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DEPARTMENT OF COMMUNITY MEDICINE, FACULTY OF HEALTH SCIENCES
UNIVERSITY OF TROMSØ

MATERNAL CONCENTRATIONS, PREDICTORS AND CHANGE IN PROFILES OF ORGANOCHLORINES, TOXIC AND ESSENTIAL ELEMENTS DURING PREGNANCY AND POSTPARTUM

The Vietnamese Mother-and-Child Study and the Northern Norwegian Mother-and-Child Study

Solrunn Hansen

A dissertation for the degree of Philosophiae Doctor

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Department of Community Medicine
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Tromsø, Norway

"Walker, there is no road;
the road is made by walking."
Antonio Machado, 1912

To Jacob and my parents

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Hillesøy, May 2011
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ABSTRACT

Persistent toxic substances like organochlorines (OCs) and certain toxic metals have been or are extensively used, and can be globally distributed by long-range transport. The fetus and growing child are exposed *via* the placenta and breast milk and are vulnerable to their negative health effects. Concentrations measured in maternal blood or breast milk are thus potential indicators of risk for the next generation. Internal and external factors contribute to the maternal body burden of these toxicants including: age, parity, lactation, diet, past and current exposures, and the half-life of the contaminant in the body. Essential elements can modify the gastrointestinal absorption of toxic elements and thereby influence the negative impact of the latter. During the gestational and postpartum periods, remarkable physiological adaptions occur, and such changes have the potential to affect the maternal blood levels of persistent toxic substances and essential elements during these critical windows.

The main objectives of this thesis research were to: investigate maternal concentrations of OCs and non-essential (toxic) and essential elements in the context of a northern-southern latitude perspective; identify exposure predictors; and investigate the influence of physiological changes and related pregnancy adaptations during the gestational and postpartum periods.

The present work included pregnant and delivering women from two mother-and-child-studies from Northern Norway (participant subsets of 50 and 211) and two communities in Southern Vietnam (total participants of 189), carried out respectively in 2007-09 and 2005. A suite of selected OC contaminants were analyzed in both study groups, and 5 toxic and 5 essential elements were additionally analyzed in the Northern Norwegian group. For the latter, changes in concentrations of all substances were investigated between three different collection periods: during the 2nd trimester, and at 3 days and 6 weeks postpartum.

In the North Norwegian study, low maternal concentrations of both OCs and toxic elements, and normal levels of essential elements, were generally observed. The Vietnamese study demonstrated relatively high levels of *p,p'*-DDE and *p,p'*-DDT, among the highest globally speaking and possibly reflecting recent or current use. In contrast, the concentrations of PCBs were somewhat lower than those found among the Norwegian mothers.

For the OCs, age (positive) and parity (negative) were strong predictors, with the latter being strongly associated with lactation. For the elements, the exposure predictors were limited to mercury, namely age (positive) and parity (negative). Place of living was associated with the observed OC concentrations for the Vietnamese participants, and Sámi ethnicity for elements in the North Norwegian survey; both findings probably reflect different dietary patterns. Diet as a source was only assessed for the toxic and essential elements. Fish consumption was found to be a strong predictor for arsenic, mercury and selenium. Although not investigated in detail, fish and seafood intake can also be an important contributor to serum or plasma OCs levels. The lower PCB concentrations observed in Vietnam in combination with published suggestions of higher fish intake suggest the consumption of smaller, younger, and lean fish

species in combination with low environmental deposition by long-range transport and minor local sources.

It is concluded that precaution (including dietary advice) is still relevant and important. In Vietnam, there is also a need to make pesticide-use restrictions more effective by providing the public with information on their possible health effects.

The most important findings are probably the patterns revealed for the concentrations of OCs and the non-essential (toxic) and essential elements as they appeared to be driven by the physiological adaptations during pregnancy. The wet-weight concentrations of the lipid-soluble OCs followed the changes in lipid profiles that peaked at birth. In addition to paralleling metabolic, hematological and physiological changes during the gestational and postpartum periods, the concentrations of the elements also reflected their biochemistry and their accumulation preferences within the whole-blood compartment and breast milk. Our systematic approach and findings give a new understanding of the changing concentrations of toxicants and essential elements during pregnancy and have implications for the optimum monitoring time.

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LIST OF PAPERS

The thesis is based on the following three papers, and they will be referred to by the use of their roman numbers.

I. Maternal levels of organochlorines in two communities in southern Vietnam.
Hansen S, Odland JØ, Phi DT, Nieboer E, Sandanger TM.
Sci Total Environ. 2009 Dec 20;408(2):225-32.

II. Levels of organochlorines and lipids across pregnancy, delivery and postpartum periods in women from Northern Norway.
Hansen S, Nieboer E, Odland JO, Wilsgaard T, Veyhe AS, Sandanger TM.
J Environ Monit. 2010; 12:2128-2137.

III. Changes in maternal blood concentrations of selected essential and toxic elements during and after pregnancy
Hansen S, Nieboer E, Sandanger TM, Wilsgaard T, Thomassen Y, Veyhe AS, Odland JO.
J Environ Monit., provisionally accepted for publication on April 19, 2011.

ABBREVIATIONS

AhR	Aryl hydrocarbon-receptor
AM	Arithmetic means
AMA	American Medical Association
AMAP	Arctic Monitoring and Assessment Programme
ANOVA	Analysis of variance
As	Arsenic
BMI	Body mass index
Ca	Calcium
Cd	Cadmium
CHL	Chlordane
Co	Cobalt
Cu	Copper
CYP	Cytochrome P450
DDD	Dichlorodiphenyl dichloroethane
DDE (or *p,p'*-DDE)	Dichlorodiphenyl dichloroethene
DDT (or *p,p'*-DDT)	Dichlorodiphenyl trichloroethane
DK	Dien Khanh
dl	Dioxin-like
FFQ	Food Frequency Questionnaire
GM	Geometric means
HCB	Hexachlorobenzene
HCH	Hexachlorocyclohexane
HDLs	High-density-lipoproteins
Hg	Mercury
Hg^0	Elemental mercury
Hg^{2+}	Mercuric ion
hPL	Human placental lactogen
IARC	International Agency for Research on Cancer
ISM	Department of Community Medicine
LDLs	Low density-lipoproteins
LOD	Limit of detection
MBR	The Medical Birth Registry of Norway
MeHg	Methyl mercury
MISA	[Miljøgifter i svangerskapet og i ammeperioden]
Mn	Manganese
Mo	Molybdenum
ndl	Non-dioxin-like
NILU	Norwegian Institute for Air Research

NIOH	The National Institute for Occupational Health
NOWAC	The Norwegian Women and Cancer study
NT	Nha Trang
OC(s)	Organochlorine(s)
OCP(s)	Organochlorine pesticide(s)
P1	2nd Trimester
P2	3 Days postpartum
P3	6 Weeks postpartum
Pb	Lead
PCB(s)	Polychlorinated biphenyl(s);
POPs	Persistent Organic Pollutants
PTS	Persistent Toxic Substances
QA/QC	Quality assurance and quality control
r	Pearson's correlation coefficient
RDAs	Recommended dietary allowances
RDIs	Recommended dietary intakes
Se	Selenium
WHO	World Health Organization
Zn	Zinc

INTRODUCTION

Both man-made synthetic substances such as organochlorines (OCs) and some naturally occurring substances like toxic non-essential elements are classified as Persistent Toxic Substances (PTS). They exhibit the following properties: *persistence,* degrade very slowly, are stable under most environmental conditions, and endure in the environment for years; *bioaccumulation,* concentrations increase in an individual living organism as it grows older; *biomagnification,* concentrations increase along the food chain; and can be *toxic* even in small concentrations [1]. The adverse effects can threaten human life as well as the next generation. Thus maternal exposure is of special concern, as it determines the risk for the fetus and lactating child. This provides one context of the current work. Another aspect concerns essential elements, which can generate disease when uptake is deficient or too high.

All humans are exposed to contaminants. Exposure sets in as early as during gametogenesis, and continues through pregnancy and the lactation period, early development, and throughout life. The gestational period, and especially organogenesis, is stated to be the most sensitive period for the growing embryo or fetus and the early postnatal life [2, 3]. Vulnerability compared to adults is increased due to undeveloped biologically systems, including physiologic and metabolic processes. The impact of contaminants during development can involve "*permanent, life-long differences in physical size, intelligence, behaviour, reproductive ability, and susceptibility to diseases*" (Carpenter, 2002, p. 26) [2]. This has been substantiated by impairment of critical hormonal, immunological and neurological developments [4, 5]. There are suggestions that *in utero* exposure is more relevant for impaired human development than lactational exposure [3, 6]. Due to the high degree of placental and lactational transfer [7, 8], the levels of contaminants in mother's blood and milk can serve as indicators of the potential risk to the fetus and the growing child [9].

Both environmental and human research has demonstrated that the Arctic is a vulnerable area due to atmospheric long-range transport [1, 9-11]. Since 1991, the Arctic Monitoring and Assessment Programme (AMAP) has been an international initiator and leader of such research. Its human health subcommittee initially did not focus on studies of delivering women and their newborns [11, 12]. One of the early studies, and a forerunner of the present project did, namely the mother-and-child study by Odland and co-workers [13-17] in arctic areas of Norway (Finnmark) and Northwest Russia. They compared both essential and non-

essential elements in maternal and neonatal body fluids between the two countries. Additional small pilot studies in 1996 and 2002 were completed respectively in Kirkenes and Bodø (Norway) in a collaborative project between AMAP, the University of Tromsø, and the Norwegian Institute for Air Research (NILU) in Tromsø [9]. Other than these studies, none has primarily focused on pregnant women and newborn in Northern Norway in relation to exposure to environmental contaminants. Populations of Northern Norway living along the coastline are known be high consumers of fish [18, 19], which is associated with intake of organochlorine contaminants and non-essential toxic elements such as mercury [9, 20]. In continuation of the initial studies, the North Norwegian Mother–and-Child Contaminant Study was initiated in 2007.

Also of interest to the University of Tromsø research group, who conducted the studies mentioned above, is the environmental situation in the Southern hemisphere recognised for its apparent extensive presence of local sources of pesticides and with limited deposition by long-range transport. Conversely, this region is a known contributor to contaminant transport to the northern hemisphere [21]. With this in mind, projects were initiated in Africa, Australia, South-America and Asia. In this thesis, the focus will be on Northern Norway with low local contaminant sources and Southern Vietnam. A specific concern there is the aftermath of the Vietnam War, during which there was extensive use of the herbicide Agent Orange and later on pesticides like DDT.

AIMS OF THE THESIS

The basis for the thesis is the North Norwegian Mother-and-Child Study and the Vietnamese Mother-and-Child Study.

The study described has three primary objectives:

(i) Assessment of exposure of pregnant women to environmental contaminants;

(ii) Identify exposure risk factors for organochlorines (OCs), and non-essential and essential elements; and

(iii) To study systematically what factors influence serum/plasma concentrations of OCs and blood levels of elements during gestation and postpartum.

BACKGROUND

Physiological adaption during pregnancy and the postpartum period

No other bodily event requires such drastic changes in physiological adaption than pregnancy, as virtually every organ system is affected. During the gestational period, the development of the uterus and fetus occurs, along with preparation for lactation. To meet this growth, tremendous maternal anatomical, physiological and metabolic processes set in [22]. In understanding the effect of contaminants on pregnancy and lactation, it is essential to have knowledge of these changes. In the following paragraphs, the most central metabolic adaptions are reviewed.

Fat metabolism

During a normal pregnancy, maternal fat deposition is elevated by an average of 3.5 kilogram [22]. Its deposition occurs primarily during mid-pregnancy, is regulated by hormones, and is followed by extensive placental transfer during the last trimester. Lipids are essential in supplying pregnancy hormones and for fetal growth [22]. Supplied from maternal stored fat and nutrition, the levels of serum lipids continuously increase throughout pregnancy, with a slight flattening pattern from week 32 on (see Figure 1). Total serum lipids are elevated by 40-60 % [23], whereas triglycerides increase by as much as 200-400 %, cholesterol by 36 – 60 % [24-26], and phospholipids by 37 % [23].

After pregnancy, the lipid levels decrease with lactation as a driving force [22]. Fat, primarily as triglycerides, is one of the main components of breast milk. Principally fat is under the influence of maternal diet, although mobilization of maternal lifetime fat stores is also activated by deficient caloric intake [27]. Lipid fractions in human milk depend on maternal diet, and its fat content varies with its maturity (2 % in colostrum to 3.6 % in mature milk), the time of the day, and during the feeding of the child [27].

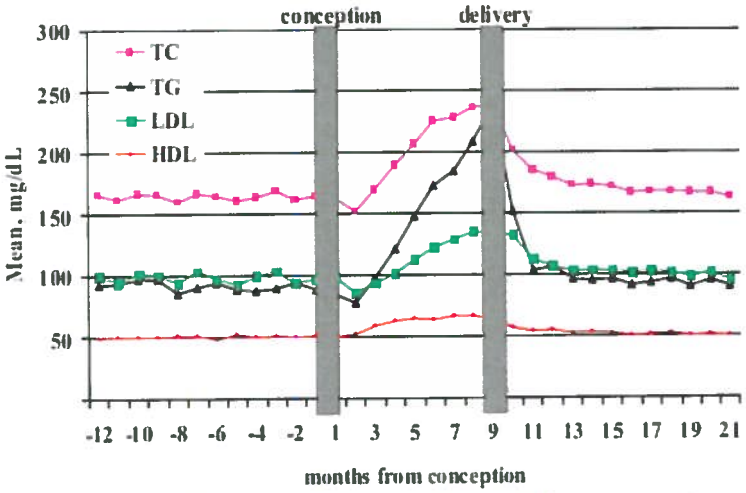


Figure 1 *Levels of total cholesterol (TC), triglycerides (TG), low density lipoproteins (LDL) and high density lipoproteins (HDL) 1 year before, during and 1 year after gestation. Reproduced with permission from Wiznitzer et al., 2009* [25] [Copyright Elsevier (2009)].

Glucose metabolism

Glucose is the major contributor to fetal growth and energy use. In supplying the fetus, the mother has mild fasting-hypoglycaemia, postprandial hyperglycaemia and hyperinsulinemia [22]. Glucose is stored as glycogen mainly in the liver and muscle, and the excess is converted into triglycerides which are transported to adipose tissues. The placental hormone, human placental lactogen (hPL), directs glucose to the fetus by blocking its maternal peripheral uptake and use; it also promotes lipolysis to generate circulating lipids in the mother. In the first half of pregnancy, and before the fetus regulates its own glucose metabolism, starvation elevates the maternal plasma levels of hPL. Fasting leads to an insufficient maternal supply of glucose for the fetus and for the mother's own needs, whereas elevated maternal lipolysis in tissues occurs [22]. Further, glucose as lactose is the main energy source in breast milk; it is generated from maternal blood glucose and its concentration remains relatively constant independent of maternal diet [27].

Hematologic changes

Due to increased demand for perfusion, expansion of the blood volume takes place because of the increased demands to supply blood the uterus, placenta, fetus and maternal vital organs. Blood volume increases rapidly within 32-34 weeks by 40-45 % followed by a plateau, with

the 2nd trimester as the most expansive period [22]. The expansion occurs for both red blood cells and plasma, with the latter almost 2-fold larger, resulting in hematological dilution (physiological anemia) and of proteins. Postpartum hemoglobin levels initially fluctuate. This is followed by an increase above non-pregnant levels due to the combination of elevated red blood cells and decreased plasma volume, although moderated by blood loss [22]. However, the return by 6-weeks postpartum of the blood volume and the extra erythrocyte volume to non-pregnant values is not well understood [22].

Protein metabolism

The increase in protein amounts to one kilo, with the fetus and placenta claiming half and the rest going to the uterus, maternal breasts and production of haemoglobin and plasma proteins [22]. Rather than elevated decomposition of muscles, a more efficient maternal use of dietary proteins is suggested [28]. With low calorie intake, protein metabolism is diverted into energy, rather than to fetal growth and development [22]. Proteins are an important component of breast milk and occur in rather stable amounts, although the exact content is influenced by diet [27].

Micro-nutritional metabolism

Minerals and trace elements are of vital necessity in supporting the fetus and the neonate after birth (through breast milk). The increased requirements are generally achieved by an adequate nutrient-rich diet. With the exception of selenium (Se), maternal supplementation does not affect the mineral milk content [27]. Enhanced uptake mechanisms are evident, including increased maternal absorption and retention as reported for calcium (Ca), and zinc (Zn) [27, 29, 30]. In case of Ca, the intestinal absorption reportedly is doubled [22] and release of Ca from maternal bone also occurs to maintain the requirements of skeletal development in the fetus and infant [29]. Indeed, Ca transfer during the 3-6 months of breastfeeding is greater than by placental transfer [29]. Further, the doubling of the glomerular filtration rate and renal perfusion not only results in elevated loss of nutrients like amino acids and water-soluble vitamins [22], but also stimulates increased reabsorption of elements such as Zn [30].

Metabolic role of the placenta

The placenta plays an important role in regulating of fetal nutrition. Glucose, lipids, hormones, proteins, and other nutritional substances are synthesized in the placenta and are transferred to the fetus in varying degrees. In addition, the placenta acts as a barrier in protecting the fetus from infections and toxicants, although not consistently. The trans-

placental transfer is regulated by several mechanisms. Whereas carbohydrates and lipophilic substances generally have free access, amino acids and fatty acids require active transport. Proteins (except immunoglobulin G) and triglycerides have no direct access, but after hydrolysis transfer as amino acids, and glycerol and fatty acids respectfully [22]. Low- density-lipoproteins (LDLs) and high-density-lipoproteins (HDLs) bind to specific receptors on the maternal syncytiotrophoblast-side of the placenta and are taken up by endocytosis, with the triglycerides, cholesterol esters and the apoprotein being hydrolyzed subsequently in the syncytium [22].

Persistent toxic substances

Organochlorines

Organochlorines (OCs) are synthetic chemicals that were introduced in the 1930s and millions of tons have been produced and disseminated worldwide. Global prohibitions and strict regulations have been in place since the 1970s, and were put into force through the 2004 Stockholm Convention [31]. OCs are lipophilic and are: stored in fatty tissues; slow to decompose; bioaccumulate in the animal food chain; and can be metabolized to yield more toxic substances. To simplify their discussion, these contaminants are divided into polychlorinated biphenyls (PCBs) and organochlorine pesticides (OCPs).

Polychlorinated biphenyls

PCBs are widespread in industrial installations because they were used as: fluids in transformers, capacitors, hydraulic, and heat transfer equipment; and as additives in a range of industrial and consumer products such as paints, flame retardants, coatings etc. [32].

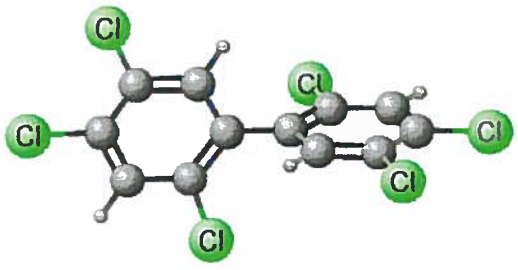


Figure 2
Structure of PCB 153. Green, chlorine atom; white, hydrogen atom; grey, carbon atom

Provided by Eldbjørg Heimstad, NILU and reproduced with permission

PCBs consist of 209 different chemical forms known as congeners and have a complex nomenclature that indicates the position of each chorine atom on the phenyl (benzene) rings (see Figure 2). Through a PCB conversion table, a short-hand nomenclature has been devised in which each congener gets assigned a number e.g. PCB 153 [33]. The exact structures are of vital importance for their physiochemical properties, bioaccumulation, toxicity, degradation, and metabolism [34]. PCBs existed mainly as industrial mixtures [34], and lower molecular weight congeners are known to accumulate less effectively in the food chain [35]. If more than one of the four ortho positions (those next to the link between the 2 phenyl rings) are occupied with chlorine atoms, rotation around this axis is prevented and the two rings cannot assume a flat (planar) orientation with respect to each other. Planar PCB forms appear to be the most toxic (see Footnote 1) [34].

[1]Footnote: Non-ortho coplanar (PCB 77, 81, 126, 169) and mono-ortho coplanar PCBs (PCB 105, 114, 118, 123, 156, 157, 167 & 189), with the remaining as di-ortho PCBs [34]

Organochlorine pesticides

OCPs have been used worldwide in larger quantities as herbicides, fungicides and insecticides for agricultural and disease vector control purposes. In this context, the most common and widespread OCPs will be described [9].

***p,p'*-DDT** (1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)ethane; also referred to as dichlorodiphenyl trichloroethane, DDT) has been widely used as an insecticide for agricultural insects and vector-borne diseases. Despite its banning, *p,p'*-DDT is still used for indoor residual spraying in accordance with the Stockholm Convention and World Health Organization (WHO) guidelines [36]. In 2009, 17 countries were still using *p,p'*-DDT because of its low cost and effectiveness [37]. *p,p'*-DDE (1,1-dichloro-2.2-bis(*p*-chlorophenyl)ethene; also referred to as dichlorodiphenyl dichloroethylene, DDE) is the main metabolite of *p,p'*-DDT. It has a longer-half-life, is more toxic, and usually occurs at higher levels than *p,p'*-DDT, but this depends on the time elapsed since exposure. *p,p'*-DDT exposure occurs primarily during its application, while diet is the main source for *p,p'*-DDE [35]. In humans, *p,p'*-DDT is metabolised to *p,p'*-DDE within about six months [38]. The ratio *p,p'*-DDE/*p,p'*-DDT provides information about how recently exposure took place. *p,p'*-DDE is the most abundant OCP both in the environment and the human body [9, 38].

Hexachlorobenzene (HCB) has been used as a fungicide, but is also employed in the manufacturing of fireworks and ammunition; it can also be a by-product of chemical production and waste incineration [39]. HCB is characterised as moderately volatile with a strong potential for long-range atmospheric transport, and is metabolised to more toxic compounds.

Chlordane (CHL) is an insecticide used for spraying agriculture crops and for indoor control of termites. It is a mixture of many related compounds; *trans*-nonachlor, *cis*-nonachlor, heptachlor, *cis*-chlordane, *trans*-chlordane, *oxy*-chlordane are some of its major forms [40].

Hexachlorocyclohexane (HCH) is an insecticide that can exist in eight chemical forms; of these α(alpha)-, β(beta)-, γ(gamma, *Lindane*)–HCH are among the most stable forms [41]. HCHs have been widely used as agricultural pesticides and for humane mite control, with lindane and especially its synthetic "by-products" (α- and β-HCH) being of highest concern with respect to leakage from waste sites and stockpiles [42]. In 2009, HCHs were included in the Stockholm Convention, and today only one manufacturing plant in India remains operational [42].

Global transportation

OCs are industrial chemicals and by-products and thus were directly released in to the environment, with leakage from waste sites constituting a current source. Their very slow degradation contributes to their environmental persistence. As vapour, or attached to small particles, they move from air, water and soil and vice versa. They can travel long distances, with south to north the main route, *via* the ocean streams and especially by atmospheric transport (see Figure 3). Evaporation and precipitation are regulated by temperature and it accelerates the process [43]. In general, the Arctic area was, or is, far from the production and emission sites. Consequently, rather than the earth's cleanest site, the Arctic has become a sink for global pollutants [1, 9].

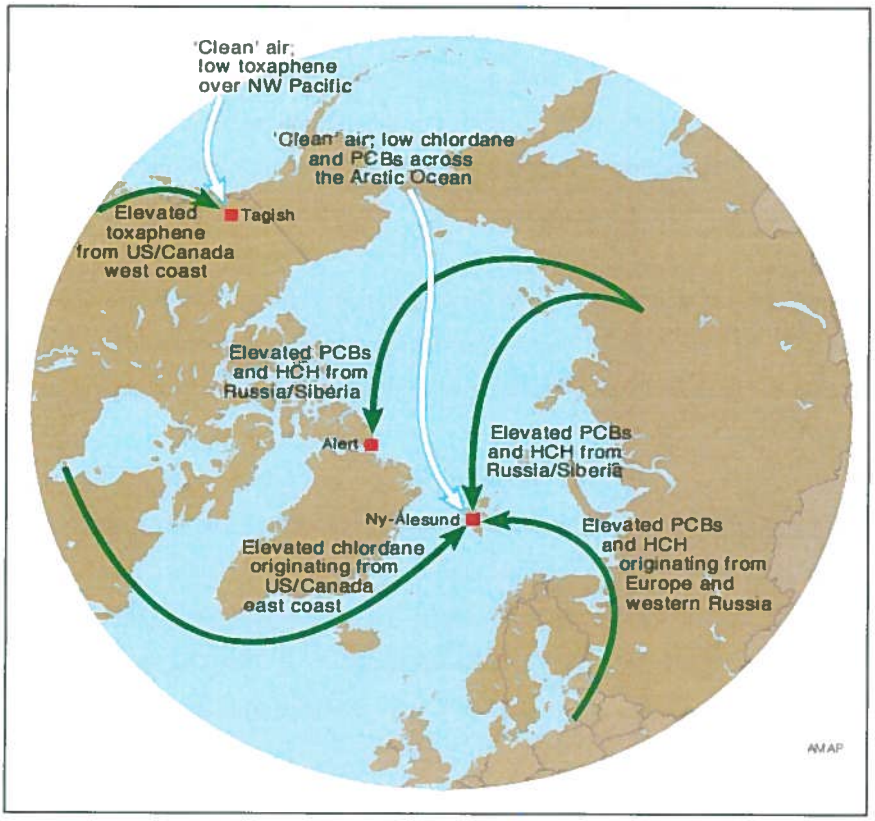


Figure 3 *Long transportation into Arctic area (Source: www.amap.no)*

Environmental distributions of OCs in Norway and Vietnam

Long-range transportation of PCBs and OCs into Norway is calculated to be larger than current local sources [44]. Contamination of the Norwegian coastline by POPs (Persistent Organic Pollutants) is declining and is generally low. Northern Norway is classified as relatively non-polluted. The Climate and Pollution Agency of Norway report a consistent reduction in the use of PTSs during the period 1995-2008; national emissions were halved or more, as illustrated for PCBs in Figure 4 [44]. PCBs were prohibited in 1980 and this involved strict regulations for phasing them out. The main sources today are still rather historical and occur in older building materials, capacitors, transformers and paints. Further, local sources of OCPs in Norway are non-existent. DDT was prohibited in Norway in 1972 and the industrial emission of HCB in Norway has since then declined by more than 90 % [44].

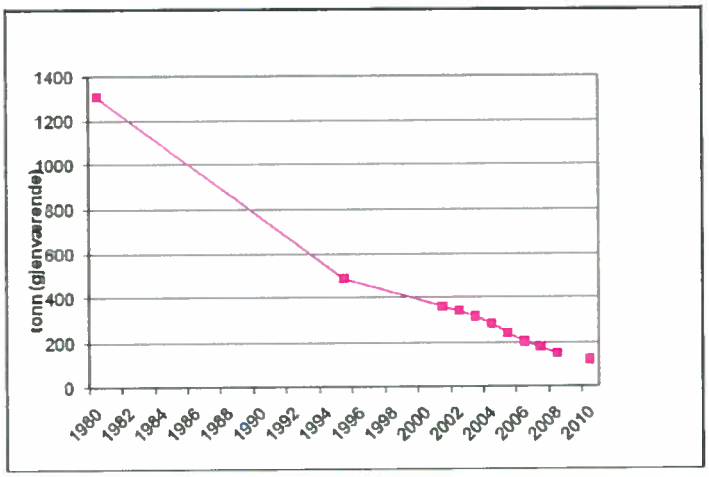


Figure 4 *Out-phasing of PCB in Norway after the prohibition of PCB in 1980 (Reproduced with permission from KLIF [44])*

Due to its geographical location, climate, and atmospheric activity, Vietnam is barely affected by long-way transport [21]. Sources of POPs are primarily of local origin, with PCBs, DDT and HCH having been extensively used in industry, agriculture, vector control and sanitary purposes [45, 46]. Current sources of PCBs are mainly from an expanding industry, including imported PCB-containing transformers oil; contaminated equipment used in the Vietnam War is also of concern [21]. Despite their official prohibition since 1995, illegal supply and recent use of pesticides have been suspected [21]. Even though levels in the environment have been reported to be decreasing in Vietnam, they remain relatively elevated globally speaking [21]. Environmental PCBs concentrations in Vietnam are generally lower than in some developed countries, however with huge local differences in sediment levels [21]. High levels of DDT and DDE have been found in river sediments and soil in both the northern and southern regions of Vietnam, as well as in marine food [21, 47]. Declining trends have recently been reported for DDT and HCH [46].

Exposure of OCs to humans

The routes of human exposure to OCs are by inhalation, skin contact, or through the gastrointestinal tract by eating and drinking. Diet is the main pathway and is estimated to account for 90 % of the total exposure of PCBs [48]. The fetus is exposed by transport across the placenta, and the newborn child *via* breast milk.

OCs bioaccumulate in the fatty food chain, and thus top predators like humans have higher concentrations then the animal species consumed. Low-level contamination of food is found to be the major source of exposure for the general public [49]. Fish, shellfish and marine mammals are the main sources of POPs in the Arctic population [9]. Consumption of meat, poultry and dairy products also contribute somewhat, although they are part of a shorter terrestrial food chain [38, 50]. Of 289 items of Norwegian foods tested, PCB levels were reported to be highest in fish liver, seagull eggs and brown lobster [48].

Among the European and Nordic countries, Norwegians have among the highest fish intake, although with geographical variations [19, 51]. Due to their proximity to the coast, populations living along the Southern Vietnamese coastline are also known to consume significant amounts of seafood [52]. In 1992, Kannan et al. reported fish, shellfish and prawn to be the main source of DDT, and cereals and fruits for PCBs [47]. The latter suggests relatively low fish intake since the highest levels of PCBs were detected in seafood. Recommendations and advice for reducing exposure commonly target vulnerable groups [9]. In Norway, consumption guidelines focus on specific seafood and other items and are based on their content of both OCs and mercury [53].

