoels et al., 2008; Polder et al., 2010). Other food groups supplementing the total PCB intake appear to include: meat (Sweden, 17 %; Belgium, 20 %; and Russia, 10 %), dairy products (Sweden, 14 %; Belgium, 15 %; and Russia, 18 %), and eggs (Sweden, 1 %; Belgium, 9 %; and Russia 13 %). Similarly, and based on calculated serum PCB 153 concentrations observed in the MoBa study, the primary exposure was assigned to the consumption of seagull eggs, fish liver and roe (Caspersen et al., 2013), while Kvalem et al. (2009) determined that semi-oily and oily fish contributed 43 % to the PCB 153 intake for representative consumers and 46 % for high consumers. For the sum of DDTs, fish was found to be a major contributor, namely 51 %

in Sweden and 45 % in Denmark. Dairy products added 26 % (Törnkvist et al., 2011; Fromberg et al., 2005), whereas meat contributed the most in Russia (48 %, with 23 % from fish; Polder et al., 2010). HCB seems to derive from dairy products rather than fish (Törnkvist et al., 2011; Polder et al., 2010). Although current food intake food is relevant, accumulation (and thus age) constitutes an important predictor for body burdens of POPs (Furberg et al., 2002; Hansen et al., 2009; Caspersen et al., 2013; Nøst et al., 2013). This reflects their relatively long half-lives in the body (1–10 years or more, depending on the specific POP; Wolff et al., 2000; AMAP, 2003; Wimmerová et al., 2011). A Norwegian study investigating OC pesticides and toxic elements in farmed salmon for the period 1999–2011 demonstrated decreasing concentrations, and estimated for 2011 that 1.3 kg farmed salmon could be consumed safely before reaching the tolerable weekly intake (TWI) for dioxin and dioxin-like PCBs; by comparison, the amount per week was only 370 g in 1999 (Nøstbakken et al., 2015). Although current exposure is important, a subject's birth year and year of peak exposure ought to be taken into consideration in understanding the body burden in cross-sectional studies (Nøst et al., 2013).

5.3.2. Elements in whole blood

The element axis PC-2 ('All contaminants') in Table 3 of Paper III included high loadings for As, Hg and Se, and demonstrates clearly to be related to seafood intake and in a somewhat weaker fashion to vegetables. The shift from age and parity dependence for OCs to food intake for elements indicated the greater turn-over in the blood compartment for elements (days to months; Nieboer et al 1999) compared to the long half-lives in years of OCs (see Section 5.3.1). Although Hg concentrations were positively associated with age, this predictor did not endure the multivariable linear regression model when food items were included. The grouping of As, Hg and Se corresponds well with other findings from Norway and elsewhere and reflect seafood intake (Birgisdottir et al., 2013; Brantsæter et al., 2010).

The positive association of PC-2 ('All contaminants') with the PC-1('fruits and vegetables') axis in one of the models could be a proxy for the influence of maternal age, since PC-2 Diet ('Marine fish') also shows a positive age dependence, while PC-3 Diet ('Junk food') does not (see Table 5 in Paper III).

Cd and Pb too appear to have unique predictors. It is well established that cigarette smoking is the primary source of Cd in the general population (Charania et al., 2014), and this concurs

with our findings as non-smokers had significantly lower Cd concentrations than smokers (0.15 *versus* 0.42 µg/L; $P_{MV} < 0.001$). These concentrations are approximately in the same range as earlier findings for pregnant women in Norway (Odland et al., 1999), but are lower than reports for the general population (Birgisdottir et al., 2013) and international levels of concern of 1.4 -1.7 µg/L (Charania et al., 2014). Grains and cereals can also be sources of Cd as discussed by Adams et al. (2011) and confirmed in our study (see Paper III). Smoking constitutes a minor source of Pb and this is suggested by our data for current smokers (P_{MV} = 0.004). Contaminated soil and vegetables grown in them, as well as drinking water due to Pb-plumbing in older homes, are also recognized as exposures of concern (Nieboer et al., 2013). Gun use (fumes given off during gun firing contain Pb) and consumption of hunted game (because of embedded Pb pellets and /or fragments) are established sources (Nieboer et al., 2013; Meltzer et al., 2013). In the current study, women living inland were highly represented in the 4th quartile of the whole blood Pb concentrations and higher intake of local terrestrial foods is suggestive (Spearman's correlation coefficient of $\rho = 0.14$, $p = 0.02$). Interestingly, Jain (2013) concluded for women of age 17-39 that pregnancy itself might accelerate the clearance of Cd and Pb (as well as Hg) from blood.