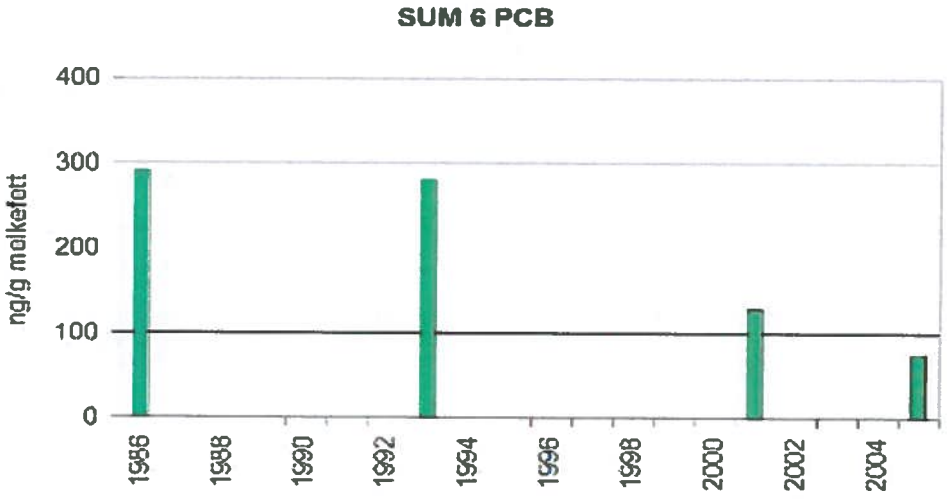


Figure 5 *Concentrations of PCB_6 in maternal breast milk in Norway 1986-2005.*
Reproduced with permission from: The Norwegian Institute of Public Health (www.fhi.no)

Human trends in OCs exposure

As a result of prohibitions and regulations, levels of reported OCs [9, 54-56] are generally declining in most parts of the world. PCBs and DDE are among the most abundant OCs found in human adipose tissues, blood and milk [9, 35]. Higher human levels are primarily associated with recent or ongoing exposures as mentioned above [21]. Since the 1980s, human breast milk levels have declined substantially in Germany as demonstrated by Päpke and Fürst (2003) [57]. Similarly in Norway, breast milk concentrations of PCBs have dropped over time (expressed as the sum of six congeners, PCB_6: namely, PCBs 28, 52, 101, 138, 153, and 180; see Figure 5), as well as of DDT, HCB and HCH [58, 59].

In contrast to the declining trends globally, some increase in levels of breast milk have been observed in Asia (likely due to a later ban and phase out) [45]. Residues in Vietnamese breast milk determined in 2000 were in the following order: DDT>PCBs>HCH>CHL~HCB [60]. Levels of DDT and DDE have been reported to be among the highest globally, whereas CHL was below concentrations observed in developed countries [60]. The elevated PCBs compared to those reported in other Asian countries, and are lower than in developed nations. However, a recent study conducted in 2007 suggests declining levels of OCs but with recent or continued exposure to PCBs [45]. Data on maternal blood plasma/serum levels are very limited.

Absorption, distribution and elimination of OCs

The pathway of OCs involves lipids. OCs are absorbed through the gastrointestinal tract by passive diffusion (as much as 90 % [61]), and are transported through the lymphatic system bound to lipoproteins known as chylomicrons *via* the portal circulation to the liver, and through the systemic circulation to all body tissues [32, 39, 62]. OCs are metabolised mainly in the liver, during which oxidation, reduction or hydrolysis, conjugation and methylation reactions take place [32, 62]. In the liver chylomicrons are broken up, and the OCs are transferred to plasma lipoproteins or to albumin [49]. After entering the blood, OCs achieve a *steady-state* equilibrium condition between the different tissue compartments [61]. Due to continued lipolysis in adipose tissues, regular release of OCs to the circulation occurs [38]. Factors like stress, exercise, weight-loss, and pregnancy increase the lipolysis [22, 38]. In addition, continuous recycling takes place from the liver into the intestine and back, involving bile and cholesterol. A small proportion of the OCs is excreted in the feces, with the rest reabsorbed through enterohepatic circulation. The latter prolongs their half-lives [4, 63], which can exceed 10 years [64]: PCB, ±10 years [65-68]; DDT, 6-8 years [35, 69] with DDE>DDT>

dichlorodiphenyl-dichloroethane (DDD) [62]; HCB, not well known [39]; HCH, 7 years [70]; and CHL 30-60 days are suggested [71]. Half-lives appear to be influenced by the body burdens of OCs, as well as other individual factors [64]. In addition to fecal elimination of these lipophilic pollutants from the human body, breast milk is another route in females. By contrast, water-soluble OC metabolites are excreted *via* the urine [39, 62].

Unadjusted and lipid adjusted blood levels

OC concentrations in plasma or serum are reported as weight per volume (referred to as wet-weight) or weight per unit weight of total lipid (referred to as lipid adjusted). Wet-weight concentrations reflect current exposure and the steady-state circulating levels [61]; they determine the exposure experienced by the fetus. The lipid-adjusted values under steady state conditions are interpreted to constitute a measure of the adipose tissue levels [64]. Wet-weight levels are more sensitive to changes caused by recent dietary intake, for which variations around 30 % have been reported [61].

OCs and human health effects

Humans are exposed to a great number of contaminants. The metabolic mechanisms and the link between contaminants and health are often not well understood. Different pathways exist that allow specific cellular targets to be attacked, with potential disease-related outcomes [2]. Toxicity and type of metabolism depends not only on the dose, individual congeners structure and composition and time of exposure, but also on the concurrent exposure to a mixture of PCB congeners, pesticides and other chemicals; they are probably also influenced by lifestyle, diet and individual genetic make-up [2, 9, 72, 73]. Although less active than dioxin (2,3,7,8-tetrachlorodibenzo-p-dioxin) itself, coplanar PCBs are characterised as dioxin-like (dl) with the same binding to the aryl hydrocarbon-receptor (AhR) and mechanisms of action [2, 34]. Carcinogenic outcomes are of greatest concern. By comparison, non-dioxin-like (ndl) PCBs and OCPs induce other cytochrome P450 (CYP) systems, have affinity for other receptors [34, 74], and elicit other health effects [2]. Further, HCB is a "mixed-type inducer" [75], as it is found to activate both AhR and other cytochrome-mediated pathways.

Experimental animal studies and occupational or environmental accidents have unquestionably demonstrated the toxicity of OCs. PCBs and OCPs are potential endocrine disrupters, and have the potential to induce endocrine, neurodevelopmental, immunological and reproductive dysfunctions, and many are designated by IARC (International Agency for Research on Cancer) as *possibly carcinogenic to humans* (Group 2B; DDT, HCB, HCH,

CHL) or *probably carcinogenic to humans* (Group 2A; PCBs) [76, 77]. Undoubtedly, *"it is clear that exposure to POPS can adversely affect prenatal and postnatal development in human populations."* (AMAP, 2009, p.187) [9]. Background studies involving exposure primarily from normal diets have generally demonstrated inconsistent findings [35, 78, 79].

The most abundant OCs such as PCBs and DDE have been most studied in terms health effects. Recent reviews by Goodman (2010) [80] and Boucher (2009) [81] on neurodevelopmental disruptions involving impairment of cognitive functions related to prenatal PCB exposure provide some insight. Low and high exposures of infants and children have been reported for fish consuming populations. Despite some inconsistency in results, neurotoxicity and background levels of PCB are suggested relevant [9, 80, 81]. Methodological aspects of the studies are highlighted as factors that contribute to explaining the discrepancies between studies [80, 81]. For DDE, Rogan et al. (2005) [78] and Eskenazi et al. (2008) [82] have reviewed the inconsistent findings for DDE and neurodevelopment in infants and children, but do suggest that a negative association of mental and psychomotor development with maternal DDT serum levels exists [82]. Further, both PCB*s* and DDE studies indicate associations with abortions, gestational age, low birth weight and postnatal growth, but the results are inconsistent [9, 35, 78, 83]. Also effects on the endocrine system involving changes in thyroid hormone levels are not clear [78, 79]. Associations with impaired immune systems and reduced effect of vaccinations (PCBs) and elevated rate of infections (PCBs, but also DDE and HCB) have been reported, respectively for infants and children in the Faro Islands, Germany and among Inuit populations [84]. However, these children are among the most highly exposed [9]. For prenatal exposure of HCB and other OCPs, data for less exposed populations are rather limited. For example, findings for HCB and impairment of neurodevelopment have been mostly inconclusive. By contrast, a study from Spain found negative association, but only among the highest exposed group [85].

Non-essential and essential elements

Preface

Ten elements were selected in the mineral component of this biomonitoring study. Five of these are essential elements, namely copper (Cu), manganese (Mn), molybdenum (Mb), selenium (Se), and zinc (Zn). By contrast, the other five are non-essential and include arsenic (As), cadmium (Cd), cobalt (Co), mercury (Hg) and lead (Pb). Their selection is based on those determined in earlier work conducted by our Department of Community Medicine

(ISM) biomonitoring research group [13, 15, 86, 87]. All of the 10 elements are considered to be trace elements. This term was adopted at a time when their detection and quantitative measurement were a challenge [88].

The designation essential element is a nutritional term, and reflects experimental and observational evidence in more than one animal species that a deficient intake results in some impairment, and that the latter is restored on supplementation [88]. American Medical Association (AMA, 1979) Recommended Dietary Intakes (RDIs) or Recommended Dietary Allowances (RDAs) are available for the essential trace elements [89, 90].

Non-essential elements

Sources

Cd, Co, Hg and Pb are metals with known toxicities and colloquially are designated to be "heavy metals". As pointed out by Nieboer and his colleagues [91, 92], this term are ill-advised and toxic metals or toxic trace metals are more appropriate terms. Arsenic is a toxic element and has properties in between a metal and a non-metal and is designated a metalloid [92].

These elements are naturally found in the earth's crust and rocks, are emitted by volcanoes, and are present in fossil fuels, sediments, and soils, ground water and the atmosphere. Anthropogenic sources include mining, industry, combustions, agricultural, waste disposal, and are present in many industrial and commercial products like structural materials, electronics, fuels, batteries, tobacco, ammunition and fishing equipment, paints, jewellery, pottery, toys, and cosmetics [93-97]. They occur in different chemical forms, are persistent, and some accumulate in the aquatic and terrestrial food chains. They have no biological roles, and may rather be toxic even in small doses. However, Co is a biochemical component of vitamin B12, which is an important vitamin. It is not synthesized in humans nor animals [98].

Global transportation

Global transportation by way of ocean streams and the atmosphere to remote areas occurs for the non-essential elements [43]. Climate changes [43] and natural disasters [99] like volcanoes and earth quakes may alter the global cycling of metals. For Pb and Cd, the capture into Arctic is low (10-15 % of the airborne load) and varies with the amount of precipitation [43]. Since the arctic atmospheric Hg is relatively constant and the levels in aquatic species appear to be increasing, physical changes in ice cover, permafrost and organic carbon cycling are suggested to be important as well [43]. Unlike the others, 50 % of the emissions from Hg is

from ocean stores [96]. It is the most volatile (as the element), participates in photo-chemical reactions, and is transformed from elemental Hg to methyl-Hg (MeHg); the latter bioaccumulates in the aquatic environment [43]. The dissemination of Co appears to originate mostly from local point sources such as metal refineries, and its long-range transport is limited [95]. The metalloid As undergoes biotransformation to methyl derivatives, but is not biomagnified in the food chain [93].

Environmental distribution in Norway

With the exception of Hg, environmental concentrations in Norway are declining due to emission restrictions which have diminished both global transport and local release [9, 100]. Since 1995, local emissions of As, Hg, Pb and Cd have been substantially reduced (30-70 %) [44]. Local sources are mainly from industry (oil and gas, mining, metallurgical, shipping), electronic and electrical products, fish line sinkers, ammunition, combustion, and waste disposal. For Pb, Hg and Cd, the atmospheric long-transport amounts to 3-5 times more than local emission into air, water and soil [44]. For Hg, some fjords and lakes have fish consumption restrictions [53].

Human exposure sources

The primary source of non-essential elements is the diet, but respiratory contact with contaminated air, soil and dust may also contribute. MeHg bioaccumulates in the marine food chain and is found in relatively high concentrations in whale meat and large fish [43, 101]. In Norway, national dietary advice for Hg is in place for vulnerable groups like pregnant and breastfeeding women, and includes fish species to avoid [53]. For smokers, tobacco smoke is the main source of Cd, while in non-smokers it is the diet [102]. Cd preferably accumulates in kidneys and liver of animals, although agricultural products constitute the primary dietary source for most individuals [103]. As and Co do not bioaccumulate in the food chain, and hence dietary sources are generally low [93, 104]. In contrast, seafood (including fresh water fish) have high levels of arsenobetaine [2-(trimethyl)acetate] which is a non-toxic form of arsenic [93].

Trends in human levels

As for POPs, concentrations of toxic elements like Hg, Cd and Pb in the general population have been declining [9, 55, 105]. Despite elevated concentrations of Hg in Arctic marine biota, those in blood (or hair) of Inuit women from Greenland and eastern Canada have declined during the last two decades (see Figure 6). In addition to the global decline discussed above, a shift away from traditional diets likely is a contributing factor [9]. The global prohibition against leaded gasoline has contributed extensively to the reduction in Pb emissions and human blood Pb concentrations [55, 106, 107]. Elevated blood Pb is still prevalent in populations who consume meat from bagged animals shot with leaded ammunition [9]. However, the ban on the use of lead shot in some jurisdictions has had significant impact [107].

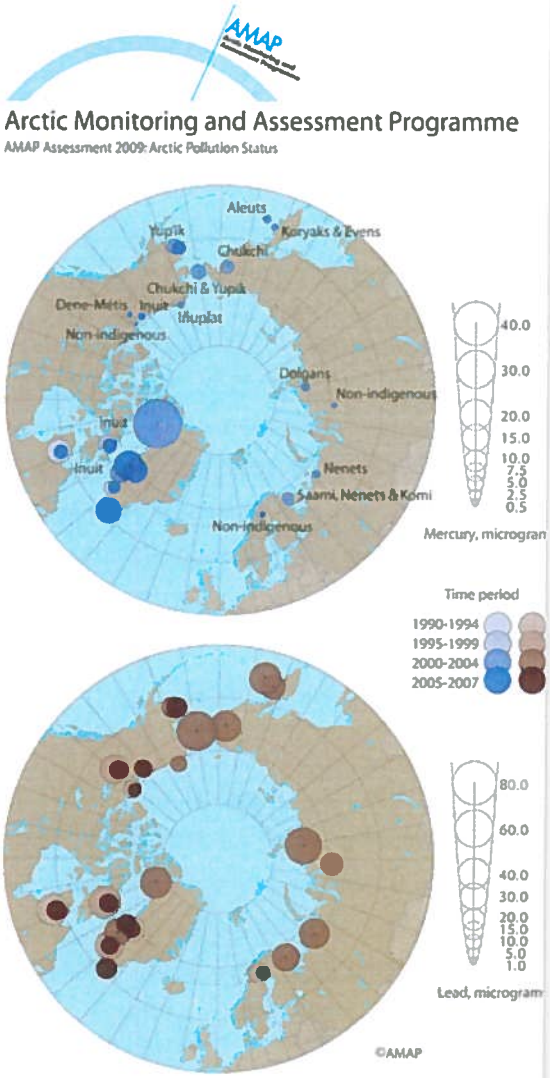


Figure 6 *Total mercury and lead in whole blood of mothers, pregnant women and women of child-bearing age in Arctic regions. (Source: AMAP Assessment 2009: Human health in the Arctic(www.amap.no [9])*

Absorption, distribution and elimination

The non-essential elements considered are absorbed from the gastrointestinal system *via* passive diffusion or receptor mediated transport to the liver *via* the hepatic portal circulating system, and then and into to the circulating blood [108-110]. The absorption rates from the gastrointestinal tract varies and depends on the stomach contents: As, 60-90 % [93]; Cd, 5-40 % [110]; Co, 5 - 50 % [95, 104]; MeHg and mercuric ion ($Hg2^{+}$) 95 % and <10 % respectively [111]; and Pb, 6 % [112]. In whole blood, metals distribute between erythrocytes, plasma proteins and low-molecular weight complexes with amino acids and other ligands [91]. Further, As [113], Cd

[114], Pb [115] and MeHg [116] have a preference for erythrocytes, and Co and Hg [i.e., as Hg^0 (elemental Hg) and Hg^{2+}] are nearly evenly distributed between plasma and erythrocytes [116]. Generally, about 70% of blood mercury is methyl mercury [116]; metallothionein is the primary binding protein for Cd [117]; and most of the arsenic in whole blood is present in the non-toxic form (i.e., arsenobetaine) [118].

For all the non-essential elements considered except Hg, the primary excretion pathway is by way of urine (for Hg it is the biliary route) [119]. Interestingly, the half-lives in the blood compartment are comparable, in days: 1-2 (As); 40-90 (Cd); 1-2 (Co); 45-70 (methyl-Hg); 20-30 (Pb) [91, 119]. Of these elements, Cd and Pb have significant long-term storage compartments, respectively in the kidney and liver (half-life of ≥10 years) and bone (≥6 years, depending on age) [91, 120]. Slow release from these compartments into the blood stream contributes to the observed blood concentrations.

Based on comparisons between maternal and cord blood, the placenta appears to act as a partial barrier for Cd, but not for the other four elements. For the latter, the data suggest that the concentrations in the cord and maternal blood are comparable for Pb, Co and As, and slightly higher in cord blood for Hg [86, 87, 121-123].

Compared to whole blood concentrations, As [124], Pb and Hg [125] in breast milk are low and thus transfer to the breast-feeding newborn is limited [125]. These elements are known to have a preference for erythrocytes relative to plasma [126, 127]. Transfer of Cd into breast milk is suggested to be less constrained, even though its levels are relatively low compared to the other 3 elements [128].

Non-essential elements and human health effects

The fetus and infants are especially susceptible to the toxicity of the non-essential elements, even at low-level exposures [5]. The developing fetal brain with the most sensitive stage at early pregnancy weeks [115], Hg and Pb are of particularly concern [5, 97]. At low levels neurodevelopmental disorders like impaired memory, language, attention, learning problems, lowered IQ, speech and hearing and behavioural disturbances, are evident [5, 97, 106].

In addition to skin and internal cancer for individuals highly exposed to As, dermal effects (hyperkeratosis and hyperpigmentation) are recognised outcomes, as well as adverse

neurological and cardiovascular consequences [129]. A perusal of the literature indicates the occurrence of fetal/infant developmental toxicities when there is maternal toxicity [129]. Recently, some concern has been expressed about such outcomes for low-level exposures [124].

Long term stores of Cd occur in the kidney and to some extent the liver as well. Not surprisingly, the primary consequence of Cd exposure is renal dysfunction [94]. Both high and low molecular-weight molecules appear in the urine even for low-level Cd exposure. This has been demonstrated for subjects living close to zinc smelters in Belgium. Not only was proteinuria established [130], but also bone fractures and demineralisation among women [131]. Subsequently, associations between urinary Cd levels and bone density reduction and osteoporosis have been reported in both smoking- and non-smoking post-menopausal women [132, 133].

There are no known essential functions of Co in humans other than its role in vitamin B12, and demonstrated toxic effects are limited to occupational exposures [95, 104]. There are limited data on cobalt-related reproductive effects [95, 104]. A minor public health issue is cobalt contact dermatitis, although it is somewhat rare. However it is often found in association with nickel sensitivity, which is quite common in females in the general population with prevalences around 10 % or higher [134], and a prevalence of 7% of positive reactions to cobalt has been reported in eczema patients [135].

As and Cd are classified as human carcinogens (IARC, Group 1), Pb is designated a probable carcinogen (Group 2A) and methyl-Hg and Co as possibly carcinogenic to humans (Group 2 B) [76, 77].

Essential elements

Preface

Cu, Mn, Mo, Se and **Zn** are required nutrients for human metabolism and health, and RDAs have been issued by age and developmental stage [89, 90]. Continuous dietary supplies are required to maintain basal function and uptake and/or excretion are regulated.

Copper

In the portal blood Cu are bound to the protein albumin and is incorporated in the Cu-protein ceruloplasmin, which is the form in which it is delivered to the tissues. Not only is the uptake regulated, it's urinary/biliary excretion is as well [136]. This metal has many important

biochemical functions, of which electron transfer and the use of molecular oxygen are examples [98]. Other than congenital Menkes' disease, Cu deficiency is not known; similarly, overt toxicity is limited to congenital Wilson's disease [137]. Both involve impairment of multiple functions.

Manganese

Mn appears to share the iron uptake pathway, its delivery to the liver is the same as Cu, and its transport to the tissues in part involves transferrin; excretion is by way of the bile [98, 138]. In blood, Mn prefers to be associated with the erythrocytes. One of its primary biochemical roles is its presence in the enzyme superoxide dismutase which protects tissues against the superoxide radical; Mn is also a component of a number of other critical enzymes. Mn deficiency is not documented [98], and its most well-known toxicity is manganism (a type of Parkinson's disease) [138].

Molybdenum

Mo is readily absorbed and is excreted in the urine. Its deficiency has not been well documented in healthy people and it has low toxicity. It serves as an important co-factor in a number of enzymes, namely oxidases and dehydrogenases [98, 139, 140].

Selenium

Although inorganic forms of Se (e.g., selenate and selenite) can come from soils (especially of industrial contaminated ones), it enters the food chain mainly as selenomethionine from plants [98]. These forms are readily taken up by the gastrointestinal tract and urine is the major route of excretion. Se deficiency is recognised as Keshan disease which involves serious heart disorders and selenoproteins provide protection against reactive oxygen species [141]. This is the basis for the hypothesis that it is protective against cancer. Its ability to complex with Hg is believed to render protection against the toxic effects metal [141].

Zinc

Like Cu and Mn, Zn is delivered to the liver by the portal pathway. A plasma pool of Zn bound to protein and amino acids is in equilibrium with multiple tissue pools including liver and soft tissues [98]. Fecal excretion dominates. The importance of Zn is clear from the following quotation: "*More than 300 zinc metalloenzymes occur in all six categories of enzyme systems*" (Shenkin et al.; p. 1138 in Burtis et al. (ed), 2006) [98]. Zn enzymes play an important role in gene expression, developmental biology, hormone synthesis, and multiple other functions. Not surprisingly, deficiencies result in impairment of growth, the immune

system and neurological functions. Overdoses of Zn can induce GI upset. In the industrial setting, inhalation of Zn fumes is known to result in metal fume fever.

Concluding comments

Clearly, essential elements are of vital necessity in maintaining good and balanced maternal health and proper fetal and infant growth and development.

Ions of toxic elements can be of comparable size and chemical properties than those of essential elements [91]. They therefore influence the absorption, and functions of essential elements. For example, low iron stores can elevate the uptake of Cd, Co and Mn [109, 138]; and Pb and Cd can inhibit Zn enzymes [91, 142]. By contrast, we have already mentioned the protective effect of Se for the toxic effect of Hg [143].

MATERIALS AND METHODS

Study populations

The thesis involves two different mother-and-child cohorts.

The Vietnamese Mother-and-Child Study (Paper I)

Figure 7 *Map of the Vietnamese study area (Source: Rod Wolstenholme, UiT)*

The Vietnamese study was initiated in 2005 in two communities in southern Vietnam (Figure 7). All pregnant women from three delivery units, respectively two in the coastal city Nha Trang and one in the rural district Dien Khanh, were invited to participate. The criteria for inclusion were that the mother had lived in the community for the last five years and provided a street address. As Figure 8 illustrates from May to July 2005, 241 women were initially registered in the study with 202 women fulfilling the mentioned criteria; furthermore, blood plasma specimens were not available for 13. Consequently, the study group consisted of 189 participants.

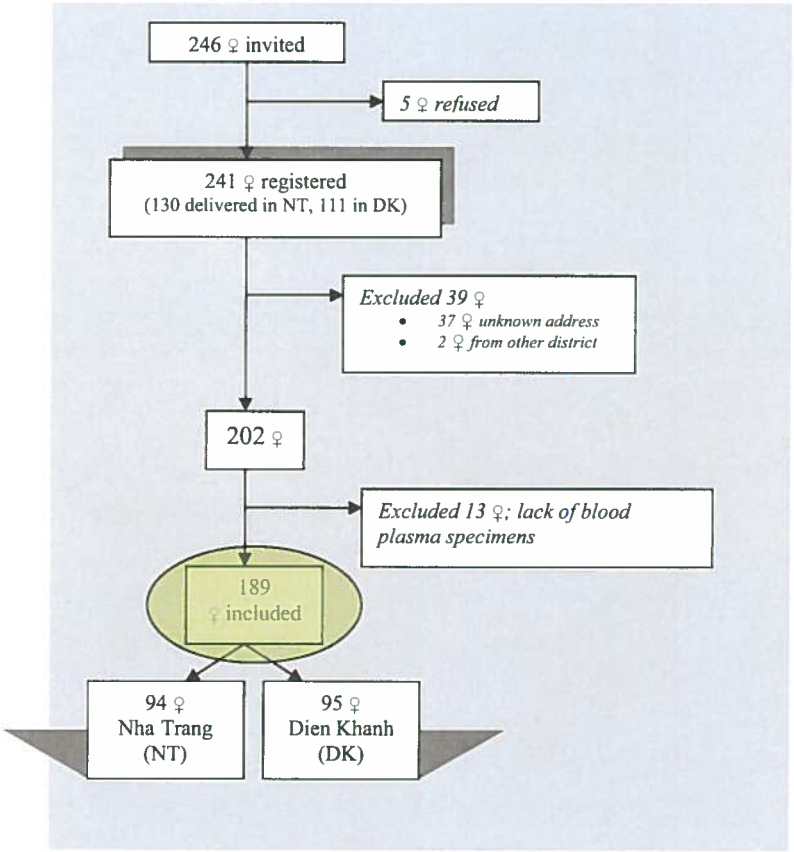


Figure 8 *The Vietnamese Study Group (Paper I)*

The North Norwegian Mother-and-Child Study (Papers II and III)

The North Norwegian Mother-and-child Study [also referred to as the MISA Study (Miljøgifter i svangerskapet og i ammeperioden)] took place from 2007 until 2009 in different regions of Northern Norway. The study populations lived in the northern counties of Nordland, Troms and Finnmark. Pregnant women in the study area were invited by a written invitation administrated by ultrasound clinics personnel, or during midwife consultations linked to places illustrated in Figure 9. The participating delivery departments were: Nordland Hospital (in Bodø and Lofoten), University Hospital of North Norway Trust [Tromsø and the labour wards of North-Troms (Nordreisa) and Mid-Troms (Lenvik)], and Finnmark Hospital (in Kirkenes, Hammerfest and the labour ward of Alta). The cohort study had three different sampling points: P1, with week 20 in the 2nd trimester the optimal target; P2, 3 days postpartum; and P3, with 6 weeks postpartum the target. As illustrated in Figure 10, 515 (20% of the invited) women were included in the study at P1; 458 of these presented at P2, and 394 completed the study at P3. The study group of Paper II consisted of women with serum samples collected during June 2007 – October 2008. Of these, 51 women were randomly selected, of which one woman was excluded due to her recent arrival in Norway (Figure 10). In Paper III, the subjects who provided whole blood specimens until the end of January 2009 were included (see Figure 10).

Figure 9 *Map of the MISA study area (Source: Rod Wolstenholme, UiT)*

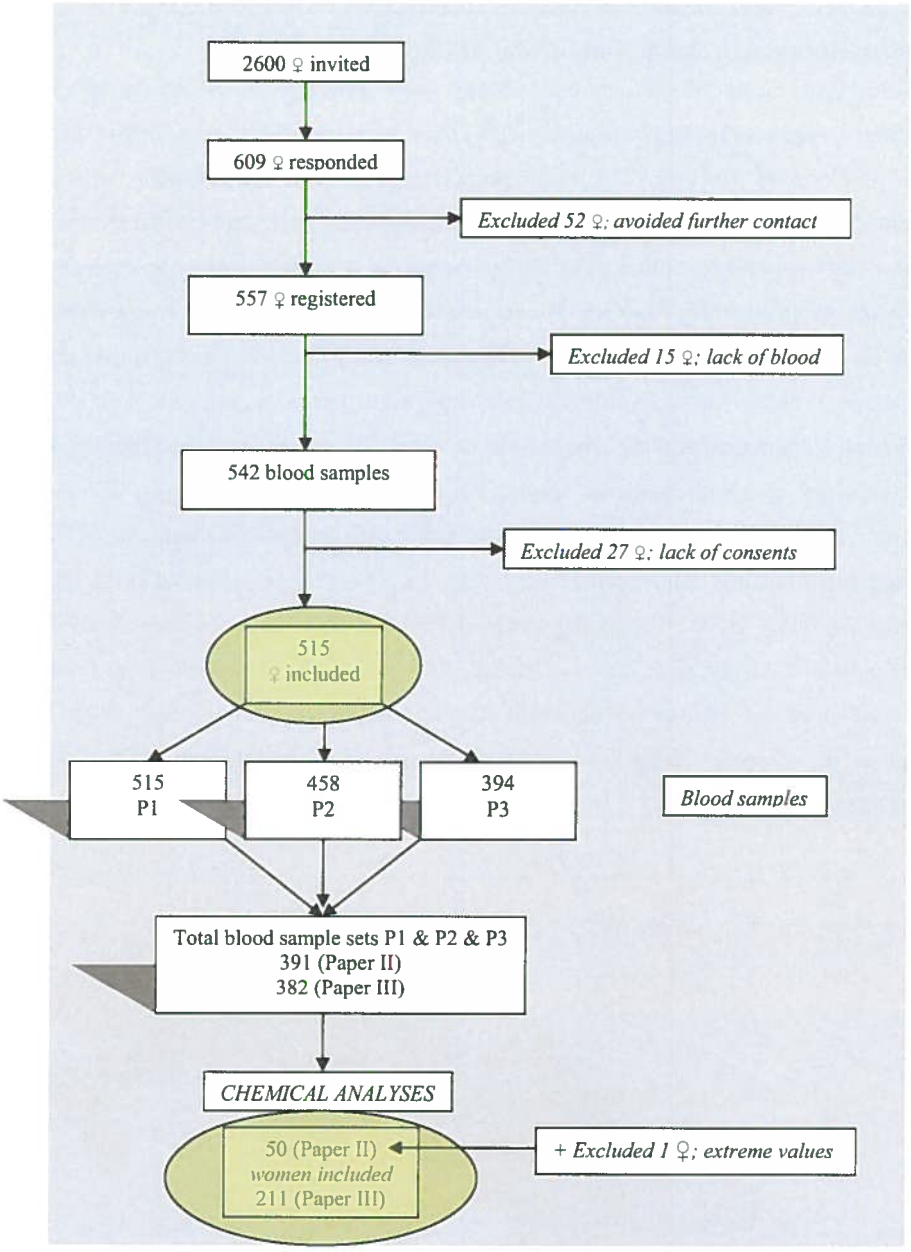


Figure 10 *The MISA Study Group 2005 (Papers II and III)*

Data collection

In the Vietnamese cohort, medical personnel in the delivery units recorded maternal obstetrical history, personal characteristics, and weight and height measurements. Additionally, within four months after delivery data pertaining socioeconomic and life style

status, living conditions, diet, and supplementary medical and obstetrical history were collected. The women were interviewed at home by trained staff from the Pasteur Institute in Nha Trang. Dietary data were not brought into the analysis due to uncertainty in the data sampled.

The data collection protocol used in the MISA cohort is presented in Figure 11. At enrolment, the participants complete a detailed information questionnaire pertaining to personal characteristics, obstetric history, diet and life style. Permission to consult their medical records was obtained. In addition, at all blood sampling time points a simple questionnaire was administrated to obtain personal information about current diet, smoking and alcohol habits, medication and dietary supplements. Maternal weight was measured at each period, and pre-pregnancy weight and height were self-reported. A questionnaire about lactation history was sent to the participating women during late 2009.

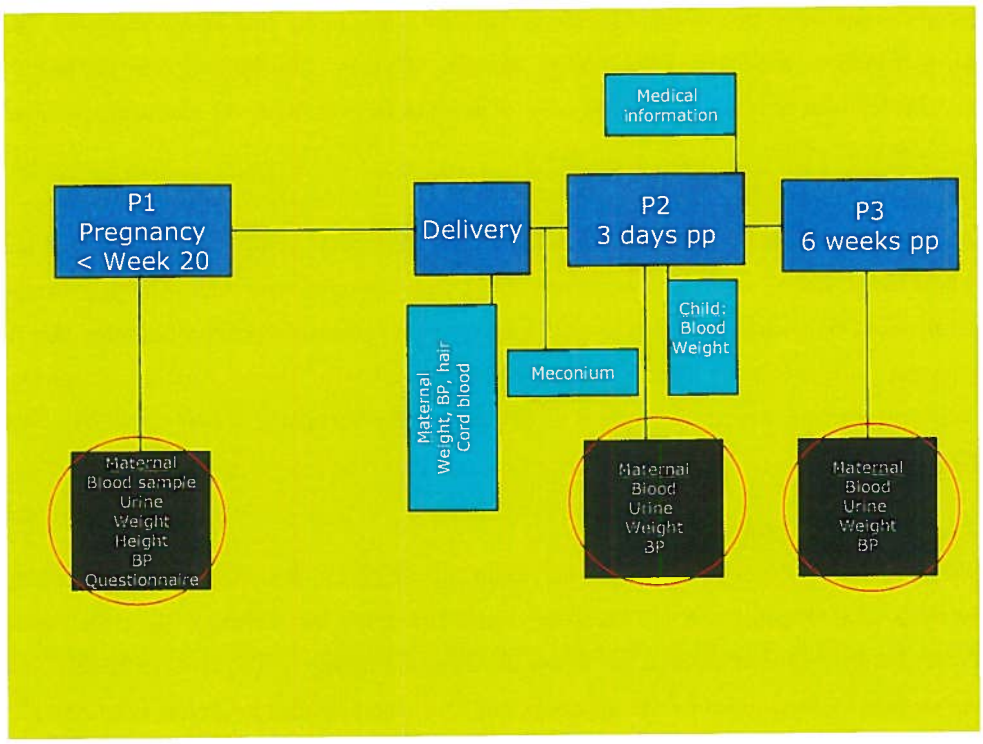


Figure 11 *Flow chart of the MISA Study*

In Paper III, dietary information (primarily fish consumption) was obtained by way of a validated food frequency questionnaire (FFQ), based largely on a FFQ used in The Norwegian Women and Cancer study (NOWAC) [144-146]. Using an established program developed at the Department of Community Medicine, University of Tromsø, consumption of each food item was expressed in grams per day based on the Norwegian Weight and Measurement Table 13 [147], and the daily intake of energy and nutrients were computed based on the Norwegian Food Composition Table 2006 [148].

Blood sampling and chemical analyses

In the Vietnamese cohort, maternal blood (plasma) sampling was done within 3 h after delivery. Most plasma samples were analysed at the Pasteur Institute in Nha Trang. As a part of the quality assurance and control (QA/QC) protocol, pooled samples and some duplicates of OCs were also analysed by the Norwegian Institute for Air Research (NILU), Fram Centre in Tromsø. The lipids could not be determined in the majority of samples due to limited sample volume and lack of reproducible gravimetric scales in the Nha Trang laboratory. Due to constrained resources and limited sample volumes, the lipids were determined enzymatically at NILU in a subset of only 20 samples from each region, and hence were not used for lipid adjustment of OCs in Paper I.

As illustrated in the flow chart of the MISA cohort (Figure 11), maternal blood (serum and whole blood; fasting conditions were prescribed), were collected at all three sampling periods. Analyses of OCs were completed by NILU, and analyses of serum lipids profile were done by enzymatic methods by the Unilab Analyse AS, Fram Centre in Tromsø. Analyses of essential and toxic elements were done by the National Institute for Occupational Health (NIOH), Oslo, Norway.

Statistical analyses

All statistical analyses were carried out using the SPSS for Windows statistical package [version 15.0 (Paper I and 17.0 (Papers II and III) SPSS Inc. Chicago, IL, USA]. Non-detectable levels and concentrations below the detection limits (LODs) were replaced by the appropriate LODs divided by the square root of 2, as recommended by Anda et al. (2007) [7]; however in the Vietnamese paper, they were replaced by ½ LOD [1]. For all studies, the concentrations of both OCs and elements were not normally distributed, and the compounds were log-transformed (base 10) before the statistical treatments.

In general, statistical analyses were based on ANOVA (Analysis Of Variance), t-test, the Univariate General Linear Model, simple linear and multiple regressions, and the Linear-Mixed Model. Back-transformed regression coefficients were used to measure the influence of the independent variables, such as age and parity, on the OCs concentrations. Details of the statistical approaches are further elaborated in the individual papers.

Ethical considerations

The Vietnamese study was approved by the Medical Ethics Council of The Ministry of Health of Viet Nam and the University of Tromsø, Norway. The invited women signed an informed consent form, and participation was voluntary.

The MISA study was approved by the Regional Committees for Medical Research Ethics and the Norwegian Data Inspectorate. Participation was voluntary, and the women signed an informed consent form.

MAIN RESULTS

Paper I

Maternal levels of organochlorines in two communities in southern Vietnam

The study among 189 delivering women from southern Vietnam was initiated in 2005 with the aim to establish local analytical capacity for OCs analysis; to determine levels of organochlorines; and to identify risk factors. Two different communities in the Khanh Hoa Province were studied: the coastal city of Nha Trang (NT; n=94) and the rural district of Dien Khanh (DK; n=95) located about 10 km inland.

Relatively high concentrations of *p,p'*-DDE (11.8 µg/l) and *p,p'*-DDT (1.2 µg/l) in maternal plasma were observed, however with no significant community differences. The ratio of *p,p'*-DDE / *p,p'*-DDT (12.2) indicates, as in other Vietnamese OCs studies, a relatively recent use of this pesticide. The generally high levels of *p,p'*-DDE and *p,p'*-DDT reported for the Vietnamese communities may give reason for concern like the long-term effect on children's health. Concentrations of other congeners were low in both communities. The observed significant ($p<0.001$) community differences in levels of PCB-153 (0.15 and 0.10 µg/l, respectively in NT and DK) are suggested to reflect differences in the dietary patterns, with more marine food consumption in Nha Trang and home-garden grown food in Dien Khan. Age and parity appeared as the most dominant predictors for the chosen OCs, with the highest levels among primiparas and the oldest age group.

Paper II

Levels of organochlorines and lipids across pregnancy, delivery and postpartum periods in women from Northern Norway

The main objective of this study was to systematically investigate changes in the levels of common organochlorines (OCs) and lipids in maternal serum during and after pregnancy. A subset of 50 pregnant women from the North Norwegian Mother-and-Child Study was included. Blood (serum) samples were collected during the 2nd trimester and postpartum (Day 3 and 6 weeks) in different regions of Northern Norway, and were analyzed for the Arctic Monitoring and Assessment Programme (AMAP) suite of PCB and OCP contaminants.

Few studies have systematically investigated the pattern of OCs during pregnancy and the postpartum period. This survey revealed a distinct pattern with peaking of wet-weight OCs

and lipids at delivery and with a reduction 6 weeks postpartum. After lipid-adjustment of OC concentrations, the differences between the periods were mostly removed. Wet-weight concentrations of OCs appear to be driven by the physiological lipid profiles and are interpreted to constitute biomarkers of lipidemia. It is suggested that this observation may have implications for the biomonitoring of individuals at risk of Type 2 diabetes.

Both age and parity were strong predictors for the OCs measured, but no consistent association with body mass index (BMI) was evident. Independent of lipid-adjustment, all compounds were positively and significantly correlated with each other (within and across the three collection time periods). The peaking of OCs during pregnancy suggests that the period spanning the last weeks of the 3rd trimester and the early postpartum days constitutes an optimum sampling window purely from the analytical perspective.

Paper III

Changes in maternal blood concentrations of selected essential and toxic elements during and after pregnancy

In this study, changes in the levels of toxic metals and trace elements in maternal whole blood during pregnancy and postpartum period were systematically studied. A subset of 211 pregnant women from the MISA Study was included. Blood samples collected during 2nd trimester of pregnancy, 3 days and 6 weeks postpartum were analysed for 5 essential elements (copper, manganese, molybdenum, selenium and zinc) and 5 toxic elements (arsenic, cadmium, cobalt, mercury and lead). Three distinct concentration patterns across the three collection periods were prominent. These trends are interpreted in the context of metabolic, hematological and physiological changes and elemental accumulation preferences within the blood compartment.

A second objective was to identify factors that influenced the relative concentrations in the blood of these elements. For Hg, As and Se concentrations, the association with fish consumption was strong. Parity and age were not important predictors, except for Hg. Multivitamin intake was positively associated with Se levels, and parity with Co. Interestingly, Sámi affiliation was associated with lower levels of Hg, As and Co, though it should be stated that the sub-sample size was small.

DISCUSSION

Main findings

Maternal concentrations

- Low concentrations of PCBs in both Southern Vietnam and Northern Norway *(Papers I and II)*
- Low concentrations of *p,p'*-DDE in Northern Norway *(Paper II)*
- Relatively high concentrations of *p,p'*-DDT and *p,p'*-DDE in Southern Vietnam *(Paper I)*
- Low concentrations of toxic metals in Northern Norway *(Paper III)*
- Normal concentrations of essential elements in Northern Norway *(Paper III)*

Predictors retained in multiple regression models

- *Paper I:* Age, parity/lactation, district(only *PCB*), BMI (only *p,p'*-DDT)
- *Paper II:* Age, parity
- *Paper III:* Fish/seafood for Hg, As, Se; Sámi affiliation (Co, Hg, As); Multivitamin (Se), Interval (Co)

Concentration patterns across the gestational and postpartum periods

- OCs follow the changes in lipid profiles *(Paper II)*
- Non-essential and essential elements follow metabolic, physiologic, and hematological changes(depending on group) *(Paper III)*

Limitations and strengths

- Low participation rate in the MISA Study
- Small numbers in the comparisons of certain sub-groups
- Sample-size calculations and increase of sample size justified the numbers studied
- Standardised methods

Concentrations of organochlorines in a global perspective

Different exposures between and within countries are reflected in population studies. Geographical variations on the human body fluid concentrations of persistent contaminants such as OCs are well established. Both global emissions with long-range transport and local sources are of importance for the exposure of individuals and populations. However, when comparing population concentrations between studies, a number of factors [149, 150] have to be taken into considerations such as: year of sampling, and characteristics of the study group such as age, gender, area of residence, diet and obstetrical history. Also of special importance are the analytical methods and quality assurance measures used; whether whole blood, serum

or plasma concentrations are reported; and the units the concentrations are expressed in (e.g., wet-weight or lipid-adjusted for OCs in plasma or serum).

PCBs

Since strong inter-congener correlations have been demonstrated for PCBs, and since PCB-153 is one of the most abundant congeners, the discussion that follows is limited to it. The statements made and trends discussed also apply to other PCB congeners. All OC concentrations for the Vietnamese mothers refer to plasma, while those in the North Norwegian survey it was serum. Plasma and serum concentrations of OCs may be considered comparable.

Relatively low maternal levels of PCBs were found in both the Vietnamese (Paper I) and the North Norwegian survey (Paper II). Interestingly, in both cohorts geometric (GM) unadjusted concentrations of PCB-153 were in the same range (Figure 12; respectively, 0.12 μg/L *versus* 0.19 μg/L in Vietnam and North Norway). In Norway where long-range transport is more relevant, low levels of PCBs probably reflect the absence of local point sources. Previously published maternal data is not available for Vietnam. By contrast, the Norwegian lipid-adjusted concentrations at delivery (23 ng/g lipids) are observed to be lower or comparable to those measured in 1996 in Kirkenes and 2004 in Bodø (52 and 23 ng/g plasma lipids, respectively) [9].

Lipid-adjusted values are most often reported. Concentrations of OC levels in the Vietnamese cohort were not lipid adjusted due to lack of lipid measurements. But as observed in Paper II, correlations between unadjusted and lipid-adjusted concentrations are rather strong [Pearson's correlation coefficients, $r \geq 0.90$]. Since geometric mean PCB levels in Vietnamese mothers were just below the Norwegian values, we can assume that possibly lipid-adjusted levels for the Vietnamese cohort would have been more or less in the same range as found in the MISA study (Figure 13).

In a global comparison with studies of maternal serum or plasma collected since 1999 (Figures 12 and 13), the Norwegian and Vietnamese PCB levels are in the lower range. Rather limited maternal data from other Asian developing countries exist. For a wet-weight comparison, our PCB 153 levels are also lower than what has been reported in pregnant women from Russia [150] (Figure 12); the latter are strongly community dependent. Our

observed lipid-adjusted PCB 153 concentrations are also relatively low compared to those reported for other countries (see Figure 13) and far below the Health Canada guideline for PCBs (as Aroclor) Level of Concern for pregnant women (5 µg/L) [55].

Figure 12 Maternal plasma or serum of PCB 153 from Russia [150], Norway (Paper II) and Vietnam (Paper I)

Unadjusted geometric means, µg/L; sampling period 2001-03 (Russia), 2005 (Vietnam) and 2007-08 (Norway) within 3 days postpartum

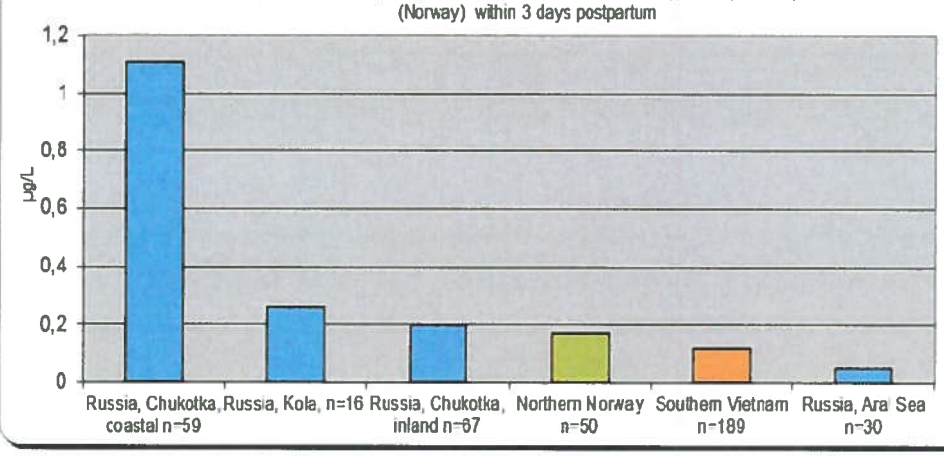
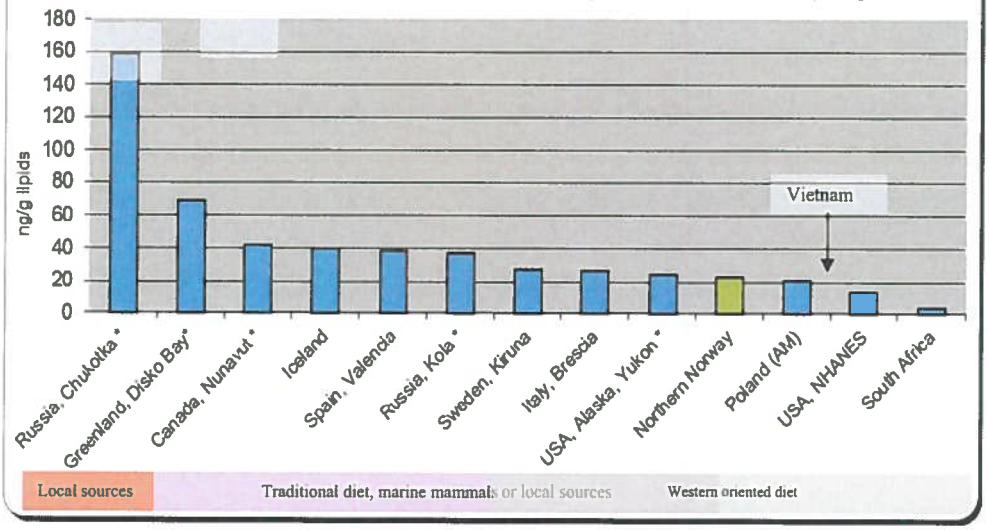


Figure 13 Global distributions of PCB 153 in pregnant or delivering women

Plasma or serum geometric mean (ng/g lipids), sampling period 1999-2008, *indigenous



Nation, n, period[ref]
USA, NHANES, 179, 1999-2002 [151]; Russia, 68 (C), 16 (K), 2001-03 (9); Spain, 541, 2003-05 [152]; Iceland, 40, 2004 [9]; Poland, 21, 2004 [8]; USA, Alaska, 206, 2004-06 [9]; South Africa, 61, 2005-06 [153]; Canada, Nunavut, 99, 2005-07 [9]; Greenland, 20, 2005-07 [9]; Italy, 70, 2006 [154]; Sweden, 25, 2007 [9]; Norway, 50, 2007-08 (PaperII)

The concentrations in Figure 13 for the Chukotka and South Africa study groups reflect different dietary patterns, environmental exposures and long-range transport deposition. It is clear that the highest levels are seen for populations consuming relatively high amounts of seafood, and especially marine mammals [9, 156]. The Coastal Chukotka population differs from the others. Not only do they have marine-mammal rich diets, but also because of the presence of a high degree of foodstuff contamination due to indoor and outdoor environmental conditions [9]. In contrast are the lower Aral Sea concentrations (Figure 12), with no consumption of such lipid-rich traditional foods and more western-oriented diets. Further, limited fish intake has been reported for South Africans [86] for which low PCB levels are even evident for fish consumers [154]. It may reasonably be concluded that low environmental exposures occur due to limited local sources and little influence by long-range transport.

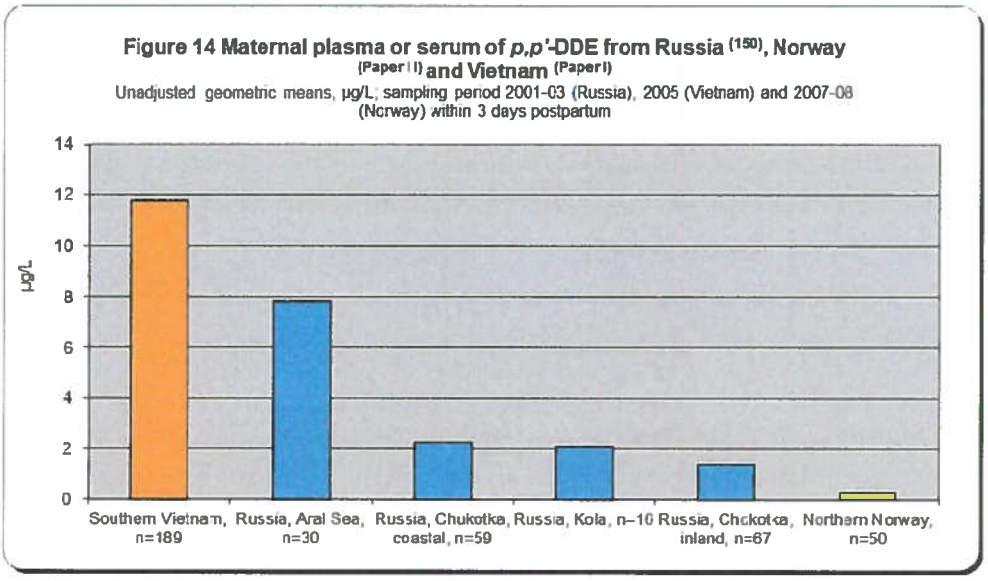
It is worth mentioning that the global overview presented provides only a limited qualitative picture since the data for these studies are not available for a statistical comparison, and the number of samples varies, as do the analytical methods. However, the samples for which data are reported in Papers I (Vietnam) and II (Northern Norway) and of the South-Africa study mentioned have all been analysed by the same protocols. Further, all laboratories in the Arctic studies were participants in the AMAP Ring Test.

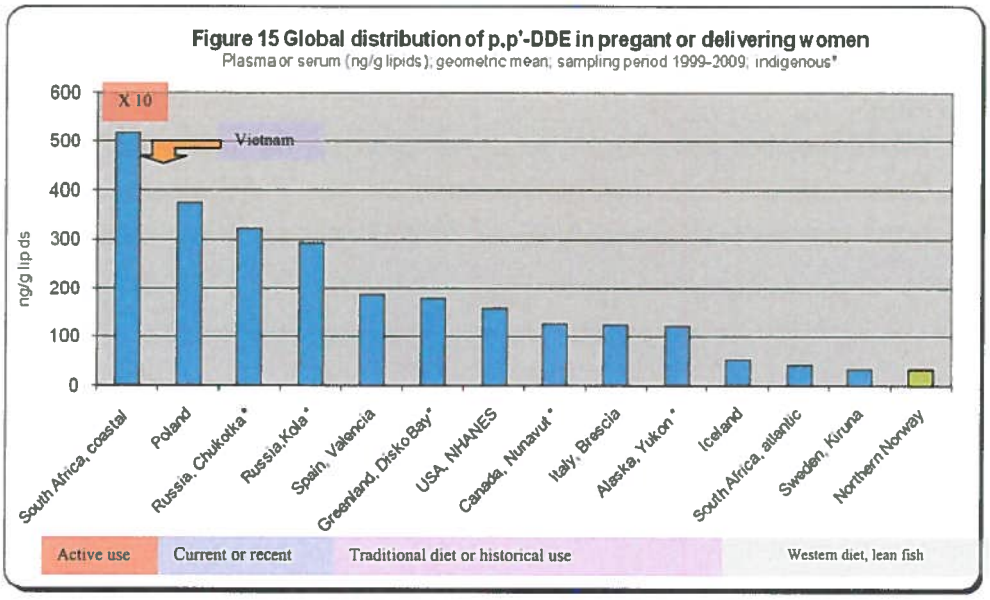
p,p'-DDE

p,p'-DDE is the most prominent of the OC pesticides (OCPs). Because of the good correlations observed between *p,p'*-DDE and other OCPs (Paper II), the trends described for *p,p'*-DDE largely apply to them as well. The *p,p'*-DDE/*p,p'*-DDT ratio is interpreted to reflect current or past use of pesticides in addition to the usual dietary sources; *p,p'*-DDE/*p,p'*-DDT ratios >30 are usually thought to indicate that dietary sources prevail, with ratios < 5 are taken as a strong indicator of current or recent use of the parent pesticide [12].

Previously published Vietnamese maternal data are sparse for *p,p'*-DDE. With reference to Papers I and II, and as illustrated in Figure 14, levels of *p,p'*-DDE were almost 40 times higher in the Vietnamese mothers' plasma compared to those in the Norwegian study. As pointed out in Paper I, *p,p'*-DDE plasma concentrations for the Vietnamese group were somewhat lower than observed in pregnant women from Thailand in 1998 [151]. Similarly, the Norwegian-lipid adjusted GM concentration at delivery (38 ng/g lipids) shown in Figure 15 is

lower than those observed in 1996 in Kirkenes and 2004 in Bodø (79 and 67 ng/g plasma lipids, respectively) [9]. From the global perspective (Figures 14 and 15), the Norwegian levels of *p,p'*-DDE are among the lowest observed.





Nation, n, period [ref]
USA, NHANES, 179, 1999-2002 [151]; Russia, 68 (C), 16 (K), 2001-03 [9]; Spain, 541, 2003-05 [152]; Iceland, 40, 2004 [9] Poland, 21, 2004 [8]; USA, Alaska, 206, 2004-06 [9]; South Africa, 12 (A), 11 (C), 2005-06 [153]; Canada, Nunavut, 99, 2005-07 [9]Greenland, 20, 2005-07 [9]; Italy, 70, 2006 [154]; Sweden, 25, 2007 [9]; Norway, 50, 2007-08 (PaperII)

Elevated plasma levels of *p,p'*-DDT and low values for the *p,p'*-DDE/*p,p'*-DDT ratio are associated with active or recent use of this pesticide. This is the case for the South Africa coastal site depicted in Figure 15, where there is still active control of malaria [154]. By contrast, this does not occur for non-sprayed areas of this country, such as the Atlantic Ocean site in Figure 15 [154]. The respective *p,p'*-DDE/*p,p'*-DDT ratios are 2.9 and 21.6; by comparison it was 12 for the the Vietnam group. Recent or current use is also suggested for some sites in Russia [7, 9, 50]. However despite being far away from emission sources, most Arctic populations accumulate pesticides through lipid-rich (marine) diets.

Predictors of exposure to organochlorines

Fish consumption

Diet is the main source of OCs unless direct sources are present, with fish and marine mammals as the main contributors to the body burden. In Paper II the dietary influences on the serum OC levels were not investigated due to small sample size (n=50), and this will be included in later studies involving the whole cohort. But as found in Paper III (n=211), consumption of fish and seafood was relatively high compared to young Norwegian people [18] and is probably due to the northern coastal location of the study sites [18, 19]. Nevertheless, they are still below the Norwegian national consumption recommendations (50 % should be fatty fish) [51]. In a Norwegian study (men and women, aged 21-80) by Kvalem et al. (2009) [20], fish and seafood were associated with coastal living; it was estimated to contribute 70 % to the total intake of PCBs and dioxin. Fatty fish constituted the main source, whereas only fish liver and seagull egg consumption was associated with elevated serum levels. Sandanger and colleagues [61] have demonstrated that boiled fresh cod-liver oil contained significant levels of *p,p'*-DDE and PCBs. In a study by Furberg et al (2002) [157] involving coastal North Norwegian women (aged 40-42) with high fish/seafood intake (mean 134 g/day, 70 % lean), only a significant association between OC plasma levels and seagull egg intake was observed. It seems likely therefore that lean fish do not contribute strongly to the intake of OCs. Details of these associations remain to be sorted out for the MISA cohort.

Fish consumption appears to be substantially higher in Vietnam compared to Norway. In Paper I, self-reported dietary frequencies and intake information was collected. However, we could not take the diet information into the statistical analysis due to the uncertainty in the reporting, and lack of knowledge about the Vietnamese dietary habits. After excluding 4 extreme outliers, preliminary calculations of fish/seafood intake indicated 940 g fish and 580

g shellfish (crab, snail and scrimp) per week with significantly higher ($p<0.001$) intake of shellfish in Nha Trang compared to Dien Khan. Again, these data only give us some qualitative indication about high consumption, and cannot be interpreted further. However, a recent survey of shellfish consumption in Nha Trang reported an intake of 616 gram per week [52], which supports the high shellfish intake reported in Paper I. The lower PCB concentrations observed in Vietnam in combination with higher fish intake suggest the consumption of smaller, younger, and lean fish species in combination with low environmental deposition by long-range transport and minor local sources. The local differences observed for plasma PCB 153 concentrations likely reflect dissimilarity in the species of fish and amount consumed. However, participants in Dien Khan are known to grow more of their own food, and in the city of Nha Trang cultivated food from different rural districts are available. Interestingly, cereals and vegetables have been reported as the largest contributor of PCBs intake in the Vietnamese food items in relation to contaminated soil, however this calculation was based on relatively low fish consumption [47].

Age

In Papers I and II, age constituted the most important predictor of plasma or serum OCs, with older women having higher concentrations. This age-related effect is well established [152, 153, 155, 157-159]. This reflects the relatively long half-lives (in years [66]) of many of the OCs in human tissues. Pharmacokinetic modelling suggest that accumulation with age requires a continuous supply, and that the body burden (and thus the serum/plasma levels) can reflect the time since peak exposure (past, recent and current), the year born, and body type (lean *versus* obese) [64, 149, 160]. The latter factors pertain to the window of exposure from placental transfer, childhood to adult. OC compound-specific effective half-lives are believed to be influenced by age of the exposed individual (↑, increase with age), weight change (↑↓), and serum/plasma OC concentration and thus body burden (↑ with low levels) [64, 68, 158]. Interestingly, half-lives of PCBs in Faroe children 4-14 years who were highly exposed through breast feeding were not shorter than in adults [66].

In the Vietnam study group, the average maternal birth year was 1977 (range 1956-1987, mean age of 28), and 1976 (range 1967-88, mean age of 31) in Norway. Widespread use of both PCBs and DDT has been curtailed by bans in the 1970/80s (Norway) and 1995 (Vietnam). Thus older women (and their mothers) were closer to times of higher environmental abundance of OCs, as well as experiencing longer exposure time frames. The

lower (parity adjusted) age effect on the PCB levels observed in the Vietnamese study compared to the Norwegian cohort (25 % versus 110 %), likely reflect differences in exposure intensity and timeframe, as observed in other studies [149]. In Norway, as previously pointed out, good data exist on the declining levels. However, in Vietnam no indication of such time dependence exists due to a lack of historical monitoring data. Recent exposure to PCBs is indeed suggested in a Vietnamese breast milk study [45].

Parity and lactation

Negative associations between plasma/serum OC concentrations and parity (or lactation) are generally observed [152, 153, 157, 159, 161]. In both cohorts (Papers I and II), parity was observed as a robust indicator of the lactational history, since the observed correlation between parity and breast feeding duration was strong (r>0.9). The age-adjusted PCB and *p,p'*-DDE plasma or serum levels in both studies were 25-45 % lower in multipara mothers, with the *p,p'*-DDE exhibiting the higher values. Other studies have also reported a higher degree of lactational transfer of *p,p'*-DDE compared to PCBs and HCB.

Both pregnancy and lactation effectively correspond to a condition of maternal detoxification, with transfer of lipid-soluble OCs *via* the placenta and breast milk. Breast feeding seems to be the dominant pathway [161, 162], with a depuration rate (i.e., loss of body burden) of 3 - 6 % per month for *p,p'*-DDE and PCB [45, 163]. For example, a 50 % decrease in maternal lipid-weight concentrations of OCs have been observed after 6 months of breast feeding [164]. The contribution of OCs to the total body burden received by way of breast milk is suggested to persist into adulthood, especially in the context of decreasing current exposures. This largely reflects the long turnover time in humans. Further, the gender effect often seen for OCs (i.e., lower levels in women) is a lactational effect.

Other predictors

The body burden of OCs depends on an interplay of many factors. In addition to those mentioned (i.e., diet, age and parity), BMI and demographic influences also make a difference [153, 159]. Almost half of the Vietnamese women had low BMI (mean BMI 19.3 versus 25.4 in the Norwegian). Associations were not prominent for BMI, other than an increase in the Vietnamese *p,p'*-DDT levels of 6 % with a one unit increase in BMI. As already discussed in Paper II and described by Wolff et al. (2007) [64], changes in body composition (BMI, weight loss or gain) can be both negatively and positively associated with the OCs or not at all. Apart from the observed district dependence in Vietnam mentioned earlier, no differences in OC

levels between the municipalities of Finnmark (n=17) and Troms (n=29) in the Norwegian group were observed. This probably reflects the somewhat similar dietary patterns and thus exposures especially since 83% lived in coastal urban settings.