The discussion in Paper III was limited to those PCA axes that correlated with dietary and/or personal characteristics, namely PC-1, PCA -2 and PCA-6 of Model 1 ('All contaminants') and PC-1 and PC-2 of Model 2 ('POPs only'). It seems appropriate to focus briefly on the grouping of the elements in Model 3 ('Elements only'). The following pairing of axes for Models 1 and 3 occurred and the elements that had prominent loadings in each are indicated: respectively, PCA-2/PCA-1 (As, Hg, Se); PCA-3/PCA-2 (Co, Mn); PCA-4/PCA-5 (Cu and Mo); PCA-5/PCA-4 (Zn); and PCA-6/PCA-3(Cd, Pb). Of these, Zn and the Co & Mn, Cu & Mo pairs have not yet been discussed. Zn stands out because its concentration in whole blood was 8 000- to near one million-fold higher than the other elements, except Cu for which the factor was around 50. As mentioned in Sections 1.8.1 and 1.8.2, Mn and Co share leafy vegetables and cereals as sources, and legumes stand out for Cu and Mo. As pointed out earlier (Section 1.8.1), the latter two elements participate in critical biochemical oxidation-reduction reactions, and excess Mo can block Cu uptake. These examples demonstrate the discriminating versatility of PCA.

5.3.3. POPs in meconium

The most distinct predictor of POPs in meconium was maternal serum concentrations (Paper II). On a wet-weight basis, median maternal serum/meconium ratios of pesticides and PCB 118 favoured meconium, while the other PCBs and their metabolites favoured maternal serum. Lipid adjustment in the small subset of 15 meconium samples showed that all contaminants showed a preference for meconium except 4-OH-PCB 146 (a ratio of 1.04). Needham et al. (2011) and Vizcaino et al. (2014) both analysed transport of POPs across the human placenta and found the dominant concentrations occurred in maternal serum rather than cord blood, both for wet-weight levels and lipid adjusted concentrations. Cord blood depicts a snapshot of the present exposure because of the steady exchange with maternal blood, whereas there is a continuous accumulation of meconium throughout pregnancy with practically no leaching. This likely explains the higher concentrations observed in meconium compared to maternal serum. The precursor (PCB 138 or 153)/hydroxylated form (4-OH-PCB 146) ratios were almost 3 times higher in meconium compared to maternal serum, while the precursors showed little preference. This supports the suggestion that metabolism in the mother is more efficient than in the fetus (Vizcaino et al., 2014), and that the hydroxylated form prefers maternal serum.

5.3.4. Pertinent dietary issues

A consideration of whether to exceed or limit seafood intake during pregnancy is often seen in light of a balance between the intake of essential nutrients and contaminants. As mentioned earlier, younger women tend to have a lower fish intake. In this context, our findings in Papers I and III indicate that the consumption of junk food was negatively associated with maternal age and education, but positively for BMI. Similarly, intake of unhealthy food intake (including soda pop, fast food, snacks, sweets and sugar added to coffee or tea) was most profound among young men and women selected from the general population, while consumption of local traditional food increased with age (Bjerregaard and Jeppesen, 2010). In Spain, the term Mediterranean diet is considered local traditional food, and includes fruit, vegetables, high levels of monounsaturated fatty acids (MUFA; primarily from olive oil), moderate intake of fresh fish, poultry and eggs (Olmedo-Requenaet al., 2014). These authors also report low adherence to this diet by pregnant women: younger age, lower social class, primary educational level, and aspects of an unhealthy lifestyle (e.g., smoking and lack of exercise) were associated with low adherence to a Mediterranean diet.

The consideration to limit or increase fish intake during pregnancy can be guided by available sources and personal choices. Mahaffey et al. (2011) provide a framework for dietary advice on how to maximize the dietary intake of n-3 PUFAs, while minimizing MeHg exposure. This is in accordance with the Norwegian recommendations on seafood intake (Matportalen, 2015). Since women in the USA tended to avoid fish and fish products, the U.S Food and Drug Administration (FDA, 2014) has issued updated recommendations. Pregnant women are not only advised about a maximum intake of fish but also a minimum (although some specific species are still to be avoided, such as tilefish from the Gulf of Mexico, shark, swordfish and king mackerel). The motivating rationale was to avoid omitting nutrients with known positive impact on fetal growth and development.