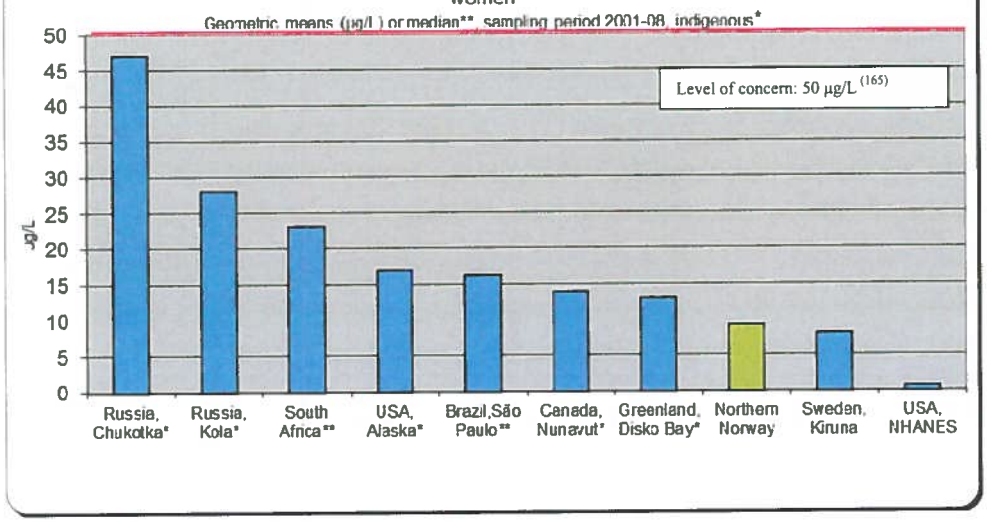
Non-essential (toxic) and essential elements

Concentrations of non-essential (toxic) elements in a global perspective

Concentrations in body fluids and tissues of toxic elements have been reported for pregnant or delivering woman in the Arctic region for more than two decades, and a declining trend is generally observed [9]. Figures 16 and 17 provide a global overview for 2001-2009 of selected geometric mean (or median) concentrations of Pb and Hg. Suspected primary sources are also indicated, as well the Level of Concern adopted in some jurisdictions. Note that the samples from South Africa, Brazil and Norway (i.e., the current study) were all analysed by the same laboratory.

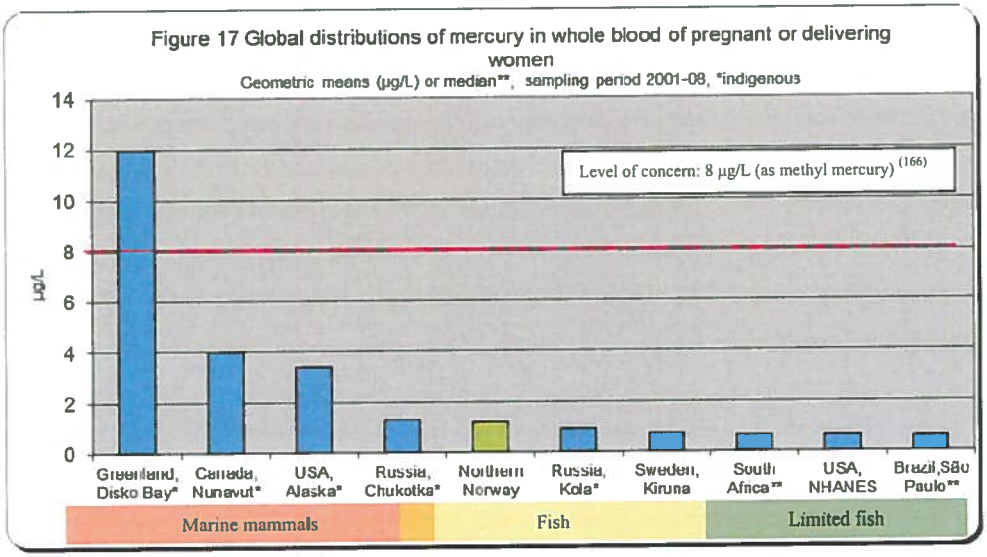
In 1999, Odland et al. [15] reported a mean whole blood lead level of 12.4 µg/L for Norwegian delivering women. This value was lower than other published values. From Figure 16 it is clear that currently the Norway blood (Paper III) lead levels remain among the lowest observed. Again, indigenous Arctic people have the highest concentrations of lead and mercury (see Figures 16 and 17). For Pb, none of the populations studied exceeded the current Level of Concern adopted in some jurisdictions, namely 100 µg/L or 50 µg/L [165]. For Hg, pregnant Inuit women in Disko Bay, Greenland, exceeded the Health Canada recommendation of Level of Concern for MeHg of 8 ug/L [166], (about 70 % of blood Hg is MeHg) [116]. The elevated Hg levels among the Inuit is no doubt related to its accumulation in marine and fresh-water fish, especially in marine meat [9, 122]. Elevated Pb levels have previously been linked to the global use of leaded gasoline, but after its prohibition human tissue levels have declined substantially. The elevated blood concentrations in today's Inuit are primary linked to the consumption of game and waterfowl because of contamination by lead shot or fragments thereof [167, 168]. However, the prohibition movement against the use of

Figure 16 Global distributions of lead in whole blood of pregnant or delivering women



Nation, n, period[ref]
Russia, 26 (C), 20 (K), 2001-03[(9)]; USA, NHANES, 622, 2003-06[(105)]; USA, Alaska, 75, 2004-06[(9)], South Africa, 62, 2005-06[(123)]; Canada, Nunavut, 24, 2005-07[(9)]; Greenland, 27, 2005-07[(9)]; Sweden, 23, 2007[(9)]; Brazil, 155, 2007-08[(87)]; Norway, 211, 2007-08 [(Paper III)]

Figure 17 Global distributions of mercury in whole blood of pregnant or delivering women



lead-shot accounts for the additional decline in levels among native peoples [107, 122]. Despite of the apparent increasing environmental levels of Hg, dietary advice has generally resulted in lowering blood concentrations [9, 122]. Interestingly, due to the very low fish consumption in South Africa and Brazil, local industrial activities rather than fish intake are suggested to be the main contributor to Hg exposure [86, 87]. In Paper III, three other toxic elements were measured in whole blood, namely As, Co and Cd. Compared to South Africa and Brazil, the three-fold higher concentration of As in the Norwegian samples confirms the substantial higher fish intake [87, 123]. Cd levels in Norwegian non-smokers were similar to those from South Africa and Brazil, and Co concentrations were two-fold higher in South-Africa (probably connected to the mining industry there).

Predictors of exposure to non-essential (toxic) elements

Fish consumption

Paper III investigated the impact of fish/marine mammals and game consumption on the concentrations of toxic metals and non-essential elements. These items were chosen due to the knowledge of the patterns of traditional food consumption in the North Norwegian diet [18, 19, 157] and the known association of daily intake with some of these elements (specifically, Hg, As and Se [122, 169-171]. Consequently, the robust relationships observed (Paper III) between As, Hg (and Se) suggest seafood as a common source [172-174], although Hg/Se correlations also are observed with limited or no fish intake [123, 175]. In the multiple regression model of Paper III, the strongest predictor was the consumption of whale/seal (Hg) and shellfish (Hg, As and Se), but the wide confidence interval due to low consumption and a small number of consumers, make these estimates uncertain. Nevertheless when replacing the different species with the composite variable "total fish and marine seafood", a 7 % increase (As and Hg) and 2 % (Se) of the fractional whole blood concentration per unit of consumption (10 gram/day) resulted; when excluding processed fish from this "total" variable, it corresponded to 12-15 % (Hg and As) (data not shown).

The low consumption of several items such as whale/seal, shellfish and fresh-water fish could be due to limited availability or personal dietary habits. National recommendations exist in Norway that target reproductive, pregnant and lactating women, and this may also have played a role (see Table 1) [53]. The low levels of Hg in combination with relatively high fish consumption, but low intake of restricted food such as large fresh-water fish (0.7 g per day), suggest compliance with dietary advice. With regard to the half-life of 45-70 days for methyl-

Hg, the measured levels reflect most strongly the intake during the last 3 months [176]. Since the women reported their diet for the previous year, a change in diet after confirmation of their pregnancy seems therefore reasonable.

Table 1 Norwegian national advice

Pregnant and lactating women should avoid the following fish and seafood species:

- Whale and seal
- Greenland halibut > 3 kilo
- Fresh water fish: Trout and char > 1 kilo; pike and perch > 25 cm
- Exotic fish like: Shark, swordfish, skate, fresh tuna fish
- Fish liver and fish liver spread
- Brown meat from crab and lobster,
- Digestive glands from escallop and kidney from mussel
- Local advice is available for different fjords

Source: www.matportalen.no

Age and parity

Despite adjustment for fish consumption in the multiple regression model, age was identified as an independent predictor of Hg blood levels. Mothers older than 30 years had higher Hg levels (50 %; $p<0.001$). Since pharmacokinetics indicates that the release of tissue inorganic mercury derived from the demethylation of methyl mercury into the blood compartment has a considerably longer half-life (170 days) than the 40-70 days for methyl mercury in blood [177], the observed association between Hg (measured as total mercury) and age ($p<0.001$) probably reflects greater long-term consumption of foods containing this element. However the age effect is not clearly established, as other studies have demonstrated both positive and no association [116, 178-180]. Nevertheless the effect of parity, corresponding to 20 % lower whole blood levels in multipara, is consistent with previous lactation and the slow pharmacokinetic issue mentioned. By contrast, for As the non-significant parity and age effects are in accordance with its short half-lives (in hours) for all of its chemical forms, including the primary As species arsenobetaine in fish/shellfish [118, 170, 181].

Other predictors

In other studies, residence, ethnicity, and both high and low income and education levels (all of which are determinants of diet), have been reported to be positively associated with elevated Hg blood concentrations [176, 182]. In our simple regression analysis, education and income were significantly associated with Hg (and Se), but this was no longer evident in the multiple regression model (probably because of rather homogeneous socioeconomic conditions). Place of living was not an issue as most lived in coastal city communities. We

found close to 40 % lower levels of Hg, As and Co in the Sámi participants (n=20) compared to others (n=185). Generally speaking, indigenous peoples have been documented to have higher blood concentrations [9, 122] of the toxic elements in question. Our findings could be due to chance due to the small sub-sample size. However, the Sámi total self-reported fish consumption was indeed somewhat lower (non-significant), but at the same time they reported significantly higher (p=0.027) intake of fresh-water fish. Hg sources other than fish seem plausible as our model only explained 36 % of the variation in concentrations of this element. Other dietary sources such as chicken or other meat have been suspected as a Hg source, since fish meal is used in animal feed [116, 173]. Amalgam dental fillings are also known to be an important contributor to the body burden, and thus blood levels of total Hg [173, 180]. However this was not investigated in our model.

Pb was the most dominant toxic metal, with women from the municipality of Finnmark having significantly (p=0.010) higher levels compared to the others; Nordland subjects exhibited the lowest. Despite the fact that no association with intake of game were found, the usual explanation given of consumption of animals shot with leaded ammunition could be a possible explanation [167, 168]. Unfortunately, information about hunting activities was not collected. Clearly, other possible local sources need to be considered.

Concentrations of essential elements

Concentrations of Cu, Mn, Mo, Se and Zn in whole blood were within the ranges reported in the few studies available for pregnant women [86, 87, 123, 170] and women of reproductive age [109]. In general, the primary intake route of these elements is the diet. However the blood, plasma or serum levels of Se for example are reported to vary between countries, due to vegetables and cereals grown in soils with high levels of Se, or by way of fortified food [141]. In comparison with South Africa and Brazil, the observed Se levels found (means of 86, 73, and 90 µg/L) were comparable to those reported for Brazil, but lower than those reported in the South African study (median, 104 µg/L) [86, 87]. Interestingly, fortified diets and prescribed supplementation during pregnancy was common for the latter group. In all these studies, Mn blood concentrations at delivery were just above the normal range quoted for the general population (15 µg/L) [138, 183]. This reflects the increasing concentration trend observed across pregnancy and six week postpartum. However, and as mentioned earlier, low iron status promotes Mn uptake and thus anemia is an issue (perhaps aggravated by postpartum bleeding).

Predictors of exposure to essential elements

Other than for Se (as discussed in previous section), we did not find any associations with the use of supplements. In should be mentioned that in terms of supplements, only multivitamins were put into the regression model (Paper III). However after investigating all participants with any kind of supplementation (yes/no), the results were unchanged (data not shown). The positive associations with the week of sampling for concentrations of Cu, Mn and Co seem reasonably, as the levels were found to elevate during pregnancy. However, age and parity were not associated with these elements, thereby highlighting the importance of continued dietary supply.

Profile of PTS during gestational and postpartum period

In previous literature, both concentrations of OCs in serum/plasma and non-essential and essential elements in whole blood have been suggested to be influenced by physiological and related changes during pregnancy. However, Papers II and III are the first to systematically explore the potential influences of physiological, metabolic and hematological changes during pregnancy and postpartum.

Organochlorines

In Paper II, the serum wet-weight OC profiles during gestational and 6-weeks postpartum reflected established changes in the lipid profile. As previously shown in Figure 1 and generally speaking, serum lipids peak at delivery and nearly return to pre-pregnancy levels at 6 weeks postpartum. Interestingly, only our wet-weight serum OCs concentrations showed similar peaking.

As pointed out in Paper II, other studies on changes in OCs during the gestational period are available, but do not report the consistent pattern we have observed [152, 184-186]. In a recent paper Glynn et al. (2011) [187] demonstrated an increase (but not statistically significant) of wet-eight levels of PCB 118, 138, 153, 156, and 180 between the 1st and 3rd trimester, but with a decline ($p \leq 0.05$) in lipid-adjusted PCB 180, 153, and 180 concentrations. Generally speaking, the peaking at delivery of PCB wet-weight levels and, after lipid adjustment, some suggestion of a decrease across pregnancy support our findings. However, Glynn et al [187] indicate that their study has limited statistical power due to small sample size (n=10), and differences in design and methodology should also be taken into account for a more rigorous comparison. Since our sample size (n=50) could also be improved, our findings need to be confirmed for the whole cohort (n= 394).

From a clinical perspective, wet-weight OCs represent the actual concentrations available for fetal exposure, with the peaking at delivery therefore constituting the highest exposure. The latter is reinforced by the robust correlations reported between maternal serum and cord blood levels [7, 8]. Strictly speaking from an analytical perspective, sampling would be most opportune around delivery. However, it is well established that the most critical time for the fetus is development in the 1st trimester, and thus sampling at this time would seem more toxicologically relevant. On the other hand since maternal serum OCs at delivery are strongly correlated with subsequent breast milk concentrations [7], both sampling times appear important. Furthermore, lipid-adjusted OCs concentrations are interpreted to reflect the body adipose burden of OCs [64]. In conclusion, reporting both wet-weight and lipid-adjusted concentrations seems to have inherent merit. This adds weight to the recommendation the both should continue to be reported [7, 61].

Non-essential (toxic) and essential elements

In Paper III, the non-essential and essential elements were divided into three different groups with reference to the concentration patterns they exhibited across the three sampling times. Concentrations of Group 1 [As, Pb, Cd (non-smokers), Mn and Zn] show a steady increase and has as a common feature a strong association with erythrocytes, and likely also reflects the metabolic demand for Zn, Mn and perhaps Ca; the V-shaped concentration pattern for Group2 [Hg, Mo, Se and Cd(smokers)] concurs with binding to plasma proteins as concentrations of the latter reflect the increase in plasma volume (i.e., a dilution effect); and the upside-down V concentration pattern of Group 3 [Cu and Co] is interpreted to reflect pregnancy-induced demands for Cu and perhaps Zn (Co can replace Zn at many protein Zn-binding sites).

The higher demand for essential elements during pregnancy and the lactation period should in general be met with an adequate nutrient-rich diet. Several confounding factors may impact and perhaps modify the observed patterns. As mention in Paper III, low iron status (during pregnancy and postpartum bleeding) appears to increase the uptake of Mn, Co and Cd [109]. Unfortunately, we did not have any measurement in place to evaluate iron deficiency. Further, mobilisation of Ca from bone stores, especially during the trimester and breast feeding, will contribute to the blood Pb concentrations [188]. As pointed out in Paper III, Pb is stored in bones with a long half-life (≥6 years) and in part has Ca-like chemical properties, and thus is

mobilised along with it. Thus the increase in blood lead in individuals with high bone Pb would exhibit even further enhancement during pregnancy and postpartum. Change in smoking habits during the pregnancy and the postpartum period has the potential of influencing the blood levels of Cd, since the latter primarily reflect current exposure. As shown in the regression model (Paper III), fish consumption is an important predictor of blood Hg, As and Se, and any change in fish intake will most likely affect the levels of these elements. Lowering mercury intake such as by switching to less contaminated species has been suggested to be effective in reducing blood Hg [189, 190].

For Hg, other studies of pregnant women with low fish consumption support our findings: a decline in levels across the 1st, 2nd trimester and delivery in Canadian mothers [180]; and declining levels during pregnancy up to delivery, with a gradual increase to 15 month postpartum for MeHg in a Swedish study [116].

The significant variations in the whole blood concentrations of the 10 elements studied across the 3 collection periods highlights the importance of reporting the time of sampling. When comparisons between studies are made, time-dependent changes in the underlying maternal physiological and metabolic processes have to be considered as a potential source of bias. Clearly this is also relevant for fetal risk evaluations involving toxic elements. For Hg there is another issue. Unlike other toxic metals, cord blood concentrations of Hg are established to be substantially higher than maternal blood [191], with the cord blood concentration reflecting fetal exposure more precisely [116].

At the time of writing, elemental analysis data for an additional 71 subjects became available (data not shown). When merging these two dataset (n=282), the same significant patterns ($p<0.001$) were pertinent across the three time periods, as well as between them; the magnitude of the changes were also comparable. This strengthens the findings of Paper III.

Methodical aspects

Study design

Both the Vietnamese and Northern Norwegian studies are based on mother-and-child cohorts. The Vietnamese study has a cross-sectional population-based format, and the MISA study has both cross-sectional and prospective longitudinal aspects. A cohort is an assembly of people with common characteristics [192]. Cohort studies (or follow-up or incidence studies) start with a group without disease, and who are divided into subgroups by exposure. The cohort is followed up to see how the subsequent development of new cases of the disease differs between the exposed and unexposed. Since exposure and disease refer to different time points, such studies are said to be longitudinal [193]. By contrast, a feature of a cross-sectional study is that exposure and its effects are examined at the same time. However, if the exposures measured reflect those before any outcome occurs, the data obtained approximates that generated in a cohort study [193].

The focus of Papers I, II, III is on the exposure component. To understand this aspect better, associations were explored between blood compartment concentrations of toxic environmental contaminants and of selected essential elements, their recognized sources, as well as with underlying metabolic and physiological changes that occur in mothers. In this section, the strengths and limitations of the three studies are discussed.

Study sample size

Both the sub-sets analysed in Paper II and III may have reduced the statistical power somewhat, as well as the internal and external validity. However, the primary objective of this study was to document patterns of change in the concentrations of OCs and elements at 3 time points spanning the 2nd trimester and 6 weeks postpartum. Consequently, external validity may be considered secondary. However, the sample-size calculations described in Paper II justified the sample size thereby reducing the probability that, similar to the wet-weight concentrations, a systematic pattern of significant differences (α=0.05 and β=0.2) occurred after lipid adjustment. This conclusion of acceptable sample sizes can be extended with confidence to Papers I and III since their numbers of participants were considerably larger.

Random and systematic errors

To obtain high validity and thus dependable results, the challenge is to minimize sources of random and systematic errors [192]. Random errors reflect low precision and reliability, while systematic errors (also called bias) appear when the measurements systematically deviate from true values due to weakness in the design, methods and implementation. Random errors in measurement can be reduced by quality control measures, and in sampling by increasing sample size [193]. The latter has already been addressed. Method errors are deemed minimal as all field protocols procedures and measurements (including body-weight measurements and blood sampling) were standardized. In terms of the chemical analyses, the quality assurance and control practices of both the Norwegian Institute for Air Research Laboratory and the National Institute for Occupational Health Laboratory met high standards (use of reference and control samples and participated in external-proficiency testing). Minimizing systematic errors involves reducing selection and classification errors [193], and these are discussed below.

With reference to the statistical methods, although non-parametric testing did not change the significance levels observed much it does strengthen the validity of our findings.

Validity

Internal validity is an expression of accuracy in the findings within the selected study group and is minimized by good design, methods and implementation (absence of bias equals validity). External validity or generalizability is the extent to which the results apply to the general population and others [193].

Selection bias

Selection bias occurs when the recruiting and selection involves different probabilities for potential recruits to be included in the study. This results in the study group not being representative of the population they were to represent [194]. In cross-sectional studies and cohort studies, both selection and follow-up biases are challenges [192]. The Vietnamese cohort had a high participation rate (92 %, participants with blood samples), compared to that in the MISA OCs study (20 % with blood samples at P1; 15 % with blood samples at all three periods) The latter likely has introduced some selection bias. As already pointed out in Papers II and III, there was evidence that "study tiredness" (i.e., requests to participate in too many studies) contributed to the low participation. This was difficult to overcome, even with vigorous promotion strategies. In addition, the time commitment and the frequency of sample

donation may also have lead to lower participation. Consequently, it is likely that the study cohort is not as representative of the maternal population of Northern Norway as planned.

Evaluation of non-response biases is important in evaluating external validity. The information available in the Medical/Birth Registry of Norway (MFR) on our cohort permits some insight. When comparing the study cohort with delivering women in Northern Norway in the period 2004-2006 (Table 2), the study subjects were somewhat older and parity was somewhat lower. Interestingly, the MISA study group included a high proportion of "older" well-educated women, which may have influenced the life-style, such as selection of healthier food and less smoking.

Table 2 Personal characteristic across samples in the MISA study and maternal data from Northern Norway 2004-06

	The MISA Study				MBR*
n	515	391	211	50	____
Age	30.6	31.0	31.0	31.0	29.1
Parity	0.93^	1.0^	0.9	0.84	1.02
Education	15.6	15.9	15.9	16.2	____

* Data from the Medical Birth Registry of Norway (MBR); delivering mothers from Northern Norway; 2004-06 (ref. personal communication, AS Veyhe, 2011)
^ Calculation is based on data from the Medical Birth Registry of Norway (personal communication, AS Veyhe, MISA, 2011)

Loss-to-follow-up and use of sub-samples can affect the internal validity. However, when comparing the sub-sample populations (n=50 or 211) with the group who provided blood samples for all three periods (n=392) and also with the initial cohort of 515 women, personal characteristic like age, parity and education were similar (Table 2). This strengthens the internal validity.

Information bias

Information bias is incorrectness in reporting or treatment of information, unconscious or intentional, which may not only lead to discrepancy in comparisons of sub-groups, but also can impact continuous variables. Misclassification of exposure or outcome variables can be non-differential or differential and can affect estimates in more or less both directions [(194)]. Non-differential misclassification is random and affects all sub-groups equally, while differential misclassification does so unequally and constitutes systematic error that can influence both exposure and/or outcome.

In Paper III, the FFQ and the calculations of the consumption rates are self-reported and are based on standardized portions and national food composition tables. They have a high degree of inherent uncertainty [195] and may lead to non-differential misclassification. The reported fish intakes were relatively high compare to what has been reported in young people, and were comparable with those reported for North Norwegian women aged 17-79 [18, 170]. Our FFQ was largely based on that from the Norwegian Women and Cancer Study (NOWAC), which has previously been validated by Parr et al. (2006) [146] and Hjartåker et al. (2007) [144]. Lower intakes were reported by them in the retest of both the FFQ and the 24 hour recall. The FFQ used in the MISA survey was supplemented with: 12 questions about fish and shellfish; 8 about items eaten during childhood, youth and adulthood; and 3 items concerning game. The fish and seafood questions may therefore lead to information bias, with over-reporting a real likelihood [196]. Missing information was replaced by zero or smallest amount, and this may have contributed to under-estimation [197]. The missing and inaccurate information might have been due to recall bias, misunderstanding or tiredness due to answering multiple questions. It seems also likely that the self-reported data could reflect over/under reporting caused by recall-bias, or to give the impression of a "healthy" life-style. In addition, changes in diet during the follow-up period may have occurred. Pregnancy itself might have been the cause, especially in relation to dietary advice related to toxicants in fish. Since the women reported the diet intake for the year before pregnancy, contaminants with relatively short half-lives in the blood compartment may therefore not accurately reflect dietary intake (e.g., Pb, Hg and As). In addition to soliciting information on intake during past years, seasonal variations were taken into account in the MISA study. In contrast, the Vietnamese survey had no seasonal questionnaire and had a rather short sampling period in the "high" season of seafood consumption [52], which may have contributed to some over-reporting.

In addition to the FFQ, the women in both the Vietnam (Paper I) and Northern Norway studies (Papers II and III) provided self-reported height, lactation, life-style and socioeconomic information. This may have lead to non-differential misclassification involving both under- or over-reporting.

In Paper III, ethnicity was brought into the analysis when comparing Sámi participants with other participants (Norwegian and others). The relative broad definition of Sámi used, may have introduced non-differential misclassification in this subgroup with regards to traditional Sámi culture and life-style [198]. Of the 21 women designated as Sámi, 10 reported Sámi as

self-perceived ethnicity and 11 claiming ethnic background. Due to the small number of Sámi enrolled, this classification was the optimal approach we could take. These limitations lower the confidence in the regression analyses results involving this subgroup.

Confounding

"*Confounding occurs when the effects of two exposures (risk factors) have not been separated*" (Bonita et al. 2006, p.56) [193]. A confounder is linked to both the exposure and outcome, and thereby introduces error if not equally distributed among subgroups. Effect modification is therefore introduced when two causal factors, or one causal or one protective factor, interact and exert down- or up-regulation of the outcome [192]. The way of handling confounding is by randomising, matching, stratifying or adjustment, with the latter two especially pertinent for cohort studies.

In all three papers, multivariable regression models were used to reveal associations between independent variables and OCs/elements concentrations. In Paper I, both adjustments and stratifying methods were used in controlling for confounders. In Papers II and III, adjustment was employed. Age and parity (lactation) were consequently used in all models due to their known and potentially related influence on the dependent variables. Due to the limited sample size in Paper II, only BMI was additionally tested, but it was non-significant. The samples were larger in Papers I and III, and thus besides age and parity, several additional factors depending on simple linear association were controlled for: BMI, weight-gain during pregnancy, education, income, duration at present address, district, use of pesticides, and growing own food in the garden were included in Paper I; and education, income, smoking, alcohol, municipality, ethnicity, interval, lactation, supplementations, several fish items, and game in Paper III. Interestingly, being Sámi had a protective effect on the levels of Hg, and this is interpreted as an effect modifier. Perhaps it is not a causal factor, but rather a proxy for an unknown confounding variable. Thus the dietary information remains to be more fully investigated.

With regards to the near-delivery time point, blood loss and blood transfusion were not taken into consideration. It is possible that this may have modified the observed concentrations of the analytes.

CONCLUDING REMARKS

In a global comparison the North Norwegian study documented generally low maternal concentrations of both OCs and toxic elements, and normal levels of the essential elements. The Vietnamese study demonstrated relatively high levels of *p,p'*-DDE and *p,p'*-DDT, among the highest in our global comparison and reflects recent use as documented in other studies. In contrast, the concentrations of PCBs were somewhat lower than the Norwegian measured.

Because of the generally low levels detected, the implications for vulnerable groups like the fetus, newborns and growing children in terms of possible adverse health effects are minimal. However, negative effects at background levels remain a concern such as the neurotoxicity of Hg, Pb and OCs. The ongoing addition of new chemicals to the already complex environmental exposure mixture adds to such worry. Therefore in preventive work, precaution and advisories for these vulnerable groups (including reproductive and pregnant women) are highly relevant. Thus the Vietnamese finding of relatively high *p,p'*-DDE and *p,p'*-DDT levels requires extra attention in preventing possible health effects, especially before and during the educational years, including restrictions of pesticide use and dietary advice for the family. In addition, further monitoring of levels and health effects of the growing children are necessary.

Our studies demonstrated relatively high fish consumption in the North Norwegian mothers compared to other young Norwegian women, but still below the national recommendations, and possibly substantial higher intake in Southern Vietnam. The benefits of fish and seafood consumption constitute a paradox since they are a source of toxicants. This highlights the importance of risk communications and following fish-intake guidelines.

Of the tested predictors, age and parity were the most dominant for the OCs. Place of living, which likely reflect dietary patterns, was also of importance in the Vietnamese study. These findings are in accordance with previous studies and the general understanding. For the toxic elements Hg and As and the essential element Se, fish consumption constituted an important source. In terms of the elements, age and parity were associated only with Hg (and parity with Co).

The most important findings are probably the observed concentration patterns across the three collection periods revealed for the OCs and the elements. They reflected the physiological and

related adaptions during pregnancy and postpartum. The wet-weight concentrations of the lipid-soluble OCs followed the changes in lipid profiles, which peaked at birth. In addition to paralleling metabolic, hematological and physiological changes during the gestational and postpartum periods, the concentrations of the elements also reflected their biochemistry and their accumulation preferences within the whole-blood compartment and breast milk. Our systematic approach and findings provide a new understanding of the changing concentrations of toxicants and essential elements in the blood compartment during pregnancy, and have implications for the optimum monitoring time. Furthermore, and as discussed in Paper II, our results suggest that the positive associations frequently reported between OCs and Diabetes 2 do not necessarily imply causation as lipidemia is an important risk factor for this disease.

FUTURE PERSPECTIVES

Extended use of the current database

1. Conduct a fuller analysis of the dietary information.
2. Using the results of item 1, repeat the Paper II study using the complete cohort. This is important to clarify the numerous associations now being reported between OCs and diabetes
3. An analysis of the PCB hydroxylated metabolites in relation to the parent PCB levels and their concentration patterns across the 3 collection times.
4. Assessment of OCs and elements in meconium (first fecal excretion of the newborn child).
5. Assessment of emerging contaminants in maternal serum samples.
6. A prospective biomonitoring and developmental study of the children since low levels of Hg, Pb and OCs are known to have an impact on development, learning and behaviour

New Studies

Studies in Vietnam and other Southern Hemisphere countries similar to Papers II and III would be helpful to confirm the external validity of the findings. It would also add to the world-wide documentation of exposures to OCs and toxic elements. Inclusion of breast milk would also enhance this biomonitoring research. This would be facilitated by the fact that the laboratory in Nha Trang Vietnam is currently participating in the international inter-calibrating AMAP ring test.

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ERRATA

Paper I

Page 229, 3.4 Contaminant concentrations, line 1-7 should be corrected to:

The normality of the distributions of the compounds with substantial detection frequencies was assessed by using the Kolmogorov-Smirnov test, and normality was indicated for log-transformed concentrations of PCB congener 153 (p=0.086) and the pesticide p,p□-DDT (p=0.200). Log p,p□-DDE suggested minimal violation of the normality assumption (p=0.014), but did not when considering Nha Trang and Dien Khanh separately (p>0.05). The distributions in both population groups were skewed to the right.

Page 231, 2. Paragraph:
A 1997 study among women (age 24-56) in India reported lower levels, namely 0.08 μg/L.

Replace with:
A 1997 study among women (age 24-65) in India reported lower levels, namely 0.08 μg/L.

Paper II

Page 2129, Section 2.1 Geographical description and study population
Line 2 from the bottom: *replace* 395 *by* 391

Page 2130, Section 2.5.1 Sample treatment and analyses
1. Paragraph 1, Line 1: *replace* plasma *by* serum
1. Paragraph 1, Line 6: *replace* plasma *by* serum
3. Paragraph 3, Line 3: *replace* plasma by serum

Table 2: *delete* Footnote b
Supplementary data depository: *delete* Note 1. Organochlorines compounds not quantified

Paper III

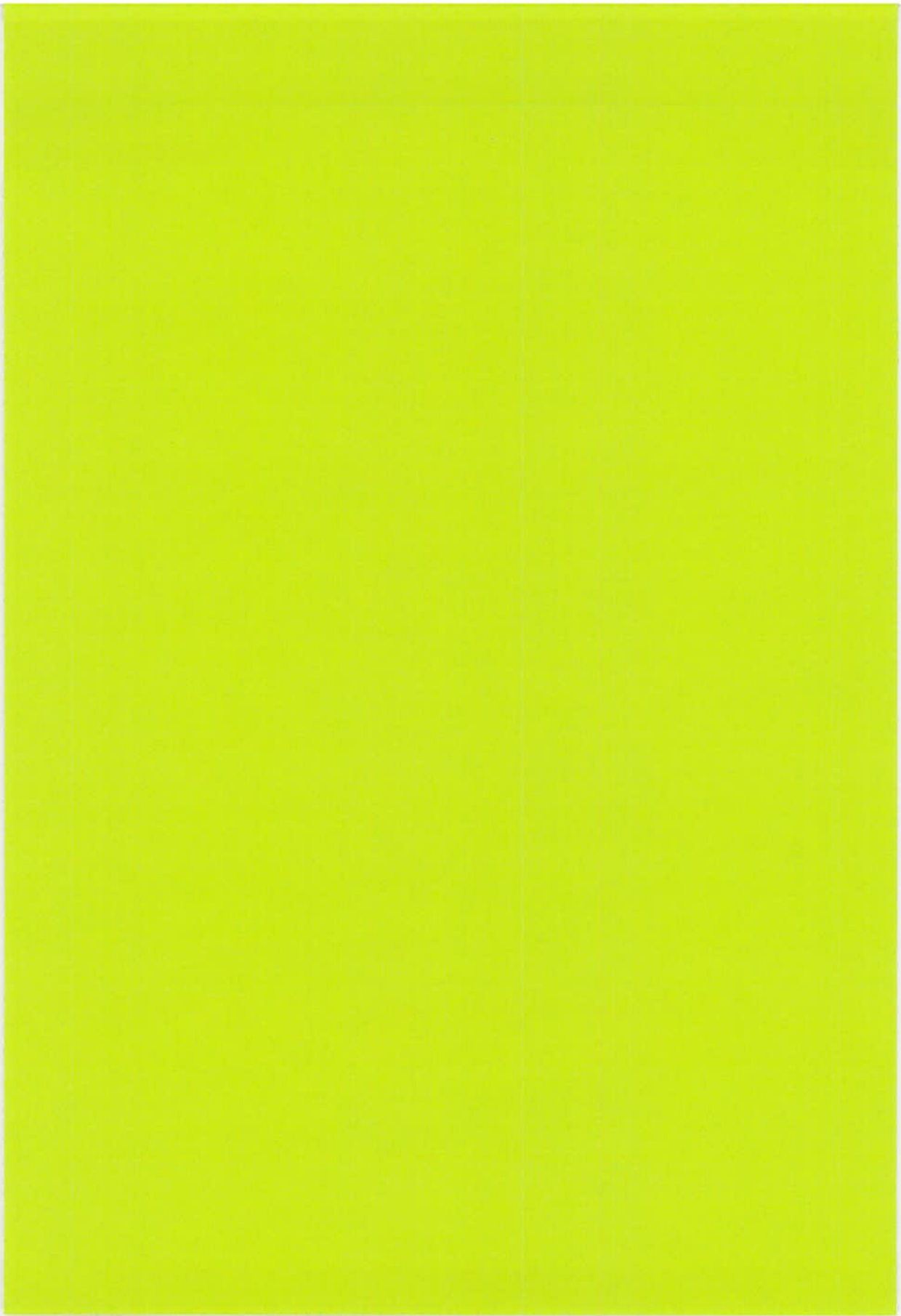
Page 3, 1. Paragraph, line 5 from below: *replace* 395 *with* 391

Page 19, 2. Paragraph, line 2 from below: *delete* reference number 2.

Thesis

References in the discussion part (in the text, but not in the figure) involving **page 51, 53, 54, 55 and 61**:
Reference 151, 152, 153, 154, 155 *and* 156 *should be corrected to* 156, 151, 152, 153, 154 *and* 155, *respectively.*

PAPER I



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Maternal levels of organochlorines in two communities in southern Vietnam

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ABSTRACT

Some pesticides and PCBs continue to be reported as environmental problems in some areas of Vietnam. In 2005, a study among delivering women took place in two communities in south-central Vietnam (Khanh Hoa Province), namely the coastal city of Nha Trang and the rural district of Dien Khanh located about 10 km inland. The main findings in plasma ($n=189$) were relatively high mean concentrations of *p,p'*-DDE (12.2 μg/l in Nha Trang and 11.4 μg/l in Dien Khanh) and *p,p'*-DDT (1.2 μg/l in Nha Trang and 1.1 μg/l in Dien Khanh) with no significant community differences. The ratio of *p,p'*-DDE/*p,p'*-DDT (11.5 in Nha Trang/12.7 in Dien Khanh) suggests, as in other Vietnamese OCs studies, a relatively recent use of this pesticide. Mean concentrations of PCB 153 (0.15 μg/l in Nha Trang and 0.10 μg/l in Dien Khanh) and other congeners were low in both communities. Age and parity (all compounds), as well as community of residence for PCB 153, were the most important predictors of plasma OCs concentrations.

1. Introduction

There is increasing apprehension about the negative health impacts of organochlorines (OCs) and other environmental contaminants. A number of potential negative health effects have been reported pertaining to reproductive health and developmental effects (including physical, mental and psychomotor development) (ATSDR, 2000, 2002; Longnecker et al., 2001; Ribas-Fitó et al., 2003; Eskenazi et al., 2006), endocrine metabolism (Asawasinsopon et al., 2006), the immune system (Dewailly et al., 2000), and cancer risk (Ahlborg et al., 1995; Longnecker et al., 1997).

OCs are liphophilic and have the ability to bioaccumulate and be stored in fatty tissue (Thundiyil et al., 2007); they also cross the placenta (Waliszewski et al., 2000) and are secreted into breast milk (Jaraczewska et al., 2006). The most vulnerable stages of human development appear to be the embryonic and fetal periods, making studies of exposure during pregnancy and pregnancy outcome especially important (AMAP, 1998).

Recognized predictors of exposure to OCs include maternal age, parity, lactation frequency, dietary and current exposures (Skaare and Polder, 1990; Furberg et al., 2002; Glynn et al., 2003; Barraza-Vázquez et al., 2008).

1.1. The situation in Vietnam

Some pesticides and PCBs (polychlorinated biphenyls) continue to be reported as environmental problems in some areas of Vietnam, despite their official prohibition since 1995 and the ratification of the Stockholm convention in 2002. These compounds are under inadequate control, and their industrial use/generation continues. Pesticides have been employed since the 1940s in agriculture and for malaria control. Furthermore, they are often stored in households, with no knowledge of the dangers or the need for caution while using them. Illegal supply and use of pesticides are also suspected (Nhan et al., 2001; Minh et al., 2002, 2004, 2006, 2007a).

p,p'-DDT[1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)ethane] and *p,p'*-DDE[1,1-dichloro-2,2-bis(*p*-chlorophenyl) ethylene] have been found in river sediments and soil (Nhan et al., 2001; Hung and Thiemann, 2002; Minh et al., 2007a,b) in both the northern and southern regions of Vietnam, as well as in marine food (Kannan et al., 1992; Minh et al., 2002) and in human body fluids (Schecter et al. 1997; Minh et al., 2004). Even though levels in the environment have been reported to be decreasing in Vietnam, they remain relatively elevated globally speaking (Minh et al., 2002, 2007a). Higher concentrations occur in urban samples compared to more rural, agricultural sites (Schecter et al., 1997; Nhan et al., 2001; Minh et al., 2002, 2004, 2006). The authors suggest that the exposure likely results from active use of pesticides for vector control and hygiene purposes in urban areas. By contrast, Schecter et al. (1997) reported threefold higher levels of

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p,p'-DDE and *p,p'*-DDT in sera of urban women than in their rural counterparts suggesting that the main source was contaminated food. Minh et al. (2004) reported rather high levels of *p,p'*-DDE in breast milk collected in both northern (1900 ng/g lipids; arithmetic mean, AM) and southern (2000 ng/g lipids, AM) areas of Vietnam, although they have decreased since the 1980s (Schecter et al., 1989).

PCBs were introduced to Vietnam in the late 1940s. Although current sources are mainly from an expanding industry, contaminated equipment used in the Vietnam War is also of concern (Minh et al., 2004). Environmental PCB concentrations in Vietnam are generally lower than in some developed countries (Minh et al., 2007a), however with huge local differences in PCB sediment levels for the Ho Chi Minh City area; in some places they exceeded those of DDT (Minh et al., 2007a).

1.2. Aim of the study

The study described has two objectives: to determine levels of contaminants in delivering women's plasma samples, and to identify exposure risk factors.

1.3. Geographical description

The study took place in 2005 in the Khanh Hoa Province (Fig. 1) in the south-central coastal-region of Vietnam. The study populations were located in Nha Trang and Dien Khanh. Nha Trang is a coastal city and regional capital, and Dien Khanh is a rural district located about 10 km inland.

2. Materials and methods

2.1. Study population

All delivering women from three delivery units in the study area were invited to participate when giving birth. The units involved were the obstetric departments at the Provincial Hospital and the Public Delivery Clinic in Nha Trang, and the obstetric clinic at the District Hospital in Dien Khanh. The criteria for inclusion were that the mother had lived in the community for the last five years and provided a street address. From May to July 2005, five women (2%) refused to participate, and 241 women were initially registered in the

Fig. 1. Map of study area.

study. Of these, 202 women fulfilled the mentioned criteria; furthermore, blood specimens were not available for 13. Consequently, the study group consisted of 189 participants (94 from Nha Trang and 95 from Dien Khanh).

2.2. Data collection

The study included a questionnaire on diet and life style, consulting medical records concerning pregnancy outcome, collection of maternal blood samples, and obtaining details about the neonates at different stages after birth. In connection to the birth, a standard form was filled out by the medical personnel in the delivery units. Information obtained about the mother included: name, age, pre-pregnancy weight and at delivery, height, and pregnancy and delivery data. Within four months after delivery, the women were interviewed at home by trained staff from the Pasteur Institute. Information was solicited pertaining to socioeconomic and life-style status, medical/obstetric/lactation and environmental history, and food consumption frequencies of the most commonly eaten food items.

2.3. Analytical methodology

Non-fasting samples of venous blood were collected from the women within 3 h after delivery, employing standard vacutainers with EDTA as anticoagulant. Blood samples were stored at −20 °C and kept frozen until analysis. Those analysed in Norway were shipped by courier in a frozen state. The plasma samples were extracted and purified as described previously by Sandanger et al. (2003a). In short, after the addition of an internal standard the plasma samples were extracted using liquid–liquid extraction with ethanol, deionised water saturated with ammonium sulphate, and hexane. The OCs were separated from the lipids using a florisil column manually packed with 3.0 g of 0.5% deactivated florisil and 2 g of granulated sodium sulphate on top of the columns. The OCs were eluted using 11 ml hexane:dichloromethane (3:1 vol/vol). The collected fraction was evaporated to 0.5 ml using a Zymark Turbovap 500 Closed Cell Concentrator (Hopkinton, USA) in Norway, or employing a gentle flow of nitrogen in a water bath (40 °C) in Vietnam. The sample was evaporated to 200 µl before transfer to a GC-vial with an insert capillary, was reduced further to 20 µl, and octachloronaphthalene (OCN) was added as a recovery standard.

Different GC–MS instrumentations were employed in Norway and Vietnam. In Vietnam the gas chromatography (GC) was performed using a Shimadzu GC 17A fitted with a Shimadzu AOC 20S auto sampler (Injector: AOC 20 I) connected to a Shimadzu MS QP 5050A spectrometer. A 30-m DB-5 MS column (0.25 mm i.d. and 0.25 µm film thickness; J&W Scientific, CA, USA) was used for all analyses in both laboratories. The instrument was operated in the selected ion-monitoring (SIM) mode, employing positive electron-impact ionisation (EI+) as the source. In Norway, the GC was a Fisons 8060 Mega Gas Chromatograph (Milan, Italy) (see Sandanger et al., 2003a). The GC was connected to a low-resolution Fisons MD 800 Mass Spectrometer (Milan, Italy). Quantification was achieved in the SIM mode using both EI+ and negative chemical ionisation (NCI) sources. C-13 labelled PCB 118 was used as an internal standard for the PCBs and C-13 labelled *p,p′*-DDE for all pesticides. The different compounds were identified from their SIM masses and retention times. For each analyte, the ratio of two masses was monitored. Peaks with differences in isotopic ratio greater than 20% compared to the quantification standard were rejected and not quantified. The samples were analysed for 18 PCBs and 14 pesticides. For every 10 samples, a blank was analysed to assess laboratory-derived (i.e. inadvertent) sample contamination. The method detection limit (LOD) was calculated using three times the area of the noise or, if peaks were found in the blanks, three times the area of the blank. All levels below the LOD were set to half LOD, and were included as such in the statistical analyses. PCB 138 was only partially resolved from PCB 163 and integrated as one peak, and thus was reported as PCB 138/163.

The lipids could not be determined in the majority of samples due to limited sample volume and lack of reproducible gravimetric scales in the Nha Trang laboratory. Due to limited resources and limited sample volumes, the lipids were determined in Norway in a subset of only 20 samples from each region. The lipids were determined enzymatically and the total lipids were calculated according to a formula by Phillips et al. (1989) (also see Sandanger et al., 2003a).

2.4. Quality assurance and control (QA/QC) measures

Several measures were implemented in order to ensure the quality of the data at the same time as implementing the method in the Pasteur Institute in Nha Trang.

- A common pool of plasma was analysed routinely alongside of sample batches both at the Norwegian Institute for Air research, (NILU; $n=19$) and the Pasteur Institute laboratory ($n=35$).
- Duplicate samples ($n=14$) were analysed both in Vietnam and Norway.
- Blanks were monitored continuously and with each batch of samples.
- In Norway, plasma certified reference material (NIST 1589a) was analysed concurrently with the Vietnamese samples in order to ensure the quality and comparability of these data.
- Some duplicate samples were analysed in Norway in order to see if improved sensitivity changed the results.
- Participation in the International Arctic Monitoring and Assessment Programme (AMAP) Ringtest (AMAP, 2009).
- Due to a limited budget, certified reference material was not analysed with the sample batches in Vietnam.

The main limitation of the analysis was the fact that the NCI option was not available at the Pasteur Institute. This resulted in poor sensitivity for the majority of the pesticides.

2.5. Statistical analyses

Descriptive statistics, ANOVA, and *t*-Test (independent samples) were used to compare the different groups. Data for all compounds were log transformed (base 10) before statistical analysis (including *p,p′*-DDE; see Results). Adjusted geometric means of the compounds were calculated using the Univariate General Linear Model (UGLM), adjusting for continuous variables like age and parity and for exploring associations. Multiple linear regressions were employed to explore associations between independent factors and levels of contaminants. Non-significant variables ($p>0.05$) were deleted from the model employing backward regression. All significant variables were retained in the final regression model. The regression coefficient may be considered a measure of the influence of independent variables, such as age and parity, on the log-transformed PCB 153, *p,p′*-DDE and *p,p′*-DDT concentrations. The regression coefficients were back-transformed to rate ratios ($10^{(\beta)}$) and in the text are described as % change = $(10^{\beta}-1)*100$ (Johnsen et al., 2006; Glynn et al., 2007). All statistical procedures were carried out using the SPSS for Windows statistical package (version 15.0; SPSS Inc. Chicago, IL, USA).

2.6. Ethical considerations

The study was approved by the Medical Ethics Council of The Ministry of Health of Viet Nam and the University of Tromsø, Norway. The women signed an informed consent form; participation was voluntary.

3. Results

3.1. Population characteristics

Selected characteristics of the delivering women from Nha Trang and Dien Khanh are presented in Table 1. The two groups were of equal size and of comparable age, although there were fewer young (<25 years) mothers in Nha Trang. Women from Dien Khanh had delivered more children ($p=0.010$), and reported a significant longer average lifetime breastfeeding period ($p=0.026$). Only two women did not report their breastfeeding history.

Weight before pregnancy was self-reported by only 156 women; only three did not have their assessed weight at delivery. The observed weight gain during pregnancy until delivery was on average 10.8 kg for Nha Trang women, compared to 9.4 kg in Dien Khanh ($p=0.014$). There was no difference in maternal weight before pregnancy or in height. The mean pre-pregnancy body mass index (BMI) (19.32 kg/m^2) was in the normal range (18.5–24.9 kg/m^2). Only 4 mothers had a BMI over 25, and for 34% of the women from Nha Trang and 44% from Dien Khanh it was under18.5 kg/m^2. At delivery, the mean BMI was 23.57 kg/m^2, whereas 25% were in the range of 25 to 35 kg/m^2; the rest of the women had normal BMIs.

Because only one woman smoked during pregnancy, and limited intake of alcohol occurred, these habits were not considered in the statistical analysis. Women from Nha Trang had higher levels of education and higher family income. Over 90% in both districts were married. Self-reported domestic uses of pesticides (yes/no) were reported by 111 women, which was 32% higher in Nha Trang. In Dien Khanh, almost 60% grew their own food. In both districts, women had lived at their present address for approximately 11 years.

Table 1
Population characteristic of delivering women from Nha Trang (the coastal and regional capital) and Dien Khanh (an inland district) in Vietnam.

		Nha Trang $n=94$ (49.7%)	Dien Khanh $n=95$ (50.3%)	p values
Mean maternal age/years (SD)		28.36 (5.47)	27.61 (5.46)	0.346
Range		19–49	18–42	
Under 25 (%)		25 (26.6)	32 (33.7)	
25–29 (%)		34 (36.2)	30 (31.6)	
Over 29 (%)		35 (37.2)	33 (34.7)	
Mean number of deliveries (SD)		1.53 (0.64)	1.79 (0.73)	0.010
Range		1–3	1–4	
Parity, including this one (% within locations)				
P1 (%)		51 (54.3)	36 (37.9)	
P2 (%)		36 (38.3)	44 (46.3)	
P3 (%)		7 (7.4)	14 (14.7)	
P4 (%)			1 (1.1)	
Lifetime lactation/months[a] (SD)		17 (9.06)	21 (8.8)	0.026
Range		2–48	12–53	
Mean maternal weight/kg before pregnancy[b] (SD)		46.97 (5.54)	45.77 (5.71)	0.186
Range		38–63	36–75	
Mean maternal weight/kg at birth[c] (SD)		58.10 (6.82)	55.03 (6.28)	0.002
Range		45–72	43–85	
Mean maternal height/cm[d] (SD)		155.43 (4.55)	155.44 (3.92)	0.111
Range		144–167	145–167	
BMI at delivery (kg/m^2)[e]		24.06 (2.64)	23.03 (2.54)	0.006
Range		18.43–32.0	19.11–32.93	
Education (%)	Illiterate		2.1	
	Primary school	25.5	35.8	
	Secondary school	34.0	50.5	
	High school	20.2	10.5	
	Upper high school	20.2	1.1	<0.001
Income (million VND (Vietnamese Dong))		2.14	1.26	<0.001
Pesticide use inside the house %		75.5	43.6	<0.001
Growing own food %		20.8	79.2	<0.001
Duration present address	Years (SD)	11.7 (11.0)	10.13 (10.34)	0.320
	Range	1–36	1–39	

[a] $n=42/58$.
[b] $n=73/83$.
[c] $n=92/94$.
[d] $n=93/94$.
[e] $n=102/96$.

3.2. QA/QC measures

The accuracy and precision of analysing pooled samples are presented in Table 2. The coefficient of variation (CV) was less than 40% for 8 of the 15 compounds, and the difference in mean values when compared to the reference laboratory was less than 30%. It is, however, clear that in general the CV for the data produced was high. The 16 compounds listed in footnote b to Table 2 had either poor sensitivity, low concentrations and/or the CV exceeded 70%. The major PCBs and *p,p′*-DDE/*p,p′*-DDT results did however show good comparability with data from Norway, with a slight overestimation of concentrations by the laboratory in Vietnam. For the other chlorinated pesticides, there was a systematic overestimation of levels and large CVs. The main reason for this overestimation in Vietnam was the low sensitivity and thus high LODs. Replacement of values below the LOD thus gave considerably higher concentrations than in samples analysed in Norway. It was therefore decided not to explore these data further. For the PCBs 118, 138, 153, 180, *p,p′*-DDE and *p,p′*-DDT, the levels obtained by the two laboratories were comparable. The *p,p′*-DDT concentrations did, however, seem to be somewhat overestimated (28%) by the Nha Trang laboratory. The uncertainty (20–40%) of these data are somewhat elevated compared to what could be expected from experienced laboratories with well established methodologies, but clearly well within what is required for a pilot study like the current one.

3.3. Lipid concentrations

Plasma lipid levels were comparable in magnitude for the two communities, with an average of 0.79% (wt/vol) for the mothers in Nha Trang and 0.72% (wt/vol) in Dien Khanh mothers ($p>0.05$).

Table 2
QA/QC performance by the Pasteur Institute Laboratory.

Compounds[a,b]	Average ($n=35$)	CV (%)	% deviation[c]
PCB99	0.040	51	52
PCB118	0.044	19	0
PCB138/163	0.377	29	−1
PCB153	0.334	24	7
PCB170	0.081	63	24
PCB180	0.214	35	−7
PCB183	0.025	64	32
PCB187	0.075	30	−1
p,p′-DDE	16.729	8	1
p,p′-DDT	1.355	24	28
α-HCH	0.775	62	NA
β-HCH	0.621	35	NA
γ-HCH	1.385	47	NA
HCB	0.718	47	NA
Heptachlor	1.724	63	NA

[a] PCBs, polychlorinated biphenyls; *p,p′*-DDE: 1,1-dichloro-2,2-bis(*p*-chlorophenyl) ethylene; *p,p′*-DDT: 1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)ethane; HCH, hexachlorocyclohexane; HCB, hexachlorobenzene.

[b] The following organochlorine pesticides were difficult to quantify or not quantifiable because the CV exceeded 70% and their concentrations were low: oxy-chlordane; trans-chlordane; cis-chlordane; trans-nonachlor; cis-nonachlor; heptachlor; mirex; PCBs 28, 52, 101, 105, 149, 156, 194, *o,p′*-DDE: 1,1-dichloro-2-(*o*-chlorophenyl)-2-(*p*-chlorophenyl) ethylene; *o,p′*-DDD: 1,1-dichloro-2-(*o*-chlorophenyl)-2-(*p*-chlorophenyl)ethane.

[c] Deviation in % between average values obtained by laboratory in Nha Trang ($n=35$) and average values obtained by NILU ($n=19$). A pooled sample (see text) was routinely analysed alongside sample batches.

Table 3
Levels (μg/l) of PCBs and pesticides in maternal plasma samples from Khanh Hoa Province (Nha Trang and Dien Khanh) in Vietnam.

Compound[a]	NT	DK	Overall					Nha Trang	Dien Khanh
	n	*n*	AM[b] (μg/l)	GM[c] (μg/l)	Range	LOD[d] (μg/l)	% detected	GM[c] (μg/l)	GM[c] (μg/l)
PCB28	85	94	0.02	0.01	0.01–0.41	0.024	6.7	0.02	0.01
PCB52	86	91	0.03	0.03	0.03–0.48	0.055	4.6	0.03	0.03
PCB99	94	94	0.03	0.03	0.03–0.18	0.064	3.2	0.03	0.03
PCB101	92	92	0.03	0.03	0.03–0.22	0.054	4.9	0.03	0.03
PCB105	93	94	0.03	0.03	0.03–0.13	0.053	4.4	0.03	0.03
PCB118	94	95	0.04	0.03	0.03–0.41	0.052	13.2	0.03	0.03
PCB126	68	79	0.01	0.01	0.01–0.05	0.017	2.0	0.01	0.01
PCB128	92	94	0.02	0.02	0.02–0.14	0.040	2.2	0.02	0.02
PCB138/163	94	95	0.12	0.10	0.04–0.90	0.087	65.4	0.12	0.07
PCB149	76	80	0.02	0.02	0.02–0.26	0.037	5.8	0.02	0.02
PCB153	94	95	0.14	0.12	0.02–0.90	0.046	96.3	0.15	0.10
PCB156	93	92	0.03	0.03	0.03–0.12	0.060	2.2	0.03	0.03
PCB169	68	79	0.02	0.02	0.02–0.09	0.030	3.4	0.02	0.02
PCB170	93	94	0.06	0.05	0.04–0.25	0.077	23.0	0.05	0.05
PCB180	94	95	0.16	0.13	0.06–1.01	0.127	61.4	0.17	0.10
PCB183	92	93	0.02	0.02	0.02–0.07	0.037	6.5	0.02	0.02
PCB187	94	95	0.06	0.05	0.02–0.24	0.047	59.3	0.06	0.04
PCB194	93	95	0.07	0.07	0.06–0.39	0.124	5.3	0.07	0.07
SumPCB	94	95	0.87	0.80	0.39–4.02			0.92	0.70
p,p′-DDT	94	95	1.70	1.15	0.11–38.28	0.216	98.9	1.24	1.06
p,p′-DDE	94	95	15.15	11.78	1.50–79.65	0.116	100	12.22	11.36
o,p′-DDE	84	94	0.08	0.06	0.06–0.60	0.112	7.3	0.06	0.06
o,p′-DDD	78	80	0.06	0.05	0.04–1.44	0.085	5.7	0.05	0.04
HCB	68	79	0.30	0.25	0.14–1.26	0.282	50.3	0.26	0.25

[a]See Table 2 for abbreviations and comment on the restrictions in quantifying some of the listed compounds (also see text).
[b]AM = Arithmetic mean; [c]GM = geometric mean; [d]LOD = the method limit of detection. All levels below LOD were set as 0.5× LOD.

3.4. Contaminant concentrations

The normality of the distribution of the compounds was assessed by using the Kolmogorov–Smirnov test, which indicated normality for log-transformed PCB congeners (e.g., log PCB 153; with $p=0.086$) and most pesticides (e.g., log *p,p′*-DDT, $p=0.200$), with log *p,p′*-DDE ($p=0.014$) the exception suggesting violation of the normality assumption as previously observed by Anda et al. (2007). The distributions in the population groups were skewed to the right. Extreme values were observed for PCB 153 (0.90 and 0.64 μg/l), *p,p′*-DDE (1.50 μg/l), and *p,p′*-DDT (9.8 and 38.3 μg/l). Excluding the outliers had only small effect on the mean levels (i.e., the 5% *trimmed mean* and *the mean* were not too different). For most of the OCs, the concentrations were low and below the LOD (see Table 3).

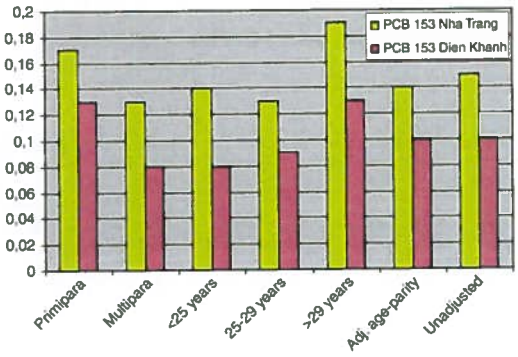
There were no significant difference in mean levels of the DDTs and HCB between Nha Trang and Dien Khanh. *p,p′*-DDE was the most abundant with mean concentrations of 12.2 μg/l (2.3–46.9) in Nha Trang and 11.4 μg/l (range 1.5–79.6) in Dien Khanh. The mean level of *p,p′*-DDT in Nha Trang was 1.2 μg/l (range 0.2–6.6) and, 1.1 μg/l (range 0.1–38.3) in Dien Khanh. The *p,p′*-DDE/*p,p′*-DDT ratio was calculated for each subject and had a mean value of 11.5 (range 1.2–34.9) in Nha Trang, and 12.7 (range 2.1–32.0) in Dien Khanh.

The measurable PCBs were detected in the order PCB 180> 153> 138> 187> 194. There was a significant difference ($p<0.001$) in PCB 153 levels between the two communities. The mean level in women from Nha Trang was 0.15 μg/l (range 0.02–0.9) and in Dien Khanh 0.10 μg/l (range 0.02–0.38).

The inter-compound correlations were moderate: *p,p′*-DDT and *p,p′*-DDE ($r=0.70$, $p<0.001$); *p,p′*-DDE and PCB 153 ($r=0.51$, $p<0.001$); and *p,p′*-DDT and PCB 153 ($r=0.57$, $p<0.001$).