5.4. Study limitations

5.4.1. Study design

The MISA study is a cross-sectional study with longitudinal aspects with the objective of establishing a new mother-and-child contaminant cohort study. The characteristic features of the cross-sectional method are to provide a point in time estimate of an outcome and to define its prevalence (Kirkwood, 2003). This is in contrast to cohort studies, in which individuals are followed over time (retrospectively or prospectively), thereby allowing the incidence of an outcome to be evaluated in relation to exposure or other determining factors (Kirkwood, 2003).

The MISA database was designed to explore associations between contaminant exposure and diet, with an objective to enhance our knowledge of the interplay of physiological changes that occur in mothers during pregnancy in the context of exposure to environmental contaminants (including their transfer to the infant before and after birth), and conducting prospective health studies of the children.

Paper I addressed the issue of representativeness, whether the selected study subjects who completed the entire study protocol differed from a drop-out group, as well from all mothers who delivered in Northern Norway during the study period (2004-06). Paper II was designed to assess the usefulness of meconium in assessing contaminant transfer from the mother to the fetus. Subsequently, Paper III was devised to investigate how the generation of new multi-contaminant and dietary variables generated by PCA might help to identify prominent sources of OCs and toxic elements.

5.4.2. Sample size

An essential component of planning an investigation is to decide how many people need to be included in a study (Kirkwood, 2003). This is referred to as sample size. Studies that are larger than needed are inefficient and wasteful in terms of both money and scarce epidemiological expertise, and when too small may provide misleading answers or at least imprecise findings (Bhopal, 2002). Sample size calculations help to determine whether the research question and the stated study hypothesis can be quantified. If a difference between groups is assessed, its minimum should be stated at the appropriate statistical significance and power. The sample size should be large enough to avoid Type I errors (usually a significance level of $\alpha \leq 0.05$ is acceptable) and Type II errors (usually a value of $\beta \leq 0.20$ is the target); α is the probability of making an error in rejecting the null hypothesis (Type I error), β the probability of conducting a Type II error, and $1-\beta$ the power of the test (i.e., probability that we *do not* make a Type II error) (Bhopal, 2002; Kirkwood, 2003).

Paper I deals with the group that completed the study protocol. The response was lower than expected and there were drop-outs. However, the agreement of selected characteristics of the study cohort (n = 391) and the drop-out group (n = 113), as well as with all delivering mothers in Northern Norway during 2004-06, implies acceptable randomization (i.e., equal distribution of confounders; Bonita et al., 2006) and thus good statistical power. Paper II includes a small subset of 40 samples, was exploratory, and its intention was to highlight the sampling and analytical processes. Furthermore, only a fraction of the 15 meconium samples were large enough for lipid analysis. Clearly, studies with larger sample sizes are needed to enhance power (i.e., the likelihood of detecting differences). Paper III included the entire study group with sample sizes between 250 and 498. Compared to our first report on OCs (Hansen et al., 2010), the current sample size increased from 50 to 266 for the 'All contaminants' group, and to 498 for the 'POPs only' category. Similarly for the inorganic elements, n increased from 219 (Hansen et al., 2011) to 266 and 279, respectively for the 'All contaminants' and 'Elements only' group PCA analyses. Consequently, the Paper III findings embody appropriate statistical power and discernment.

5.4.3. Bias

A systematic difference between the true and observed value constitutes bias. However, even the most rigorously designed investigation will be susceptible to one or more types of bias.

Reasons for this includes the manner in which subjects are selected and information is obtained, reported or interpreted (Hennekens, 1987; Laake, 2007; Bonita et al., 2006).

Selection bias

This form of bias occurs when there is a systematic difference between those individuals who are willing to enter a study and those who are not (i.e., in terms of age, socio-economic status, dietary intake, and exposure status). The challenge of representativeness is an important matter, although difficult to avoid. This can be dealt with by study design and adopting valid and reliable procedures for defining/selecting the study subjects (random sampling methods are preferred). If eligible study subjects are self-selected (i.e., self-determined selection), bias may be unavoidable. When planning a project, unforeseen errors of bias can obscure the result of a study. (Hennekens, 1987; Bhopal, 2002; Laake, 2007). Although we made several attempts to increase the participation rate throughout the recruitment period, the enrolment remained sluggish. Study tiredness among those eligible and competition with other studies are suspected. The final participation rate was 20 %.