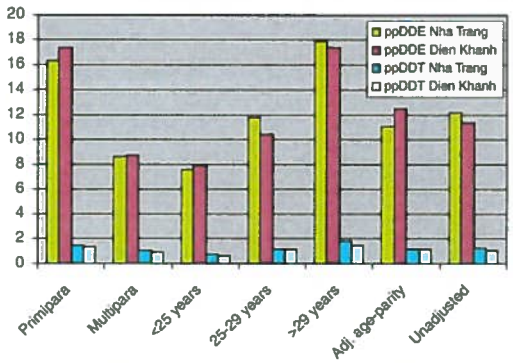
3.5. The effect of age and parity

Parity and lifetime lactation were strongly correlated ($r=0.94$, $p<0.001$), which was expected. However, parity exhibited the best associations with more compounds. There seems to be some element of uncertainty in the self-reported duration of lactation, as selections of 12, 18 and 24 months duration were most common. This suspected lack of accuracy and the stronger parity correlations support the selection of parity in the statistical analysis. Fig. 2 depicts the distributions of PCB 153 according to maternal age and parity groups in each district. Overall levels and concentrations before and after adjustment are also presented. The highest levels were observed in primipara ($p<0.001$), the oldest age group ($p<0.001$), and in Nha Trang ($p<0.001$) (data not shown). Similar patterns were observed for *p,p′*-DDE ($p<0.001$) and *p,p′*-DDT ($p<0.05$). There was a significant difference in PCB 153 concentrations between Nha Trang and Dien Khanh for all age groups ($p=0.011$), and for the primipara ($p=0.009$) and the multipara ($p>0.001$) groups. No such differences



	Multi vs. primipara	Across age groups
Nha Trang n=94	p=0.044	p=0.025
Dien Khanh n=95	p=0.001	p=0.004

Fig. 2. Levels of PCB 153 in maternal plasma in Nha Trang and Dien Khanh by parity and age groups and overall. Geometric means (μg/l) and comparisons were adjusted: parity groups were adjusted for age and age groups for parity; or both (Adj.).



	p,p′-DDE		p,p′-DDT	
	Multi vs. primipara	Across age groups	Multi vs. primipara	Across age groups
Nha Trang n=94	p=0.001	p=0.001	p=0.046	p=0.001
Dien Khanh n=95	p<0.001	p=0.001	p=0.036	p=0.002

Fig. 3. Levels of p,p′-DDE and p,p′-DDT in maternal plasma in Nha Trang and Dien Khanh by parity and age groups, and overall. Geometric means (μg/l) and comparisons were: parity groups were adjusted for age and age groups for parity; or both (Adj.).

occurred for p,p′-DDE and p,p′-DDT. The analysis provided in Fig. 3 for p,p′-DDE and p,p′-DDT illustrates this, and also depicts the p-value for significant differences between the age and parity groups in both districts.

3.6. Univariate analysis

The independent variables that were significant in the univariate analysis were: maternal age (p,p′-DDE, $p=0.003$; p,p′-DDT, $p=0.001$), parity (p,p′-DDE, $p=0.004$; PCB 153, $p=0.003$), district (PCB 153, $p<0.001$), BMI at pregnancy (p,p′-DDT, $p=0.003$), weight gain during pregnancy (PCB 153, $p=0.034$), education (p,p′-DDE, $p=0.049$; PCB 153, $p<0.001$), income (p,p′-DDE, $p=0.010$; p,p′-DDT, $p=0.046$; PCB 153, $p=0.001$), duration of present address (p,p′-DDE, p0.013; p,p′-DDT, $p=0.002$; PCB 153, $p=0.008$), use of pesticides (yes/no) (PCB 153, $p=0.030$), and growing own food in the garden (yes/no) (PCB 153, $p=0.004$).

3.7. Multivariate regression model

The multiple-regression model, summarized in Table 4, shows significant associations ($p<0.018$) for the three major contaminants and age, parity and living at the same address over the years. The independent variables in the regression model explained 22% of the variations in the levels of PCB 153 and p,p′-DDE, and 17% of the variation in p,p′-DDT.

The back-transformed beta-coefficients (Table 4) demonstrate increasing levels of contaminants with increasing age and decreased with higher parity. For a one year increase in age, p,p′-DDE in plasma increased on average by 6%, p,p′-DDT by 4% and PCB 153 by 2%. For a one unit increase in parity, the inverse trend occurred: p,p′-DDE decreased by 40%, p,p′-DDT by 24%, and PCB 153 by 23%. PCB 153 was lower by 27% when living in Dien Khanh compared to Nha Trang. Residence duration at the current address had a small effect (1–2% annually) on contaminant levels. BMI at delivery affected only p,p′-DDT concentrations, with a 6% increase per BMI unit.

Table 4
Significant predictors and their effect (expressed as rate ratios) on contaminant concentrations retained in a multivariate linear regression model.[a]

	PCB 153			p,p′-DDE			p,p′-DDT		
	β	p	Rate ratio[b] (95% CI)	β	p	Rate ratio[b] (95% CI)	β	p	Rate ratio[b] (95% CI)
Age (year)	0.010	0.011	1.023 (1.0–1.04)	0.027	<0.001	1.064 (1.04–1.09)	0.017	0.002	1.040 (1.01–1.07)
Parity (1–4)	−0.112	<0.001	0.773 (0.68–0.89)	−0.224	<0.001	0.597 (0.50–0.71)	−0.118	0.006	0.762 (0.63–0.92)
Duration present address (year)	0.004	0.009	1.009 (1.0–1.02)	0.005	0.018	1.012 (1.0–1.02)	0.007	0.002	1.016 (1.01–1.03)
District Nha Trang–Dien Khanh	−0.136	<0.001	0.731 (0.63–0.85)						
BMI at delivery							0.024	0.010	1.057 (1.01–1.10)
Residual		179			180			175	
F		12.725			17.097			8.622	
R^2 (%)		22.1			22.2			16.5	

[a] Only those independent variables that had a significant association ($p<0.05$) in the univariate analysis were considered in the model (see Section 3.6).
[b] Back transformed beta: 10^{β}.

4. Discussion

4.1. Levels of PCBs in comparison to other studies

The observed concentrations of PCB 153 and of other PCB congeners were significantly higher in urban women from Nha Trang compared to rural women from Dien Khanh even though the differences are rather small. The relatively low levels found suggest the absence of an active point source as reported for Ho Chi Minh City (Minh et al., 2007a). By contrast, diet is the most likely source of exposure in both Nha Trang and Dien Khanh, with intercommunity differences in dietary patterns.

Compared to wet-weight arithmetic means (AMs) of PCBs reported in other parts of the world, the observed concentrations (0.14 μg/l) are low and comparable with those published for non-industrialized developing countries such as by Weiss et al. (2006). They found serum levels of PCB 153 in a female population in Tanzania of 0.17 μg/kg, compared to 0.35 μg/kg in Germany. The difference was assigned to higher industrial activity and development in Germany. A 1997 study among women (age 24–56) in India (Rusiecki et al., 2005) reported lower levels, namely 0.08 μg/l. Even higher concentrations based on geometric means (GMs) for PCB 153 have been observed (especially among indigenous peoples) in arctic and subarctic regions of other industrialized countries: delivering women in Arkhangelsk Russia, 0.39 μg/l (Sandanger et al., 2003b); women married to fishermen (age 23–62) from Sweden, 0.96 μg/kg (Rylander et al., 1997); and pregnant women in Chukotka, Russia, 0.50 μg/l (Anda et al., 2007). The relatively high concentration reported for the latter community reflects the consumption of fish and marine mammals, which are known to accumulate OCs (AMAP, 2004, Sandanger et al., 2006).

Of the PCB congeners determined, PCBs 180, 153 and 138 exhibited the highest detection frequencies and concentrations. This pattern of PCBs is not unlike that reported in previous studies elsewhere (Furberg et al., 2002; Sandanger et al., 2003b; Van Oostdam et al., 2004). PCB 153 is generally highly correlated with the sum of PCBs, and this reflects the level of total PCBs.

4.2. Main findings for p,p′-DDE and p,p′-DDT and comparison to other studies

In both study populations, *p,p′*-DDE was the most abundant OC which is supported in previous human data from Vietnam (Schecter et al., 1997; Minh et al., 2004). We did not find any regional difference in *p,p′*-DDE and *p,p′*-DDT levels, which is inconsistent with previous findings in humans, sediments and biota. Higher levels occurred in urban sites compared to agricultural (rural) areas (Schecter et al., 1997; Nhan et al., 2001; Minh et al., 2002, 2004, 2006, 2007a,b). The mean *p,p′*-DDE/*p,p′*-DDT ratio of 12 (range 1.2–34.9) may indicate some current or recent use of pesticides in addition to the usual dietary sources. A *p,p′*-DDE/*p,p′*-DDT ratio > 30 usually indicates dietary sources, and ratio <5 is taken as a strong indicator of current or recent use of pesticides (AMAP, 2003). There is no indication that DDT levels were related to agriculture in the current study. If this were so, one would have expected higher plasma concentrations in Dien Khanh. On the other hand, it must be noted that the two communities are only 10 km apart.

Our observed levels of *p,p′*-DDT (1.7 μg/l) and *p,p′*-DDE (15.2 μg/l) appear to fall between AMs reported for women (mean age of 42.3 years) in a Vietnamese breast cancer study (Schecter et al., 1997) in rural (*p,p′*-DDE 9.24/*p,p′*-DDT 1.38 μg/l) and urban (*p,p′*-DDE 24.8/*p,p′*-DDT 4.61 μg/l) communities. These AM concentrations were lower than those found in pregnant malaria-free women living in northern Thailand (*p,p′*-DDE 17.0 μg/l, *p,p′*-DDT 2.1 μg/l), where *p,p′*-DDT was actively used until 2000 (Stuetz et al., 2006). In a study from Mexico, comparable levels have been observed: *p,p′*-DDE 14.5 μg/l; *p,p′*-DDT 1.8 μg/l (Waliszewski et al., 2001). Rusiecki et al. (2005) reported that Indian women had lower levels (*p,p′*-DDE 4.72/*p,p′*-DDT 0.76 μg/l). Compared to findings for circumpolar regions (Bjerregaard and Hansen, 2000; Furberg et al., 2002; AMAP, 2003; Sandanger et al., 2003b; Sandanger et al., 2006), where pesticides are not actively used, our observed levels of *p,p′*-DDE and *p,p′*-DDT are relatively high.

4.3. Body burden accumulation factors

Both the UGLM and multivariate analyses support the observation that the body burden of OCs increases with age and decreases with parity. The impact of the latter is no doubt intensified because of the long duration of the lactation periods. These findings are in accordance with previous studies (Grimvall et al., 1997; Bjerregaard and Hansen, 2000; Dorea et al., 2001; Furberg et al., 2002; Glynn et al., 2003; Glynn et al., 2007). The dependence on residence location of plasma PCB 153 concentrations most likely reflects differences in the dietary patterns. Since both positive and negative associations between BMI and *p,p′*-DDT have been reported (Perry et al., 2005), the positive correlation observed in our study is difficult to interpret.

5. Concluding remarks

Relatively high levels of DDE and DDT are reported for the two southern Vietnam communities. Further, rather low levels of PCBs with small but significant community differences were observed. Our extensive statistical analyses have shown that recognized predictors of OCs exposure and body burden apply to the comparison of the two Vietnamese study groups.

The results suggest recent use of *p,p′*-DDT in this area of Vietnam despite its ban. The relatively high levels of *p,p′*-DDE and *p,p′*-DDT give reason for concern like the long-term effect on children's health. Due to the overall benefits of breastfeeding, there is a consensus that it should remain a priority. The focus has to be education and awareness of the hazards of pesticide use, and on dietary advice for women and growing families to circumvent high body burdens. In addition, there is a need to address the lack of compliance with the DDT ban. These efforts will no doubt benefit extensively from continuation in building up the local capacity for analysing OCs in order to monitor exposure and identify potential sources.

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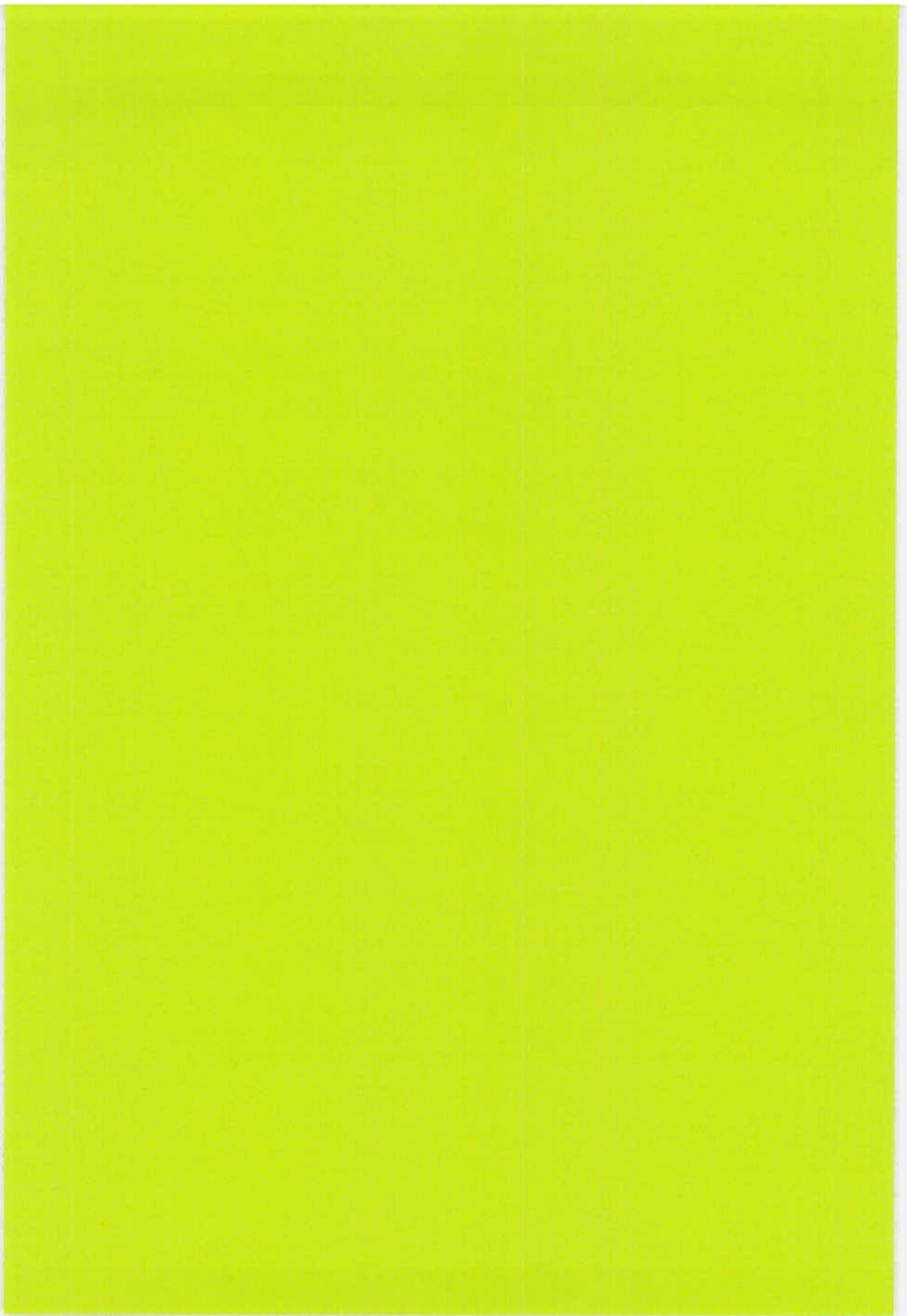
PAPER II



Levels of organochlorines and lipids across pregnancy, delivery and postpartum periods in women from Northern Norway†

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The objective of this study was to investigate changes in the levels of common organochlorines (OCs) and lipids in maternal serum during and after pregnancy. A subset of 50 pregnant women from the North Norwegian Mother-and-Child Study was included in this study. Blood samples were collected during the 2nd trimester and postpartum (Day 3 and 6 weeks) in different regions of Northern Norway, and were analyzed for the Arctic Monitoring and Assessment Programme (AMAP) suite of OC contaminants. During the gestational period, both lipids and wet-weight OC levels peaked at birth and were the lowest at 6 weeks postpartum. When the OC concentrations were lipid-adjusted, this peaking was no longer evident. Wet-weight concentrations of OCs appear to be driven by the physiological lipid profiles and are interpreted to constitute biomarkers of lipidemia. It is suggested that this observation may have implications for the biomonitoring of individuals at risk of Type 2 diabetes. Both age and parity were strong predictors for the OCs measured, but no consistent association with body mass index (BMI) was evident. Independent of lipid-adjustment, all compounds were positively and significantly correlated with each other (within and across the three collection time periods). The peaking of OCs during pregnancy suggests that the period spanning the last weeks of the 3rd trimester and the early postpartum days constitutes an optimum sampling window purely from the analytical perspective.

1 Introduction

Organochlorines (OCs) are well documented in Arctic ecosystems, mostly due to long-range transport from other parts of the world. OCs have the ability to biomagnify and persist in the environment for years. Because these substances are lipid soluble and are stored in fat tissues, the sources of OCs are mainly foods such as fatty fish and blubber of marine mammals. The lipid-rich traditional marine diet of some Arctic populations has constituted a specific concern.[1] However, recent documentation suggests that the transport of OCs to the Arctic is diminishing for many compounds. Presumably this reflects use restrictions and the outright banning of these compounds, both locally and globally. The consequence of this is less contamination of the food chain, and this is supported by the observation of decreasing concentrations of OCs in human body fluids.[1] However, a shift from traditional diet to store-bought food may also have contributed to this decrease.[1] The banning of PCBs (polychlorinated biphenyls) and pesticides in Norway was implemented decades ago. Nevertheless, OCs continue to be detected in population studies.[2–4]

Concerns about the negative health impacts of OCs and related environmental contaminants remain. Associations with a number of potential negative health effects have been documented that may impact reproductive health,[5,6] birth outcomes,[7] mental and psychomotor development,[8] endocrine metabolism,[9] the immune system,[10] and cancer risk.[5,11]

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† Electronic supplementary information (ESI) available: Note 1, OCs not quantified; Table S1, lipid-adjusted OCs levels; Table S2, linear mixed model results. See DOI: 10.1039/c0em00346h

Environmental impact

Few studies have systematically investigated the variation of maternal serum levels of organochlorine compounds (OCs) during gestation and post-partum. The current study constitutes a systematic approach to this topic. Wet-weight serum concentration profiles of pesticides and PCBs, measured during the second trimester and at 3 days and 6 weeks post-partum, reflected those observed for total and individual serum lipids; they peaked 3-days after delivery. While lipidemia is normal during pregnancy, it constitutes a clinical feature of diabetes and those at risk of this disease. Consequently, reported positive associations between OC levels and diabetes do not necessarily imply causation, as is often intimated. This novel insight, and the use of regression models to estimate quantitatively the influence of independent factors on levels of OCs, break new ground in biomonitoring.

Because of their lipophilicity, OCs cross the placenta and are secreted into breast milk.[11,12] The most sensitive stages of human development appear to occur in the embryonic and perinatal periods, making studies of exposure during gestation and early development especially important.[13]

Measurements of OCs in different tissues have been reported for newborn babies and their mothers, primarily in maternal and cord plasma (or serum) and mother's milk.[14,15] Just a handful studies have investigated OCs during critical windows of gestation, at birth and postpartum. Body fluid levels of contaminants at these different time points have been reported to be similar[16–19] or dissimilar.[20,21]

During the gestational period, tremendous physiological changes occur. Increasing renal perfusion and blood volume, dilution, substantial changes in hormones and serum lipids during the gestational period are evident.[22,23] Serum lipids increase throughout pregnancy with a peak at delivery and a decrease in levels postpartum.[23] Of these, serum triglyceride (TG) concentrations experience increases of 200–400%, compared to 35–60% for the major forms of cholesterol.[22,23] *In vitro* cellular uptake studies have demonstrated competition between lipoproteins and OCs.[24] Changes in the concentrations of serum lipids associated with fasting and postprandial states may also affect the blood levels of OCs.[25] In addition, differences in concentrations over time can reflect temporal variations in intake (*e.g.*, altered exposure) and elimination (change in body mass index, BMI).[26,27] Maternal age, pre-pregnancy BMI, parity, breastfeeding, and dietary intake of fatty fish and marine mammals are established predictors of serum concentrations of OCs.[2,4,19,28–31] Half-lives of OCs and, relative to them the shortness of the observation interval, measurement errors are also common explanatory factors.[27,32]

The aim of this study was to investigate changes in the levels of selected chlorinated pesticides, PCB congeners and lipids in maternal blood serum samples collected in Northern Norway during the 2nd trimester of pregnancy and at 3 days and 6 weeks postpartum.

2 Materials and methods

2.1 Geographical description and study population

The recruitment component of North Norwegian Mother-and-child Study took place from 2007 until 2009 in different regions of Northern Norway (Fig. 1) with the following specific objectives to: (i) determine levels of contaminants in delivering women's blood serum samples; (ii) identify exposure risk factors for the mothers and their offspring; and (iii) unveil dietary sources for women of reproductive age. The study populations lived in the northern counties of Nordland, Troms and Finnmark. Pregnant women in the study area were invited by written invitation administrated by ultrasound clinics personnel or during midwife consultations. The participating delivery departments were: Nordland Hospital (Bodø and Lofoten), University Hospital of North Norway Trust (Tromsø and the labour wards of North- and Mid-Troms), and Finnmark Hospital (Kirkenes, Hammerfest and the labour ward of Alta). From June 2007 to March 2009, 2600 women were invited, 609 responded, 557 were registered, 542 gave a blood sample, and 27 were excluded because of the lack of written consent. Thus, 515 women initially were included in the study; 461 of these presented at delivery and 395 completed the study at the 6 week postpartum sampling point.

2.2 Data collection

Data were collected during the 2nd trimester (mean 18.8 weeks, range 12–26) in pregnancy (designated as sampling time, *P*1) and at three days (*P*2) (mean 3.2, range 2–5) and 6 weeks postpartum (*P*3) (mean 6.7, range 4–12). Mothers' blood serum was collected and the maternal weight measured. When enrolled, the

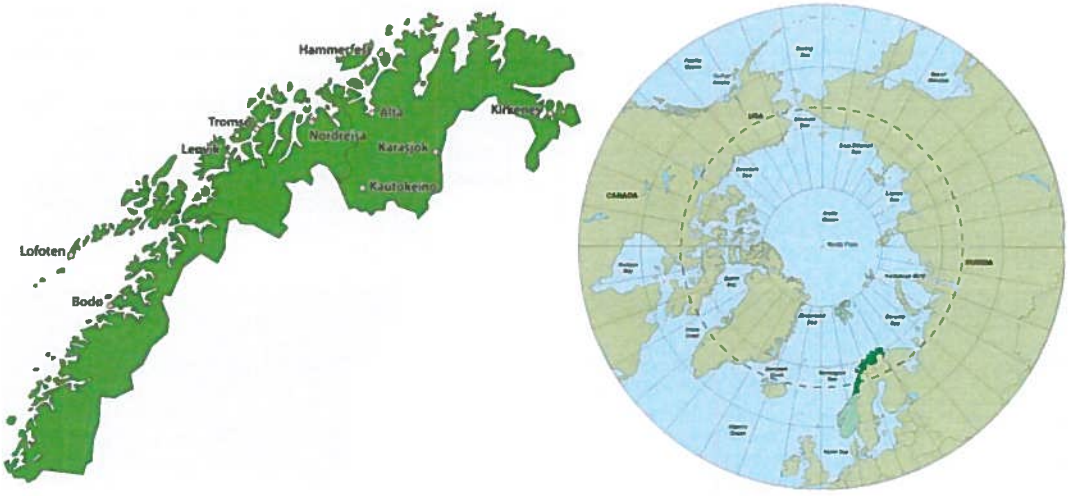

Fig. 1 Map of study area.

prospective mothers were asked to complete a detailed information questionnaire pertaining to personal characteristics, obstetric history, diet and life style. Permission to consult their medical records was obtained. In addition, at all blood sampling time points, a simple questionnaire was administrated to obtain personal information about current diet, smoking and alcohol habits, medication and dietary supplements. Pre-pregnancy weight and height were self-reported. The women were asked to fast overnight and, if they could not, were asked to eat a light non-fatty breakfast (porridge, bread, salad, no coffee) 2 hours before the blood sampling or earlier.

2.3 Study group

Due to laboratory processing and economic constraints, the specimens collected at each of the three time points for 51 women of the study subjects were selected for preliminary analysis. Selection of these participants was done randomly.

2.4 Sample collection

Blood samples were collected during June 2007 to October 2008. Blood was drawn from the maternal antecubital vein with standard equipment into BD Vacutainer (SST II Plus Advance 10/8.5 ml) and were centrifuged at 2000 RCF for 10 min. Vacutainers were transported to the University of Tromsø, where the serum was transferred to glass vials pre-rinsed with *n*-hexane/acetone and stored at −20 °C until analysis.

2.5 Analytical methodology

2.5.1 Sample treatment and analyses. Plasma samples were extracted on an Oasis HLB (540 mg; Waters Corp., Milford, MA, USA) solid phase extraction (SPE) column according to a slight modification of the method presented by Sandau *et al.* (2003) and Sandanger *et al.* (2007).[33,34] In short, an internal standard mixture was added to 2 ml of plasma before vortexing (1 minute) followed by the addition of 2 ml of formic acid and 2 ml of deionised water. The mixture was left overnight in the fridge before it was extracted on the HLB column using dichloromethane. The sample was evaporated to 0.2 ml and redissolved in 0.5 ml *n*-hexane and eluted through a column containing 1 g of activated Florisil (60–100 mesh; Fisher, Pittsburgh, PA, USA). The fraction containing the OCs was eluted using 9 ml *n*-hexane/dichloromethane (9/1 v/v). The extraction and clean-up procedures were automated using a Rapidtrace Automated SPE workstation (Zymark Corp., Hopkinton, MA), and evaporation was achieved using a heated vacuum evaporator (Rapidvap, Labconco Corp., Kansas City, MO) with the temperature set to 40 °C. The internal standard mixture contained 21 different carbon-13 labelled PCBs and pesticides, and was prepared in our laboratory from single standards (Wellington Laboratories, Guelph, ON, Canada).

The extracts (30 μl) were analysed using an Agilent 7890A gas chromatograph (GC), equipped with a 5975c mass spectrometer (Agilent Technologies, Böblingen, Germany). The GC was fitted with a 30 m DB5-MS column (0.25 mm id and 0.25 μm film thickness; J&W, Folsom, USA). Helium (6.0 quality, Hydrogas, Porsgrunn, Norway) was used as carrier gas at a flow rate of 1 ml min^{-1}. Two μl of the sample extract were injected in the splitless mode using a split/splitless injector (injector and autosampler–Agilent 7683 Series, Agilent Technologies, Böblingen, Germany). The GC temperature programme for chromatographic separation consisted of an initial temperature of 70 °C with a hold time of 2 min; the temperature was then ramped at 15 °C min^{-1} to 180 °C, followed by a temperature ramp of 5 °C min^{-1} to 280 °C with a hold time of 5 min. The electron-capture negative ionisation (ENCI) mode was used for the identification and quantification of most of the pesticides, while the electron impact (EI) mode was used for the determination and quantification of PCBs and DDTs. In both cases, the selected ion monitoring (SIM) mode was used and the different compounds were identified from their SIM masses, isotopic mass ratios and retention times. Peaks with differences in isotopic mass ratios greater than 20% compared with the quantification standard were rejected and not quantified. For every 10 samples, a blank was analysed to assess laboratory-derived (*i.e.*, inadvertent) sample contamination. A standard reference material employed in the Arctic Monitoring Assessment Programme (AMAP) ring test[15] was also included in each 10-sample batch. The limits of detection (LODs) were calculated using the signal to noise calculations in serum samples, and corresponded to 3 times the area of the noise in 8 seconds (estimated peak width at the given retention time). LODs for the *P*3 dataset were the most critical and were employed in all instances.

Lipids were determined enzymatically and the following summation formula was used to calculate the amount 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.[35]

2.5.2 Quality assurance and control (QA/QC) measures. The NILU (Norwegian Institute for Air Research) Laboratory has participated in the AMAP Human Health ring test[15] for plasma samples from the program's outset, and to date has performed well (uncertainties associated with the calculated concentrations were well within ±20%, which is considered 'best' performance). In addition, regular analysis of certified reference materials is carried out to ensure day-to-day performance. The high number of labelled internal standards also ensured the quality of the analyses. The recovery rates of the internal standards varied between 60 and 97%.

2.6 Statistical analysis

Non-detectable levels and concentrations below the LODs were replaced by the appropriate LOD divided by the square root of 2, as recommended by Anda *et al.* (2007).[15]

Both wet-weight and lipid-adjusted contaminant concentrations were skewed to the right (*i.e.* positively skewed), and were log-transformed [base 10 logarithm ($\log_{10} x$)] before statistical analysis. Descriptive statistics and independent samples' *t*-tests were used to compare the different groups. The linear mixed model[36] was used to investigate the effect of time between the collection periods to take into account the repeated measurement structure of the study. Time was included as two indicator variables (*P*1, yes/no; and *P*2, yes/no) using *P*3 log-transformed concentrations as reference. Age and parity were included in the model as possible confounders. The regression coefficients for

the indicator variables of time are estimates of the mean difference in log-transformed concentrations between each time point and the reference level. The regression coefficients were back-transformed to rate ratios (10^{β}), and in the text are described as % change = $(10^{\beta} - 1) \times 100$.[29,31] Simple linear regression was employed to explore associations between contaminant levels at each time point and independent factors such as age and parity. Only significant variables were retained in multiple regression modeling. Back-transformed regression coefficients as described above were used to measure the influence of the independent variables on the OC concentrations. Pearson correlation coefficients (r) were calculated for linear relationships. p-Values <0.05 were considered as significant. All statistical analyses were carried out using the SPSS for Windows statistical package (version 17.0; SPSS Inc., Chicago, IL, USA).

2.7 Ethical considerations

The study was approved by the Regional Committees for Medical Research Ethics. Participation was voluntary, and the women signed an informed consent form.

3 Results

3.1 Population characteristics

Selected characteristics of the 50 women are presented in Table 1. Based on ultrasound, the mean week of delivery was 40 (range 36–42). The mean interval between *P*1 and *P*2 was 154 (median), 154 mean (range 79–206) days; and 47 (median), 47 mean (range 36–82) days between *P*2 and *P*3.

3.2 Lipid concentrations

Despite being advised that fasting blood samples were required, only 21 out of 45 women (5 with unknown fasting status) at *P*1, 20 at *P*2 of 48 (2 unknown) and 21 at *P*3 of 47 (3 unknown) presented 8 hour overnight fasting samples (range 8–16). All but one of the non-fasting women donated their blood samples after breakfast; the exception did so after dinner (*P*3 collection). The lipid concentration distributions (for total and the 4 subfractions) were similar for both fasting and non-fasting women, and there were no statistically significant differences between the means of fasting and non-fasting serum total lipid concentrations or the subfractions (data not shown). The observed mean lipid concentrations peaked at *P*2 and were lowest at *P*3 (see Table 1); and the observed differences in levels across all periods were significant ($p < 0.001$). It is clear from Fig. 2 that the frequency distribution of the measured total lipid concentrations at *P*2 is quite distinct; those for the triglyceride and phospholipid subfractions most closely reflected this pattern (data not shown).

3.3 OC concentrations

The observed detection limits and frequencies are presented in Table 2. The majority of the compounds had a detection frequency above 92%, whereas PCBs 153, 180, 138, 118, *p*,*p*′-DDE and HCB were detectable in 100% of the samples for all three collection times. Due to their relatively low detection frequencies (≤70%) at one or more of the collection points, PCBs 101, 183 and 194, and *cis*-nonachlor were excluded from further statistical investigation. The corresponding means and ranges of both the wet-weight and lipid-adjusted concentrations of the excluded compounds are nevertheless reported in Tables 3 and S1, ESI†. In addition to the compounds discussed in this paper, the following were determined to have detection frequencies less than 50% in an exploratory subset of 30 samples and subsequently were not included in the final analytical protocol: PCB 28, 52, *oxy*-chlordane, *trans*-chlordane, *cis*-chlordane, β-HCH, *p*,*p*′-DDT and mirex. As reported previously,[15] large numbers of non-detects constitute a potential source of bias in statistical analyses.

After log transformation, the concentrations of all included compounds were normally distributed ($p > 0.05$) as judged by the Kolmogorov–Smirnov normality test, with the exception of log HCB ($p = 0.049$) at *P*3. A few outliers were seen, respectively 7 for wet-weight and 5 for lipid-adjusted data, but none was outside the outer fences of box plots.

Table 1 Descriptive characteristics of the study population ($n = 50$)

Variable[a]	Mean (SD) or *n* (%)	Median	Min–max
Age, years 2nd trimester	31.0 (4.8)	32.5	19–40
19–26	12 (24.0)		
27–33	23 (46.0)		
34–40	15 (30.0)		
Parity, mean	0.84 (0.96)	1	0–4
Para 0	22 (44.0)		
Para 1	18 (36.0)		
Para 2	7 (14.0)		
Para 3	2 (4.0)		
Para 4	1 (2.0)		
Total lipids/mg dl^{-1}			
*P*1	754 (167)	724	504–1585
*P*2	859 (136)	865	521–1093
*P*3	591 (84)	595	389–869
Phospholipids/mg dl^{-1}			
*P*1	262 (50)	259	175–509
*P*2	296 (40)	295	190–387
*P*3	226 (30)	224	155–312
Total cholesterol/mg dl^{-1}			
*P*1	233 (47)	231	159–460
*P*2 ($n = 48$)	253 (46)	254	158–365
*P*3	214 (38)	208	140–328
Free cholesterol/mg dl^{-1}			
*P*1	68 (15)	67	45–137
*P*2 ($n = 48$)	140 (25)	141	86–203
*P*3	121 (21)	117	81–186
Triglycerides/mg dl^{-1}			
*P*1	149 (64)	135	70–397
*P*2 ($n = 48$)	233 (76)	234	103–413
*P*3	88 (40)	76	44–232
BMI, prepregnancy, kg m^{-2} ($n = 49$)	25.4 (4.9)	23.6	19.7–39.3
Previous lactation (months)			
Previous, exclusive lactation ($n = 21$)	8.1 (4.9)	6.0	1–23
Previous, partial lactation ($n = 20$)	16.5 (12.7)	12.5	3–58
Lactation at *P*3 (number $n = 43$)			
Exclusive lactation	37 (86.0)		
Partial lactation	4 (9.3)		
No lactation	2 (4.7)		

[a] *P*1, 2nd trimester; *P*2, 3 days postpartum; *P*3, 6 weeks postpartum.

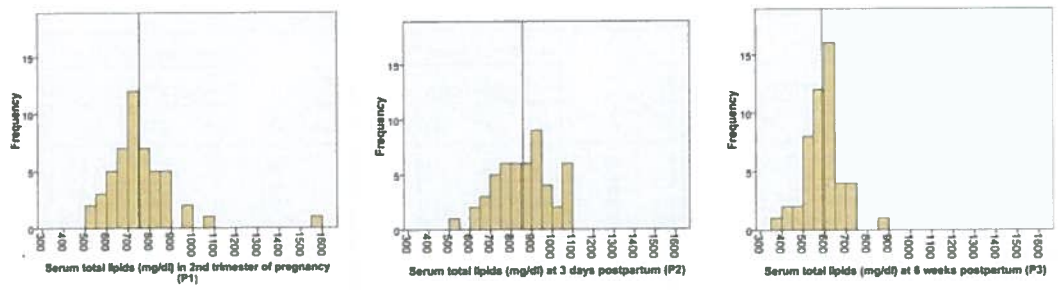

Fig. 2 Maternal serum total lipid distribution (mg dl^{-1}) for three different time periods, with the mean concentration as a reference line.

Table 2 Limits of detection (LODs) (pg g^{-1} serum) and detection frequencies above the LOD of PCBs and pesticides in maternal serum samples from Northern Norway

		2nd trimester (*P1*)		3 days postpartum (*P2*)		6 weeks postpartum (*P3*)	
Compound[a,b]	LOD[c]/pg g^{-1} serum	n^d	% >LOD	n^d	% >LOD	n^d	% >LOD
PCB-99	4	50	100	49	100	49	93.8
PCB-101	5	48	85.4	40	27.5	36	44.4
PCB-118	4	48	100	49	100	49	100
PCB-138	7	50	100	50	100	49	100
PCB-163	7	49	100	50	98	49	98
PCB-153	6	50	100	50	100	49	100
PCB-156	5	47	95.8	50	100	49	91.8
PCB-170	9	46	97.8	43	100	38	100
PCB-180	8	50	100	50	100	48	100
PCB-183	7	49	75.5	50	86.0	45	53.3
PCB-187	8	50	100	49	100	44	97.7
PCB-194	9	50	80.0	50	80.0	49	51.0
p,p'-DDE	9	50	100	50	100	45	100
HCB	1	50	100	50	100	50	100
trans-NC	4	50	100	50	98	50	96.1
cis-NC	3	50	66.7	50	76.5	50	66.7

[a] PCB(s), polychlorinated biphenyl(s); *p,p'*-DDE, 1,1-dichloro-2,2-bis(*p*-chlorophenyl) ethylene; HCB, hexachlorobenzene; *trans*-NC, *trans*-nonachlor; and *cis*-NC, *cis*-nonachlor. [b] An additional nine organochlorine pesticides and 4 PCB congeners were difficult to quantify (see Note 1 in the ESI†). [c] LOD = limit of detection. All levels below the LOD were set to LOD/$\sqrt{2}$. The LODs for *P3* were used for all three collection periods. [d] The reasons for the variation in the number of participants (*n*) are provided in footnote b of Table 3.

The wet-weight and lipid-adjusted concentrations of the PCBs and pesticides are reported in Tables 3 and S1, ESI†, respectively. *p,p'*-DDE had the highest concentrations, followed in declining order by PCBs 153 > 180 > 138 > 170 > 163 ≈ 187 ≈ 118 > 156 ≈ 99. Except for PCB-163, for all compounds (before lipid adjustment) the concentrations at *P2* were found to be the highest, and were lowest at *P3* ($p < 0.001$, Fig.3). After lipid adjustment, there was no uniform difference pattern (Fig. 4). With references to Fig. 4, lipid-adjusted *p,p'*-DDE peaked at *P3*, being 10% lower at *P2* ($p < 0.001$) and 8% lower at *P1* ($p = 0.058$), with no differences between *P2* and *P1*. Employing the linear mixed model (Table S2, ESI†), for wet-weight geomeans there were significant differences for nearly all the PCB congeners and the pesticides between *P1* and *P3* ($p < 0.001$); *P2* and *P3* ($p < 0.001$); *P2* and *P1* [$p \leq 0.001$; except for PCB-99 ($p = 0.027$), PCB-118 ($p = 0.013$) and PCB-163 ($p = 0.121$)]. By comparison, all trends across the 3 periods were significant ($p < 0.001$).

After lipid adjustment, fewer significant differences were evident in the mixed model (Table S2, ESI†): between *P1* and *P3* (p values ≤ 0.005 for PCB-99, PCB-163, PCB-187, *trans*-nonachlor and $p = 0.025$ for PCB-156); *P2* and *P3* (p values ≤ 0.002 for PCB-118, PCB-187, *p,p'*-DDE, *trans*-nonachlor, and $p \leq 0.032$ for PCB-156, PCB-170 and HCB); and *P2* and *P1* ($p \leq 0.008$ for PCB-99, PCB-118, PCB-163); and $p \leq 0.003$ across all three periods for PCB-99, PCB-118, PCB-163, PCB-187, *p,p'*-DDE and *trans*-nonachlor.

In the simple linear regression analysis for lipid-adjusted data (data not shown), age was the determinant that showed a consistent positive association with all OCs studied ($p \leq 0.002$). By contrast, parity was negatively associated reaching significance with PCB-118 at all three collection periods ($p \leq 0.024$), PCB-99 at *P1* ($p = 0.043$) and HCB at *P3* ($p = 0.034$). Interestingly, previous exclusive lactation had similar association as parity, which is consistent with the strong correlation between these two parameters ($r = 0.99$, $p < 0.001$). Of these two predictors, only parity was included in the multivariate model. There were no consistent significant associations between OCs and pre-pregnancy BMI.

Table 3 Wet-weight levels (pg g^{-1} serum) of PCBs and pesticides in maternal serum samples from Northern Norway

	2nd trimester (*P1*)					3 days postpartum (*P2*)					6 weeks postpartum (*P1*)				
	Concentration (pg g^{-1}) wet weight					Concentration (pg g^{-1}) wet weight					Concentration (pg g^{-1}) wet weight				
Compound[a]	n^b	GM[c]	AM[d]	SD	Min–max	n^b	GM[c]	AM[d]	SD	Min–max	n^b	GM[c]	AM[d]	SD	Min–max
PCB-99	50	15	16	8	4–33	49	15	18	10	5–44	49	10	12	6	3–28
PCB-101	48	6	6	2	4–11	40	4	4	2	4–11	36	5	5	2	4–11
PCB-118	48	31	35	17	11–82	49	33	38	21	10–90	49	24	27	15	6–67
PCB-138	50	94	105	50	32–267	50	106	121	64	31–335	49	72	81	41	23–212
PCB-163	49	39	46	27	10–136	50	35	41	22	5–98	49	23	27	14	5–69
PCB-153	50	167	187	94	58–540	50	188	217	122	49–655	49	130	148	80	44–452
PCB-156	47	16	18	9	4–44	50	18	21	11	5–50	49	11	13	8	4–37
PCB-170	46	46	53	28	6–141	43	52	59	30	22–153	38	34	38	19	16–98
PCB-180	50	113	123	63	34–323	50	127	146	80	29–385	48	89	100	52	30–270
PCB-183	49	10	11	6	5–31	50	11	13	7	5–38	47	8	9	5	5–26
PCB-187	50	31	35	20	10–116	49	35	41	25	8–140	44	22	25	13	6–66
PCB-194	50	13	15	8	6–35	50	15	17	11	6–49	49	9	11	6	6–31
p,p'-DDE	50	286	319	165	122–961	50	321	361	196	91–1218	45	246	278	158	75–993
HCB	50	71	78	39	31–235	50	78	87	47	32–279	50	58	63	30	28–177
trans-NC	50	20	24	14	4–62	50	25	31	20	3–82	50	13	16	10	3–45
cis-NC	50	4	5	4	2–19	50	5	7	5	2–22	50	4	4	3	2–17

[a] See Table 2 footnote b for full names. [b] The number of participants (n) varies because the observed ion-mass ratios were unacceptable (see text), the data for PCBs and *p,p'*-DDE are lacking for one individual of the *P3* group, and one donor was excluded from the study because she arrived in Norway recently. [c] GM = Geometric mean. [d] AM = Arithmetic mean with the corresponding SD, minimum (Min) and maximum (max).

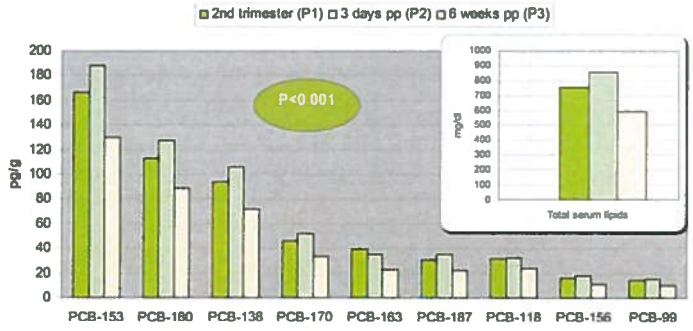

Fig. 3 Wet-weight (geomean) serum concentrations of PCBs (pg g^{-1}) and total lipids (mg dl^{-1}) for the collection periods *P1*, *P2* and *P3*. The *p*-value refers to trends across the three collection periods for both the OCs and lipids.

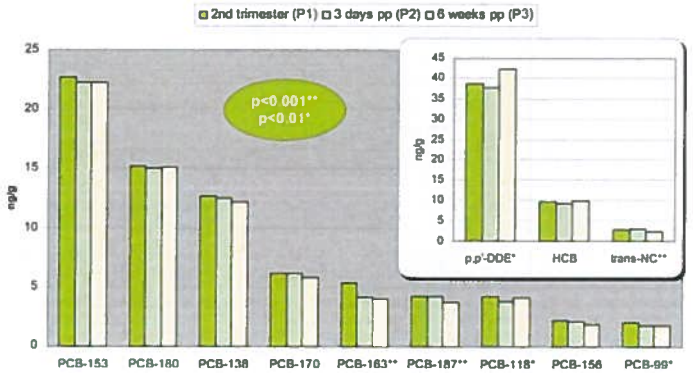

Fig. 4 Lipid-adjusted (geomean) serum concentrations (ng g^{-1}) of PCBs and pesticides for the collection periods *P1*, *P2* and *P3*. The *p*-values refer to trends across *P1*, *P2* and *P3* for both the PCBs and pesticides.

Table 4 Fractional change in PCB-153, *p,p'*-DDE and HCB concentrations (*lipid-adjusted*) per unit change in age and parity in a multivariable linear regression model[a]

	3 Days postpartum (*P2*), $n = 50$		
	Ratio[b]	95% CI	*p*
PCB-153			
Age (10 years)	2.19	1.82–2.69	<0.001
Parity (multi *vs.* primi)	0.76	0.64–0.92	0.006
Parity (0–4)[c]	0.84	0.76–0.93	0.001
p,p'-DDE			
Age (10 years)	1.82	1.48–2.29	<0.001
Parity (multi *vs.* primi)	0.77	0.62–0.95	0.015
Parity (0–4)[c]	0.83	0.74–0.92	0.001
HCB			
Age (10 years)	1.66	1.35–2.04	<0.001
Parity (multi *vs.* primi)	0.75	0.62–0.91	0.005
Parity (0–4)[c]	0.85	0.77–0.94	0.002

[a] The findings for *P1* and *P3* were comparable. [b] Corresponds to 10^{β}, with β the regression coefficient. [c] Adjusted for age.

Parity-adjusted age was positively related to all of the OCs at all periods ($p < 0.001$). Conversely, age-adjusted parity was inversely associated for most OCs with exceptions for PCB-156 at *P1*; PCB-180 at *P1* and *P2*; and PCB-170 and PCB-187 at *P2* and *P3*. The effect of age and parity in the multivariate linear regression analysis is illustrated in Table 4 for the PCB-153, *p,p'*-DDE and HCB for *P2*. For these compounds (lipid-adjusted concentrations), the effects of parity or age across the three different time periods were of comparable magnitude. The effect of age was strongest for PCB-153, with increases of 114 to 119% for each 10 year period, and a 24% decline due to parity (primipara to multipara). For *p,p'*-DDE and HCB, the parity effects were similar to PCB-153, while the age-effect was somewhat lower (*p,p'*-DDE increased by 78–82% and HCB by 45–66%). Interestingly, the effects of age and parity were not sensitive to lipid-adjustment (data not shown), although the changes for the wet-weight data were generally marginally lower. Adjustment for age and parity also had little effect in the mixed-model (data not shown).

3.4 Intra-period correlations

All compounds were positively and significantly correlated with each other (data not shown). The observed correlations were moderate to high for both wet-weight and lipid-adjusted concentrations, generally with *p*-values ≤ 0.001 and with the correlation coefficient (r) values above 0.50. Exceptions were the correlations at *P3* (wet-weight basis) between PCB-170 and 99 ($r = 0.50$; $p = 0.002$), PCB-170 and 118 ($r = 0.46$; $p = 0.004$), and PCB-170 and *p,p'*-DDE ($r = 0.47$; $p = 0.005$). Overall for lipid-unadjusted correlations between PCB congeners, PCB-153 generally exhibited the highest correlation coefficients ($r = 0.79$–0.98; $p < 0.001$) and PCB-170 the weakest ($r = 0.46$–0.96; $p \leq 0.004$). Correlations between PCB congeners were more robust than those between PCB and pesticides ($r > 0.47$–0.90; $p \leq 0.005$) or between the pesticides themselves ($r > 0.63$–0.79; $p < 0.001$). The correlation coefficients for the lipid-adjusted data were marginally lower. Independent of lipid-adjustment, the observed correlations at *P2* were the most robust for all compounds.

3.5 Inter-period correlations

The correlations for each compound between the three collection periods were very strong ($p < 0.001$), with little difference between wet-weight and lipid-adjusted datasets (data not shown). The inter-period relationships *P2*/*P1*, *P1*/*P3* and *P2*/*P3* were examined. PCB-99, 118, 138, 153, 180 and 187, as well as *trans*-nonachlor, had r values above 0.90 for the 3 correlations; PCB-156 and HCB $r = 0.86$–0.94; and PCB-163, PCB-170 and *p,p'*-DDE $r = 0.76$–0.95.

4 Discussion

4.1 Concentrations of OCs and trends

The relatively high detection frequencies attained reflect improved detection limits achievable with current instrumentation and analytical methodology. Even though the concentrations found are relatively low, the PCB congeners and pesticides are well represented in the suite of OCs that was measurable. As in other studies,[2–4,31] PCB-153 and *p,p'*-DDE had the highest concentrations, and this is consistent with their status as dependable markers of OCs' exposure. As expected from the reduced Arctic transport (see Section 1), the observed concentrations of the PCB congeners and the chlorinated pesticides are somewhat lower than those previously reported in delivering women living in urban centers (Kirkenes and Bodø) of Northern Norway during the period 1996–2002 (AMAP 2009).[1] Our study sample does not include individuals from typical small coastal communities, for which higher concentrations have been reported.[3,4] Similarly, the relatively high concentrations reported for Arctic indigenous peoples reflect primarily the consumption of marine mammals.

Just a handful of studies report findings for different points during gestation but these involved different collection time points. Bloom *et al.* (2009, 2007)[20,21] compared samples from the 1st trimester and 6 weeks postpartum and report significant decreases for *p,p'*-DDE and HCB, an increase for *trans*-nonachlor and no changes for PCB congeners; Jarrell *et al.* (2005)[17] focused on the 2nd trimester and delivery (no reported differences for OCs); Longnecker *et al.* (1999)[16] reported data for pregnant women corresponding to gestational week, 12, 19, 32 and 6 weeks postpartum (no differences for PCB and *p,p'*-DDE, both lipid-adjusted and non-adjusted); and Wang *et al.* (2009)[19] reported findings for pregnant primipara women (no reported significant differences during the trimesters for lipid-adjusted PCB and *p,p'*-DDE). Clearly, these various studies present no consistent concentration pattern across the gestation period.

The high values of the correlation coefficient and the generally good statistical significance observed for the inter-OC correlations again reflect, at least in part, good analytical sensitivity and reproducibility. Relative to correlations between PCB congeners, relationships between PCBs and the pesticides (as well as among the pesticides themselves) are less robust as observed previously by the current researchers and others.[15,37] The somewhat poor relationship for PCB-170 appears to have an analytical basis, as the determination of this congener is limited by uncertainty (noise) in calculating appropriate isotopic mass ratios.

The strong associations (as judged by the magnitude of the correlation coefficient) observed between OC levels (both

wet-weight and lipid-adjusted) across the three different pre- and postpartum sampling times suggest comparable body burdens during critical windows of gestation and the perinatal period (but see below). The magnitude of the *r* values observed was comparable or better than those reported in previous findings.[16,17,21]

The mixed-model analysis (Table S2, ESI†) confirms the concentration patterns depicted in Fig. 3 and 4 and thus the equalizing effect of lipid adjustment. Our multivariate linear regression modeling constitutes a rather novel approach to the quantitative assessment of the impact on serum OC levels (and thus the body burden) for each incremental increase in age and parity.

The lack of a clear dependence of OC concentrations on pre-pregnancy BMI is not unexpected. As pointed out by Wolff *et al.* (2007),[27] of 16 studies reviewed "10 had positive DDE–BMI correlations, 3 had essentially zero correlations, and 3 had negative correlations", while "for PCBs 10 of the 16 cohorts had negative correlations with BMI". Pharmacokinetic modeling conducted by these authors illustrated the importance of body weight (lean *vs.* obese, with the latter increasing the half-life of the OC), body weight changes subsequent to exposure, and the time since peak exposure (past, recent, and current). As implied, the half-life in humans of individual OCs also influences their body burden. BMI, weight change and time since peak exposures are key factors in the pharmacokinetics of individual OCs.[26,27] Interestingly, in our recent study[31] of plasma organochlorines for delivering women in two communities in southern Vietnam, BMI at delivery affected only *p,p'*-DDT concentrations with a 6% increase per BMI unit. By contrast, BMI was not a predictor for *p,p'*-DDE or PCBs. In this instance, the two populations studied were relatively lean (BMI values 24.1 ± 2.6 and 23.0 ± 2.5), and recent or current use of *p,p'*-DDT was suspected. Consequently, current exposure complicates the pharmacokinetics of OCs. It is clear from these various observations and modeling exercises that it is difficult to interpret the dependence of plasma OCs on BMI.

4.2 Lipid concentrations and profiles

Elevation of triglycerides during pregnancy from the first trimester on is needed as an essential nutritional energy source for the development and growth of the fetus. However, as pointed out by Wiznitzer *et al.* (2009)[23] and others before them,[19,22] hyperlipidemia can constitute a health risk for the expectant mother. Indeed, based on a large population study, these authors reported that the prevalence of gestational diabetes or preeclampsia in expectant mothers increased with the serum levels of TGs or TC during pregnancy.

An examination of the concentration profiles of the various lipid fractions across the 3 collection times indicates that they closely follow the patterns reported recently by Wiznitzer *et al.* (2009)[23] and others.[19,22] It is clear from both sets of data that the largest increase at *P*2 occurs for TGs and TC. Based on the more detailed lipid profiles from pre-conception to 10 months post-partum provided by Wiznitzer *et al.* (2009),[23] it is suggested that at 6 weeks postpartum the levels of the various lipid fractions have not completely returned to pre-conception levels.

The concentration trend across the collection periods *P*1, *P*2 and *P*3 depicted for serum lipids in Fig. 3 (inset) matches those of the PCB congeners shown in the main body of this figure, and of *p,p'*-DDE, HCB and *trans*-nonachlor (wet-weight, see Table 3). Interestingly, lipid adjustment of the OC concentrations generally removed the consistent peaking at *P*2 (see Fig. 4 and Table S1, ESI†); *p,p'*-DDE now clearly peaks at *P*3, as does PCB-118 (see Fig. 4). Interpretation of these concentration patterns requires a focus on the lipid profiles illustrated in Fig. 2, water solubility and aspects of the uptake kinetics of OCs.

In vitro studies suggest strongly that non-specific transport dominates cellular influx and efflux of OCs (*i.e.*, lipoprotein receptors are not involved), and that lipoproteins compete or can influence both these processes.[24] Furthermore, *in vivo* rat studies (*e.g.* Gomez-Catalan *et al.*, 1991)[38] and *in vitro* incubation studies of the distribution of OCs among blood components (including human blood) have shown that individual OCs exhibit idiosyncratic distribution patterns among the various lipoproteins (HDL, LDL, VLDL and cyclomicrons) and other plasma proteins (*e.g.*, albumin), as well as displaying unique cellular uptake kinetics.[24,38,39] The peaking of *p,p'*-DDE and PCB-118 at *P*3 might be interpreted to indicate a somewhat slower return to a steady-state value subsequent to the lipidemia that occurred during pregnancy. This is also supported by the high water solubility of *p,p'*-DDE. Indeed uptake by adipose tissues in rats has been reported to be lower and slower for *p,p'*-DDE compared to HCB.[38]

Our data suggest that wet-weight plasma or serum OC concentrations can constitute a marker of lipidemia. Lipidemia is one of the signature features of the metabolic syndrome that increases the risk of developing cardiovascular diseases and diabetes mellitus type 2.[40] In this context, individuals with the metabolic syndrome or diabetes are likely to exhibit relatively higher wet-weight concentrations of OCs because of lipidemia. This interpretation affords a novel explanation for the consistent observation that plasma or serum OC levels are positively associated with diabetes (especially *p,p'*-DDE and dioxins).[41–45] It also implies that such associations would not *a priori* indicate causation. Indeed, the available experimental evidence for causality is not well documented.[46] Because wet-weight and lipid-adjusted OC concentrations (log scale) are strongly correlated (*r* values ≥ 0.90 in our study), it is not surprising that this association is reported for datasets with and without lipid-adjustment. Further, the prominence of these two compounds is likely related to their specific distribution patterns among lipoproteins and other blood components, as well as their kinetics of cellular uptake and efflux. Since obesity is a risk factor for Type 2 diabetes,[40] it may well be that plasma OC levels can also be associated with other known predictors such as BMI or waist circumference in populations at risk of this disease.

Although the pathway of the observed lipidemia during pregnancy is not well understood, stimulation of triglycerides' synthesis in the liver seems likely.[23] Levels of OCs in the liver appear to parallel those in adipose tissues, based on animal studies and human autopsy results.[38,47,48] Both pools are likely major endogenous sources for plasma OCs. The wet-weight plasma OC concentrations determine the exposure experienced by the fetus, while the lipid-adjusted values under steady state conditions are interpreted to constitute a measure of the adipose tissue levels.[27] This perspective suggests that the near equalization of the OC levels after lipid adjustment across the 3 sample collection points might well indicate that little change in the

adipose burden occurred during pregnancy and the 6-week postpartum period. The current study also supports our previous conclusion that lipid adjustment allows the comparison of OC levels for media of different lipid content.[15]

And finally, the peaking of nearly all of the OC concentrations in the 3rd trimester suggests that this period and early days postpartum would provide the optimum sampling window purely from the analytical perspective (*i.e.*, most robust detection frequencies). However, the circulating concentrations during the first trimester are likely most toxicologically relevant.

4.3 Strengths and limitations

The relatively low participation rate likely has introduced some selection bias. Unfortunately, the latter occurred despite vigorous promotion of the study through news media, posters, and information sessions and regular contact with health professionals and field workers throughout the study. The low level of interest encountered likely reflects competition with other projects and "study tiredness" experienced by prospective participants.

The decision to analyse the current participant subset has limited the statistical power and thus results in some restraint on the internal and external validity. However *a posteriori* sample-size calculations (two-tails formula for a single mean, with $\alpha = 0.05$ and $\beta = 0.2$), using observed standard deviations and sample sizes for lipid-adjusted OC concentration data not showing statistical differences, indicated that observed differences between collection periods were considerably lower than what is possible to detect in the population. Such differences reflect changes that are not of clinical chemistry significance, and increasing n would most likely not enhance their magnitude. This standard calculation reinforces the findings of our significance tests and justifies the sample size of the study.

A pertinent issue is how the large proportion of non-fasting participants (44%, *P*1; 42%, *P*2; and 45%, *P*3) has influenced the lipid profiles in our study. We believe that the impact is minimal for a number of reasons. All but one of the babies were delivered in a hospital or a labour ward where food consumption is supervised. Thus eating fatty meals prior to the *P*2 collection is unlikely. The fact that there were no statistical differences in lipid concentrations between the fasting and non-fasting mothers supports this notion. Method errors are deemed minimal as all field protocols and procedures (including body-weight measurements and blood sampling) were standardized.

The approach employed for estimating serum total lipids by the enzymatic 'summation' method devised by Akins *et al.* (1989)[35] does not correct for the presence of free glycerol. Even though this method is used by many researchers, recent findings suggest that in non-obese pregnant women in the 3rd trimester circulating glycerol levels are enhanced due to lipolysis. Consequently the triglycerides and total lipids may be over-estimated.[49,50] A similar enhancement appears to occur in obese non-pregnant women.[51] This aspect needs further investigation.

5 Conclusions

During the gestational period, both lipids and wet-weight OC levels peaked at birth and were the lowest at 6 weeks postpartum. Wet-weight concentrations of OCs appear to be driven by the physiological lipid profiles and are interpreted to constitute biomarkers of lipidemia. It is suggested that this observation may be pertinent to individuals at risk of Type 2 diabetes. As expected, both age and parity were strong predictors for OCs. No consistent significant associations were observed between OCs and pre-pregnancy BMI. All compounds were positively and significantly correlated with each other within and across the three collection time periods (mostly $p < 0.001$), independent of lipid-adjustment. Purely from the analytical perspective, the optimum sampling window appears to be the period spanning the last weeks of the 3rd trimester and the early postpartum days.

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Supplementary Data Depository

Note 1. Organochlorine compounds not quantified

The following organochlorine pesticides were difficult to quantify or not quantifiable because the coefficient of variation (CV) exceeded 70 % and their concentrations were low: *oxy*-chlordane; *trans*-chlordane; *cis*-chlordane; *trans*-nonachlor; *cis*-nonachlor; heptachlor; mirex; PCBs 28, 52, 101, 105, 149, 156, and 194;
o,p'-DDE: 1,1-dichloro-2-(o-chlorophenyl)-2-(p-chlorophenyl)ethylene; and
o,p'-DDD: 1,1-dichloro-2-(o-chlorophenyl)-2-(p-chlorophenyl)ethane.