In Paper I we compared the study-subjects to the drop-outs and to all delivering women in Northern Norway during the same period. The two latter groups showed similarities and, but on average were two years younger than the study group and tended to smoke more. Other parameters were of comparable magnitude between the 3 groups, such as annual household income, parity, gestational age and birth weight. The contaminant concentrations studied are known to be associated with food intake (AMAP, 2009). Neither fish intake nor of local traditional foods differed between the study-cohort and the dropout group, as these dietary sources were predictors of concentrations of POPs and the most toxic elements (respectively in maternal serum or whole blood as described in Paper III). For these reasons, we believe that the bias introduced in the project was minimal. In Paper II, we randomly selected a small number of samples to investigate the analytical methodologies for analysing meconium, thereby making selection bias less probable.

Measurement bias

The gestational inclusion period was longer than anticipated, ranging from 9-36 weeks (95th percentile of 13-24) and thereby included some pregnancies from each trimester. However, the vast majority of the participants were sampled in the 2nd trimester (95.4 %). We cannot rule out the possibility that this wide inclusion period may have influenced the contaminant

concentrations of OCs in maternal serum and the elements in whole blood. However, we have evidence that the influence was minor for both the OCs and the toxic elements. As outlined in Hansen et al. (2010), OC concentrations changed across the 3 sampling periods (i.e., pregnancy, and 3 days and 6 weeks postpartum) and followed the measured lipid concentration profiles. Furthermore, lipid adjustment removed most of the variation, especially between samples taken during pregnancy and the early postpartum days. From the predicted geometric concentrations of the elements during the entire experimental period, it is evident that for nearly all the elements concentration changes were minimal during the pregnancy, with Mn and Cu changing the most [respectively increasing around 40 % and 30 %, with the rather low (but increasing) levels of Co stabilizing at week 24; Hansen et al., 2011)]. As outlined by the latter authors, the concentration patterns across the pregnancy, delivery and postpartum period could be interpreted in terms of underlying metabolic, haematological and physiological changes that occur in mothers, as well as the element-specific biochemistry and distribution patterns within the blood compartment and breast milk.

Information bias

When imperfect definitions of study variables or flawed data collection procedures are used (Hennekens, 1987; Bhopal, 2002; Szklo, 2007), information bias occurs. In our study, this was forestalled through joint meetings with project personnel at the sampling sites prior to recruitment (as described in Paper I). Potential errors were minimized by training and providing them with clearly written protocols and instructions. When potential errors in information/data were identified, they were investigated before entering them into the database or corrected when identified during the statistical analyses.

Recall bias

Another type of information bias of concern in dietary studies is related to recall by the participants of food intake. A selective memory can lead to either and over- or underestimation of, for example, the association between exposure and/or disease (Hennekens, 1987; Bhopal, 2002; Szklo, 2007). The FFQ helps to minimize recall errors as it focuses on foods consumed on a regular basis, and can thus assist in identifying consumer trends in the population investigated. For example, seasonal variation can be detected in the consumption of certain foods as being low, medium or high (Willett, 2013; Cameron, 1988).

5.4.4. Validity and reliability

High validity together with high reliability is the objective in all studies, which allows true values to be measured with high confidence. Internal validity pertains to whether a study applies to the population for which it was designed in terms of selection and information bias. By contrast, external validity refers to the generalizability of the research findings and its applicability to a wider population. Thus one might ask if our study participants were/or were not representative of pregnant women elsewhere such as in other parts of Norway (Bowling, 2002; Kirkwood, 2003; Bonita et al., 2006). The favourable comparisons of our findings with studies of comparable Norwegian populations and elsewhere in terms of the contaminant concentrations and their predictors/sources attest to good validity.

The validated FFQ (Parr et al., 2006; Hjartåker et al., 2007) used in the MISA study was first employed in the NOWAC study, which targeted women 14 years older than those in the MISA group (Hjartåker et al., 2007). It included eight major dietary topics, each divided into specific foods with four to seven fixed options, and with consumption ranging from never/seldom to either five to seven times per week, or 2+ times per day; when feasible, portion size was also asked for. The NOWAC FFQ was validated using a test-retest approach by mailing the same questionnaire to a random sample twice and the reproducibility of the dietary information was within the range reported for similar instruments (Parr et al., 2006). Additionally, it was compared to repeated 24-hour recalls and about 3 % of the observations on nutrient intake fell in the opposite (same *versus* extreme) quintile (Hjartåker et al., 2007). We adopted the NOWAC FFQ for the MISA study with only minor changes. This involved extending the questions about seafood and local traditional foods to include whale/seal, sea gull eggs, reindeer, moose, grouse and local berries. The latter is not expected to have impacted the validity of the FFQ.

Recorded intake in our study was converted to standard portions (Blaker and Aarsland, 1995) and to daily energy intake through macro- and micro-nutrients (Matvaretabellen, 2014). Standardization of portions and intake can lead to under and/or over estimation of the actual consumption (Willett, 1998) because portion sizes may be difficult to estimate despite being specified in the FFQ. Furthermore, precautions should be taken when a questionnaire is used in situations different from the original purpose, as well as when the length of the questionnaire is altered (Willett, 2013). In light of this, it seems reasonable to assume that the higher average intake in the MISA group compared to the NOWAC population (Hjartåker et

al., 2007) is explained by the inverse relationship between age and food intake. Compared to the MoBa study (Meltzer et al., 2008), the observed lower energy intake by similarly aged pregnant women in the present study may have been influenced by MoBa's more detailed dietary section as discussed in Paper I. Nevertheless, nutrient density (nutrient intake per MJ) was in good compliance with the NNR (2012) estimate.

In terms of applying the NOWAC FFQ to pregnant women, dietary habits may be influenced by nausea, vomiting, and constipation (Meltzer et al., 2008). The MISA dietary information covered the intake for the preceding 12 months, of which 6 to 7 months were in the pre-pregnancy period and the remainder within the first 18 weeks of pregnancy for nearly all the participants, even though the 95-percentile span was 13 to 24 gestational weeks. Despite possible dietary changes, especially in early pregnancy, it is concluded that this had a minor influence on the POP concentrations in maternal serum across the pregnancy and postpartum periods because of the long half-lives of POPs in humans (see Section 5.3.1). As discussed in Section 5.4.3, other than for Mn and Cu, the changes in concentrations of the toxic and other essential elements during pregnancy were relatively minor.

5.4.5. Confounding

Confounding is a function of the complex interrelationships between various exposures and diseases and translates into errors in estimating the magnitude of an association between a specific risk factor and disease outcome (Hennekens, 1987; Bhopal, 2002). Generally speaking, confounding occurs when a variable is associated with the exposure and also influences the outcome. Note that a variable that is part of the causal chain leading from the exposure to the outcome is not a confounder (Kirkwood, 2003). This is likely to happen in observational studies, but adjustments for this can be made in the statistical analyses. As a rule-of-thumb, confounding likely occurs when the effect estimate changes 20-25 % after adjustment. When this happens then the relationship assessed by the unadjusted effect estimate would not be valid (Hennekens, 1987; Laake, 2007; Szklo, 2007).

In Paper I, we observed that the women in our study were somewhat older and smoked less compared to all 2004-2006 mothers in the MBRN. Maternal age and contaminant concentrations (specifically POPs and the toxic metals Cd, Hg and Pb) are known to be positively associated with age (AMAP, 2009), as are choices of certain foods as indicated by the findings summarized in Supplementary Table S1 of Paper I (fish & fish products and

miscellaneous items). Since age and parity are known confounder variables in the source modelling of POPs and dietary choices, they were included in the pertinent multivariable regression models of the OC and dietary axes (see Table 5 in Paper III). The predictor variables included in the multivariable model were those that were statistically significant in the univariable regression models. Those not reported in Table 5 of Paper III did not alter the models presented. Paper II was necessarily limited to a small subset of mothers and their newborns, and only a limited number of explanatory variables could be included in the regression models; for the 15 lipid–adjusted samples multivariable models were not constructed.

6. CONCLUDING REMARKS

Although the project was comprehensive, a smaller sample size than targeted resulted, and therefore our findings are less representative than envisaged. A comparison of personal and clinical characteristics registered in the MNBR for the study cohort and the drop-out group indicated only small differences, namely that the latter were somewhat younger, had less education and smoked more. Comparisons of maternal and newborn information for the study cohort with all births in Northern Norway during the study period also indicted good agreement (e.g., for average birth weight, gestational age, parity and a proportion of obstetrical complications). Dietary findings, such as the relatively high intake of fish and fish products, were also in accordance with those reported for Northern Norway. Based on these comparisons, we conclude that a minimal of bias has been introduced into the MISA cohort study.

Our investigation of meconium as a biological medium for determining fetal exposure to POPs was the first to report the presence of hydroxylated PCBs in newborn stool. The overall multivariate linear regression model improved when gestational age and time of sample collection was included as explanatory variables. Although analytically challenging, a small subset of 15 meconium samples was adjusted for lipids and this is viewed as a crucial component for using meconium as an informative fetal exposure medium. The multivariable linear regression models confirmed that maternal serum concentration and gestational age were the most consistent predictors of POPs in meconium. Time of meconium sampling improved the models for the OC pesticides.

Maternal serum concentrations of pesticides, PCBs and hydroxylated PCBs were generally low compared to results from other countries, but comparable to findings from Norway (including data on pregnant women). It is concluded that they are not of clinical importance, and thus are of no special concern to pregnant women, the unborn, females of reproductive age and children. It was difficult to make such comparisons for meconium because of differences in the analytical methods and absence of reports on hydroxylated PCBs in this medium. Nevertheless, *p,p'*-DDE was the most prominent OC contaminant as in published studies on meconium.

The MISA cohort constitutes a homogenous group being one gender, of limited age span and with a fairly similar dietary intake. Nevertheless, the PCA analyses of OCs, elements and

dietary items revealed distinct patterns for each. This was enhanced by the novel approach that considered all contaminants and all elements measured in maternal serum or whole blood at once in the PCA analyses, or all of the POPs (in serum), or all of the elements (in whole blood) separately. The 3 PCA axes that had loadings by all OCs (Model 1), by all but one of the PCBs and *p,p′*-DDE (Model 2), or by OC pesticides and PCB-118 (Model 2) all identified maternal age (+), parity (–) and fish consumption (+) as important predictors. The OC pesticides/PCB-118 group showed a stronger dependence on the consumption of seafood than the PCBs/*p,p′*-DDE group, which is interpreted to reflect higher body stores of the latter. We also detected a clear connection between seafood intake and whole blood concentrations of Hg, As and Se, while smoking and consumption of local traditional foods was linked to Cd and Pb concentrations. The PCA was also helpful in generating new dietary variables that were labelled as 'fruit & vegetables', 'marine fish', and 'junk food' axes. All three showed a dependence on maternal age and were helpful in the multivariate models described above. Clearly, using PCA to generate new variables by linear combination facilitated our ability to identify prominent dietary sources and maternal predictors of PCBs and OC pesticides in maternal serum, and of the prominent toxic elements As, Cd, Pb and Hg and the essential element Se in maternal whole blood.

The observed concentrations of Cd, Pb and Hg in whole blood were relatively low, but some worry remains about maternal and neonatal exposures to Cd among cigarette-smoking mothers and for the participants with Hg blood values near the maximum values observed. Since the total arsenic measured in blood primarily represents its non-toxic organic forms and was present in relatively low concentrations, a comment on its risk is not warranted.

7. FUTURE PERSPECTIVES

7.1. Suggestions for follow-up experiments or investigations

- Further investigate the usefulness of meconium as a biomonitoring medium by conducting a study with a larger sample size; lipid-adjust all measured concentrations of OCs and other lipid-soluble toxicants:
    - POPs
    - Essential and toxic elements
    - Other toxic substances (see below)
- In the same study, collect and analyse umbilical cord blood, newborn blood, and maternal serum and blood to permit investigation of the inter-relationships between the measured concentrations of the indicated substances in these body fluids and meconium:
    - POPs
    - Essential and toxic elements
    - Newly emerging toxic substances
- Include samples of breast milk to enhance the infant findings.
- Plan to follow-up the children at suitable intervals as they grow-up (a prospective longitudinal study that includes collecting developmental and lifestyle information, as well conducting suitable clinical chemistry measurements).
- Molecular phenotyping might be considered.

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Appendix

Basis for Paper I, II & III
Invitation letter
Questionnaire
Enquiry (Breastfeeding history)

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

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!

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: .....

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dag mnd

Dato .....

Preparatnavn: .....

(Ikke skriv her →)

dag mnd

Dato .....

Preparatnavn: .....

(Ikke skriv her →)

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

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!

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!