Table S1 Lipid–adjusted levels (ng/g) of PCBs and pesticides in maternal serum samples from Northern Norway

	2nd trimester pregnancy (P1)					3 days postpartum (P2)					6 weeks postpartum (P3)				
	Concentration (ng/g) lipid weight					Concentration (ng/g) lipid weight					Concentration (ng/g) lipid weight				
Compound[a]	n	GM[c]	AM[d]	SD	Min-Max	n[b]	GM[c]	AM[d]	SD	Min-Max	n[b]	GM[c]	AM[d]	SD	Min-Max
PCB-99	50	2.0	2.2	1.0	0.6-5.3	49	1.8	2.0	1.1	0.5-5.0	49	1.8	2.0	1.0	0.4-4.1
PCB-101	48	0 8	0.9	0.3	0.4-1.6	41	0.5	0.5	0.3	0.3-1.7	36	0.8	0.9	0.5	0.4-2.5
PCB-118	48	4.2	4.7	2.1	1.5-10.0	49	3.8	4.3	2.3	1.0-9.3	49	4.1	4.6	2.3	1.0-10.3
PCB-138	50	12.7	14.1	6.5	4.0-28.0	50	12.5	14.0	6.8	2.9-34.8	49	12.2	13.7	6.3	2.6-34.1
PCB-163	49	5.3	6.2	3.6	1.6-17.2	50	4.1	4.7	2.4	0.7-10.8	49	4.0	4.5	2.2	0.8-11.2
PCB-153	50	22.6	25.1	11.8	7.6-55.2	50	22.2	25.1	12.8	5.6-67.9	49	22.2	24.9	12.6	5.1-72.8
PCB-156	47	2.2	2.5	1.2	0.5-5.1	50	2.1	2.4	1.2	0.6-5.1	49	1.9	2.3	1.2	0.6-5.3
PCB-170	46	6.2	7.0	3.6	1.1-15.9	43	6.2	6.9	3.3	2.5-15.8	38	5.8	6.5	3.1	2.2-15.5
PCB-180	50	15.2	17.1	8.2	5.1-36.3	50	15.0	17.0	8.6	4.1-40.0	48	15.1	17.1	8.5	3.5-43.4
PCB-183	49	1.3	1.5	0.7	0.6-3.2	50	1.4	1.5	0.8	0.6-4.0	47	1.4	1.5	0.8	0.6-4.2
PCB-187	50	4.2	4.7	2.4	1.2-11.9	49	4.2	4.8	2.6	0.9-14.6	44	3.7	4.2	2.0	0.6-9.1
PCB-194	50	1.8	2.0	1.1	0.7-4.3	50	1.7	2.0	1.2	0.6-5.1	49	1.6	1.8	1.0	0.7-5.0
p,p'-DDE	50	38.7	42.8	20.4	15.4-107	50	37.8	41.9	20.2	8.4-126	45	42.2	47.1	24.6	8.6-159
HCB	50	9.6	10.4	4.3	4.3-24.0	50	9.2	10.1	4.9	3.3-29.4	50	9.9	10.5	4.4	3.9-28.5
trans-NC	50	2.7	3.3	2.0	0.5-8.7	50	2.9	3.6	2.1	0.4-9.0	50	2.2	2.7	1.5	0.4-6.3
cis-NC	50	0.6	0.7	0.5	0.2-2.8	50	0.6	0.8	0.6	0.2-4.9	50	0.6	0.7	0.5	0.2-2.3

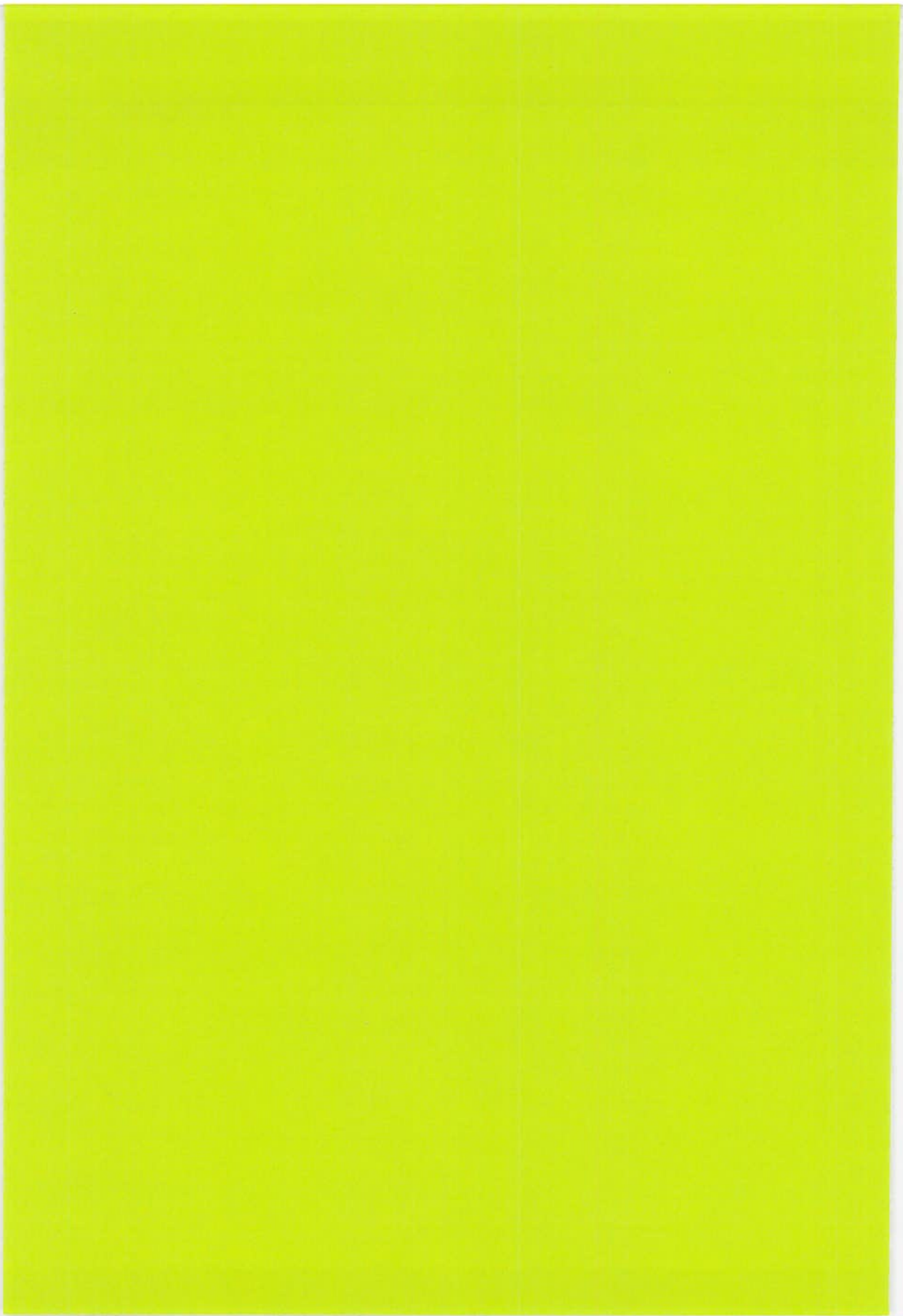
[a]See Table 2 in the article footnote b for full names.
[b]The number of participants (n) varies because the observed ion-mass ratios were unacceptable(see text), the data for PCBs and *p,p'*-DDE are lacking for one individual of the P3 group, and one donor was excluded from the study because she arrived in Norway recently.
[c]GM= Geometric mean; [d]AM= Arithmetic mean with the corresponding SD, minimum(Min) and maximum(Max).

Table S2 Changes in serum concentrations of PCBs and pesticides across the collection periods P1 (2nd trimester), P2 (3 days postpartum) and P3 (6 weeks postpartum)

		Wet-weight concentrations (pg/g serum)				Lipid-adjusted concentrations (ng/g lipid)			
		Time periods				Time periods			
Compound	Estimates of change[a,b,c,d,e]	P1/P3	P2/P3	P2/P1	p[f]	P1/P3	P2/P3	P2/P1	p[f]
PCB-99	β	0.146	0.172	0.026		0.044	0.008	-0.035	
	p	**0.000**	**0.000**	**0.027**	**0.000**	**0.005**	0.528	**0.002**	**0.003**
	Ratio	1.40	1.49	1.06		1.11	1.02	0.92	
PCB-118	β	0.104	0.133	0.028		.006	-.031	-0.037	
	p	**0.000**	**0.000**	**0.013**	**0.000**	0.667	**0.002**	**0.008**	**0.002**
	Ratio	1.27	1.36	1.07		1.01	0.93	0.92	
PCB-138	β	0117	0.169	0.052		0.014	0.007	-0.008	
	p	**0.000**	**0.000**	**0.000**	**0.000**	0.214	0.416	0.506	0.429
	Ratio	1.31	1.48	1.13		1.03	1.02	0.98	
PCB-163	β	0.216	0.175	-0.042		0.109	0.012	-0.098	
	p	**0.000**	**0.000**	0.121	**0.000**	**0.000**	0.253	**0.000**	**0.000**
	Ratio	1.64	1.50	0.91		1.29	1.03	0.80	
PCB-153	β	0.108	0.161	0.052		0.006	-0.001	-0.007	
	p	**0.000**	**0.000**	**0.000**	**0.000**	0.573	0.858	0.498	0.788
	Ratio	1.28	1.45	1.13		1.01	1.0	0.98	
PCB-156	β	0.145	0.194	0.049		0.038	0.031	-0.007	
	p	**0.000**	**0.000**	**0.000**	**0.000**	**0.025**	**0.032**	0.591	0.053
	Ratio	1.40	1.56	1.12		1.09	1.07	0.98	
PCB-170	β	0.120	0.199	0.079		0.017	0.036	0.019	
	p	**0.000**	**0.000**	**0.000**	**0.000**	0.438	**0.029**	0.366	0.085
	Ratio	1.32	1.58	1.20		1.04	1.09	1.05	
PCB-180	β	0.105	0.160	0.053		0.004	-0.003	-0.006	
	p	**0.000**	**0.000**	**0.000**	**0.000**	0.746	0.737	0.572	0.847
	Ratio	1.27	1.44	1.13		1.01	0.99	0.99	
PCB-187	β	0.148	0.202	0.055		0.045	0.043	-0.003	
	p	**0.000**	**0.000**	**0.000**	**0.000**	**0.000**	**0.000**	0.795	**0.000**
	Ratio	1.41	1.59	1.14		1.11	1.11	0.99	
p,p'-DDE	β	0.068	0.118	0.050		-0.035	-0.044	-0.010	
	p	**0.000**	**0.000**	**0.000**	**0.000**	0.058	**0.000**	0.597	**0.001**
	Ratio	1.17	1.31	1.12		0.92	0.90	0.98	
HCB	β	0.091	0.14	0.043		-0.011	-0.028	-0.017	
	p	**0.000**	**0.000**	**0.001**	**0.000**	0.378	**0.023**	0.183	0.074
	Ratio	1.23	1.36	1.10		0.98	0.94	0.96	
trans-NC	β	0.185	0.279	0.095		0.083	0.118	0.035	
	p	**0.000**	**0.000**	**0.000**	**0.000**	**0.000**	**0.000**	0.051	**0.000**
	Ratio	1.53	1.90	1.25		1.21	1.31	1.08	

[a]Analysis was by the linear mixed model; [b]Regression coefficient (β); [c]p-Value refers to the equality across 2 periods; [d]The ratio corresponds to 10^{β}; [e]In the text, ratios are reported as % change[$(10^{\beta}-1)*100$]; [f]p-Value refers to the equality across the 3 periods.

PAPER III



Changes in Maternal Blood Concentrations of Selected Essential and Toxic Elements During and After Pregnancy

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ABSTRACT

The objective of this study was to investigate changes in the levels of toxic and essential elements in maternal blood during pregnancy and subsequently. A subset of 211 pregnant women from the North Norwegian Mother-and-Child Study was included. Blood samples were collected during the 2nd trimester (P1) and postpartum (Day 3, P2; and 6 weeks, P3) in different regions of northern Norway, and were analyzed for a suite of 10 selected elements. The latter feature three general but distinct concentration patterns across the three collection periods, namely: progressive increase (Group 1: As, Cd (non-smokers only), Mn, Pb and Zn), V-shaped (Group 2: Cd (smokers), Hg, Mo and Se) and downward V (Co and Cu). These trends are interpreted in the context of underlying metabolic, hematological and physiological changes that occur in mothers, as well the biochemistry and accumulation preferences of these elements within the whole blood compartment and breast milk. Implications for biomonitoring strategies are discussed. In a multivariable analysis of the P1 data, fish consumption was a robust positive predictor for Hg ($p < 0.02$), As ($p < 0.01$) and Se ($p \leq 0.001$) blood concentrations, multivitamin intake for Se ($p < 0.001$), and parity for Co ($p < 0.002$); age reached significance only for Hg ($p < 0.002$). An inverse association was observed between parity and Hg ($p < 0.05$). For the other elements, predictor patterns were not evident.

Keywords: Elements; toxic; essential; maternal blood; pregnancy; postpartum; concentration predictors; fish consumption.

1.0 Introduction

Measurement of trace essential and toxic elements in different body fluids has focused on maternal whole blood, plasma (or serum), as well as cord blood and mother's milk.[1-3] To our knowledge, a systematic assessment of toxic elements related to physiological changes during critical windows of gestation, at birth and postpartum have not been reported. However, variations in levels of essential elements like selenium (Se), zinc (Zn) and copper (Cu) have been investigated within the gestational period.[4-6] In these studies, serum levels of Se and Zn are reported to decrease and Cu increase.

In a recent publication[7], we demonstrated changes in serum organochlorines levels in relation to the altered physiological lipid profile during pregnancy and a 6-weeks postpartum period. During the gestational period, the development of the uterus and fetus and preparation for lactation occur. To meet this growth, tremendous physiological changes occur. Alterations include the expansion of the volumes of blood, plasma and erythrocytes, enhanced metabolism (of proteins, carbohydrates and fats), as well as increased renal perfusion and substantial changes in circulating hormones, essential elements and serum lipids.[4, 8] Consequently, it seems reasonable to expect variations to occur in blood levels of metals and metalloids during the gestational and postpartum periods. Of course, known factors related to exposure will also be operative, such as dietary patterns, socioeconomic status, income, education, ethnicity, and life style (e.g., smoking/alcohol habits).[2, 9, 10]

The aim of this study was to conduct a systematic assessment of the change in levels of 5 essential [Cu, manganese (Mn), molybdenum (Mo), Se and Zn] and 5 toxic elements [arsenic (As), cadmium (Cd), cobalt (Co), mercury (Hg) and lead (Pb)] in

maternal whole blood samples during the 2nd trimester in pregnancy, and at 3 days and 6 weeks postpartum. A second objective was to identify factors that influence the relative concentrations in blood of these elements, and changes in them across the three collection periods.

2.0 Material and methods

2.1 Geographical description and study population

The recruitment for the North Norwegian Mother-and-Child Study took place from 2007 until 2009 in different regions of northern Norway (Fig. 1) It had three objectives: (i) to determine levels of contaminants in delivering women's blood or serum samples; (ii) to identify exposure risk factors; and (iii) to unveil dietary sources for women of reproductive age. Pregnant women in the study areas were invited through a written invitation, administered by ultrasound clinic personnel or midwifes. The participating delivery departments were: Nordland Hospital (Bodø and Lofoten), University Hospital of North Norway (Tromsø and the labour wards of Northern- and Mid-Troms), and Finnmark Hospital (Kirkenes, Hammerfest and the labour ward of Alta). From June 2007 to Mars 2009, 2600 women were invited, 548 responded, 542 gave a blood sample, and 27 were excluded because of the lack of written consent. Thus, 515 women initially were included in the study; 461 of these presented at delivery, 395 completed the study at the six weeks postpartum sampling point, with 382 providing blood specimens at each of the three time points. All whole blood specimens collected until the end of January 2009 were selected for analysis, and the 211 respective donors constituted the study subjects. This decision was necessitated by laboratory constraints

2.2 Enrollment and questionnaires

Personal data and blood samples were collected during the 2nd trimester (mean 18.1 weeks, median 18.0, and range 10-34) in pregnancy (designated as sampling time, P1) and at three days (P2) (mean 3.2, median 3.0, range 1-13) and six weeks postpartum (P3) (mean 7.0, median 6.0, range 4-15). When enrolled, the prospective mothers were asked to complete a detailed questionnaire pertaining to personal characteristics, obstetric history, diet and life style. Permission to consult their medical records was obtained. In addition at all blood sampling time points, a simple questionnaire was administrated to obtain personal information about fasting status, smoking and alcohol habits, medication and dietary supplements; current weight was also measured.

The dietary portion of the questionnaire was largely based on a validated food frequency questionnaire (FFQ) used in The Norwegian Women and Cancer study (NOWAC).[11-13] It was supplemented by questions that solicited information about the consumption of traditional foods such as game, berries, seagull eggs, crab, whale/seal and marine products. Frequency and amounts of food such items eaten during the previous year and when growing up were asked for, including types of fish species and seasonal variations. For each item, 4 to 7 fixed choices were given. Missing information was replaced by zero or smallest amounts if the quantity was not specified. Using an established program developed at the Department of Community Medicine, University of Tromsø, consumption of each food item was expressed in grams per day based on the Norwegian Weight and Measurement Table 13[14], and the daily intake of energy and nutrients was computed based on the Norwegian Food Composition Table 2006.[15]

2.3 Ethnicity

The Sámi are indigenous people of Norway, and the highest proportions reside in the northern areas of the country. Ethnicity was divided into 2 groups: Sámi and Norwegian, with immigrants being grouped with the latter. Sámi was defined as done in the SAMINOR study.[16] Individuals were considered to be Sámi if at least one of the following indicators applied: if the Sámi language was spoken by one of the grandparents, parents or the participant; ethnic background of parents; or self-perceived ethnicity.[16] Persons with both Kven and Sámi affiliation were considered Sámi, while those having both Kven and Norwegian affiliation were designated Norwegian. Kvens emigrated from northern Finland in the 18th century and settled in northern Norway. Norwegians and immigrants were grouped together.[16]

2.4 Analytical methodology

2.4.1 Blood collection

Whole blood was drawn from the maternal antecubital vein with standard equipment into a BD Vacutainer® for trace elements (HemogardTM/Royal Blue, Ref# 368381; plastic, 6-ml, with 10.8 mg K_2 EDTA; Becton Dickinson, Plymouth, UK). The vacutainers were transported to the University of Tromsø, where the whole blood was transferred to 4.5 ml cryo-vials and stored at -20 °C until analysis. The samples were subsequently transferred in a frozen state to the National Institute for Occupational Health (NIOH) Laboratory, Oslo, Norway.

2.4.2 Sample treatment

For the measurement of elements in whole blood, 1.5 mL of 65 % ultrapure nitric acids (Chemscan Ltd., Elverum, Norway) was added to 1 mL of whole blood in an acid-

precleaned polypropylene digestion tube. The mixture was digested by heating the tube at 95 °C for 1 hour. The acid homogenization procedure using nitric acid was performed in covered tubes at ambient pressure with no losses of the more volatile elements (*e.g.*, Se or Hg). These procedures have been carefully tested and are used extensively at NIOH, as well as by many other international laboratories.

The digest was cooled to room temperature and 200 µL of an internal standard solution was added containing ^{72}Ge for ^{75}As and ^{77,78,82}Se; ^{115}In for ^{98}Mo and ^{114}Cd; ^{205}Tl for ^{206,207,208}Pb and ^{200,201,202}Hg; ^{60}Ni for ^{55}Mn, ^{59}Co, ^{63,65}Cu and ^{64,66,68}Zn; and was subsequently diluted to a final volume of 10 mL with ultrapure water.

2.4.3 Chemical analysis

Samples of maternal whole blood for the three collection periods were analysed for levels of As, Cd, Co, Cu, Hg, Mn, Mo, Pb, Se, and Zn. Chemical analyses were performed using the inductively plasma-mass spectrometry (ICP-MS) technique, employing a high resolution magnetic sector field Element 2 mass spectrometer (Thermo Electron, Bremen, Germany) calibrated with whole-blood matched standard solutions. The instrument was programmed to determine Cd by use of the $^{114}Cd^{+}$ ion with automatic mass correction for $^{114}Sn^{+}$ ionic interference. Since the Mo concentration in whole blood is around 2 µg/L or lower, any mass interference at $^{114}Cd^{+}$ from the $^{98}Mo^{16}O^{+}$ was not considered to contribute significantly to the overall signal. The following mass resolution settings were used: low for Cd, Hg, Mo and Pb; medium for Co, Cu, Mn and Zn; and high for As and Se. Routine acid leaching of all vessels and use of ultrapure water and nitric acid assured that the blank samples were as low as possible in order to obtain adequate limits of detection (LODs). The LODs (three times the standard deviation for blank samples) were

as follows: As 0.19 µg/L, Cd 0.02 µg/L, Co 0.03 µg/L, Cu 0.002 mg/L, Hg 0.15 µg/L, Mn 0.11 µg/L, Mo 0.12 µg/L, Pb 0.26 µg/L, Se 0.93 µg/L, and Zn 0.01 mg/L. One aliquot of each blood sample was analysed in triplicate.

2.4.4 Quality assurance and control (QA /QC)

Seronorm human whole blood TM Trace Elements (Sero Ltd., Billingstad, Norway) quality control materials were used as reference materials. After every ten blood samples a control sample at two different concentrations levels was analysed.

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 $\pm$ 2-10 % deviation from the target values) and no indication of any systematic biases.

2.5 Statistical analysis

Concentrations below the LODs were replaced by the appropriate LOD divided by the square root of 2, as recommended by Hornung and Reed 1990[17] (also see Anda et al., 2007[1]). The concentrations were positively skewed, and were log-transformed [base 10 logarithm; $\log_{10}x$] before the statistical analyses to obtain normal distributions. Descriptive statistics were used to summarize the data, and the T-test and Analyses of Variance (ANOVA) for testing differences between groups.

The linear mixed model[18] was used to investigate the effect of time between the collection periods and to take into account the repeated measurement structure of the study. Time was included as two indicator variables (P1, yes/no; and P2, yes/no) using P3 log-transformed concentrations as reference. The regression coefficients for the indicator

variables of time are estimates of the mean difference in log-transformed concentrations between each time point and the reference level. The regression coefficients were back-transformed (10^{β}) to reflect the ratios of change in concentrations, and in the text are described as % change= $(10^{\beta}-1)*100$.[19, 20]

Simple linear regression was employed to explore associations between contaminant levels at each time point and independent factors such as age, parity and dietary indicators. Of these, only statistically significant predictors ($p < 0.05$) were used in the multiple regression modeling (backward stepwise approach) at time point P1. Subsequently, a new model was generated with variables having $p \leq 0.10$ and making adjustments for age and parity. Back-transformed regression coefficients were obtained to estimate % changes in elemental concentrations per unit change in the independent variables. Pearson correlation coefficients (r) were calculated for linear relationships, and p-values < 0.05 were considered as significant. All statistical analyses were carried out using the SPSS for Windows statistical package (version 17.0; SPSS Inc. Chicago, IL, USA).

2.6 Ethical considerations

The study was approved by the Regional Committees for Medical Research Ethics. Participation was voluntary, and the women signed an informed consent form.

3.0 Results

3.1 Population characteristics

Selected characteristics of the 211 women are presented in Table 1. The mean age of the women was 31.0 years, and 39.8 % were nullipara (range 0-4). Sámi affiliation was

reported by 21 participants, and of these 2 also had Kven background. In addition, 2 Kvens were considered as Norwegians and 9 persons were immigrants from Europe and Asia. In all, 48 women were classified as smokers (see footnote a of Table 1 for definition), whereas 45 women reported smoking 6 months before pregnancy, 27 at pregnancy start, and 12, 7 and 15 women at P1, P2 and P3, respectively. Average years of schooling were 15.9 years, and 59 % stated a family income exceeding 600 000 NOK. Based on hospital ultrasound data, the mean week of delivery was 40 (range 36-42). The mean interval between P1 and P2 was 22.0 (median) and 21.9 (mean; range 4-32) weeks, compared to 6.0 (median) and 6.6 (mean; range 4-15) weeks between P2 and P3. At P3, 173 of 211 women reported breastfeeding their babies. Of these, 145 practiced exclusive lactation, 28 partial, 15 daily in combination with a breast-milk substitute, and 6 did not breastfeed at all. At P1, 32 % and 60 % were taking multivitamins and omega-3 supplements during the previous week; while, respectively, 22 and 43 % did so at P2, and 28 and 58 % at P3 (see Table 2).

3.2 Fish and game consumption

Six women were excluded from the dietary analyses due to non-reporting; of these, 5 (including one Sámi) did not complete the fish consumption pages, and one failed to answer the questionnaire. Food items chosen for statistical analyses were limited to fish (marine or fresh water), shellfish, marine mammals and game (reindeer, grouse, and moose). Daily intakes of fish and game are reported in Table 2. All of the women reported inclusion of fish or other seafood in their diet and for the majority consisted of a mix of lean and fatty fish. Mean daily total fish consumption was 76 g (median, 68 g/day), of which the intake of unprocessed fish, fish spread and shellfish constituted 40

g/day (Table 2.Consumption of freshwater fish was limited to 0.7 g/day (data not shown). Intake of marine fish by Sámi was similar to Norwegians ($p \geq 0.05$), but they reported significantly higher intake of fresh water fish (1.9 *versus* 0.6 g/day, $p=0.035$). Sámi also consumed more game (4.1 g *versus* 0.6 day, $p= 0.027$).

3.3 Detection frequencies, normality and outliers

The observed detection frequencies at each collection point are presented in Table S1, ESI† along with the corresponding LODs. The majority of the compounds had a detection frequency of 100 %. Exceptions were: Hg at P1 (99.1 %); Co at P1 (97.6 %); As at P1 (98.6 %), P2 (99.5 %) and P3 (99.1 %).

After log-transforming the measured concentrations, the frequency distributions were observed to be acceptable. A small number of extreme outliers were observed for Pb (1 at P1), Mo (2 at P2), and Se (1 at P3), and were removed from the dataset since they were evaluated to represent abnormally high concentrations. Cd also had extreme outliers (2 at P1, 1 at P2 and P3), but when adjusted for smoking status no outliers were evident.

3.4 Maternal concentrations of essential and toxic elements

The maternal concentrations and ranges for the 10 elements are reported in Table 3. Of the toxic trace elements, Pb had the highest concentrations followed by As>Hg>Cd (smokers, S) >Cd (non-smokers, NS) ≈Co. This sequence clearly shows the expected impact of smoking on blood cadmium levels. The essential trace element levels were in the following order: Zn>Cu>>Se>>Mn >>Mo.

The toxic elements presented different patterns across the three collection periods. Employing the linear mixed model for log-transformed concentrations (Table S2, ESI†;

also see Table 3), all trends across the 3 time points were significant ($p<0.001$), as well as between the different periods P1/P3, P2/P3 and P2/P1; with As ($p=0.002$) and Cd(S) ($p=0.010$) exceptions. Three different patterns were evident (Fig.2 and Table S2): for concentrations of Zn, Mn, Pb, As and Cd(NS), P1<P2<P3; for Hg, Mo, Se and Cd(S), there was a minimum at P2, with P3>P1; and for Cu and Co, the levels at P2 were the highest, with P3<P1 (Cu) and P3>P1 (Co).

On average, the Sami women had lower levels of the following elements compared to Norwegians (including immigrants): Hg (0.78 *versus* 1.2 µg/L, $p=0.049$; As (0.9 *versus* 1.5 µg/L, $p=0.015$); Co (0.07 *versus* 0.10 µg/L, $p=0.027$); and somewhat higher levels of Cu (1.76 versus 1.64 mg/L, $p=0.036$) (data not shown). None of the differences for the other 6 elements was statistically significant.

3.5 Interelement Correlations

Associations between the pairs Hg/As, Hg/Se, As/Se, Mn/Zn and Mn/Co were statistically significant for all periods. The Pearson correlations (r) (log_{10} scale, data not shown) were most robust for the Hg/As ($r=0.52$-0.61, $p<0.001$) and Hg/Se ($r= 0.41$-0.49, $p<0.001$) pairs, followed by As/Se ($r=0.21$-0.34, $p\leq0.003$), Mn/Zn ($r=0.18$-0.37, $p\leq0.01$) and Mn/Co ($r=0.20$-0.35, $p\leq0.003$). Other correlations (p-values between 0.001 and 0.05 or better) were: Mo/Co , $r=0.37$ at P2; Pb/Zn, $r=0.25$ at P1 and 0.37 at P2; Cu/Zn ($r=-0.21$ at P1 and 0.25 at P3); Pb/Co, $r=0.18$ at P2 and 0.21 at P3); Se/Co, $r= -0.17$ at P2 and -0.22 at P3); As/Co ($r=0.20$) and Pb/Se ($r=0.16$) at P1; Pb/Mn ($r=0.25$), Se/Zn ($r=0.21$) and Se/Mn ($r=0.15$) at P2; and Cu/Mn ($r=0.18$), Cu/Co ($r=0.16$) and Cu/As ($r=0.14$) at P3. Furthermore, for non-smokers the following correlations were significant at all 3 collection points: Cd/Co ($r=0.29$-0.38, $p<0.001$); Cd/Pb ($r=0.27$-0.33, $p<0.001$); and

Cd/Mn (r=0.18-0.29, p≤0.023); those (p<0.05) for Cd/Zn were limited to P1 (r=0.16) and P2 (r= 0.25), and Cd/Cu to P1 (r= -0.17). For smokers (p=≤0.027), associations were evident for Cd/Pb at P1(r=0.32) and P2 (r=0.33), Cd/Cu at P2(r= -0.32) and P3 (r= -0.38), and Cd/Se (r= -0.38) at P3.

3.6 Predictors in the regression model

3.6.1 Simple linear regression

For As, Hg and Se, consumption of seafood items (especially fatty fish and shellfish p≤0.013) constituted a predictor of their respective blood levels (log_{10} scale; see Table S3, ESI†). As and Hg showed negative associations (p<0.05) with smoking, and Cd(S) with intake of omega-3 fatty acids dietary supplements at P1 (p=0.04). There was a dependence on age for As (P1 & P2; p≤0.003), Cd(NS) (P3; p=0.03), Co (P1 & P2; p<0.05), Hg (P1, P2 & P3; p<0.001), and Se (P1 & P3, p<0.05; and nearly so at P2, p=0.05). Education (duration in years) was negatively associated with Cd(S) at P2 & P3 (p<0.05), but was a consistent positive predictor at P1, P2 & P3 of Hg (p≤0.01) and Se (p≤0.008), while the latter was similarly correlated with wine consumption (p<0.02) and dietary supplements [omega-3 fatty acids (p≤0.006); and vitamins at P1 and P3 only (p≤0.006)]. Being Sámi related negatively to As (P1; p=0.015), Co (P1; p=0.03) and Hg (P1; p<0.01), but positively for Cd(NS) (P1 & P3; p<0.05); Cu (P1; p<0.04), and Pb (P2 & P3; p<0.03). Some positive dependence on parity was evident for Co (P1 & P2; p≤0.001), and Zn (P2 & P3; p<0.04), and was negative only for Se at P3 (p=0.019). Week of sample collection showed some positive influence on Cd(NS) (P1; p=0.045), Co (P1 & P2; p≤0.015), Cu (P1; p=0.004), Mn (P1; p=0.008), and Mo (P2; p=0.005), with a

negative link for Cu at P3 (p=0.018). An inverse association between lactation and Mn also occurred at P3 (p=0.024).

On a linear scale, at P1 the correlation coefficients for associations between total fish intake (including shellfish) and Hg, As and Se respectively were: 0.40, 0.39 and 0.28 (p<0.001).

3.6.2 Multiple regression models

The results at P1 for the multivariable linear regression analysis are presented in Table 4. This analysis was limited to the P1 sampling data because detailed dietary information was not obtained at P2 and P3. Adjusted for age and parity, only for Co, Hg, As and Se, were statistically significant models including several predictors, observed. Fish consumption (in units of 10 g/d), especially shellfish, were strong positive predictors for As, Hg and Se. Substantial increases, were observed, in the range of 10-216 % (Hg), 18-255 % (As), and 2-29 % (Se). By contrast, Sámi affiliation for Co, Hg and As had a negative influence (34-39 %). Interestingly, whale/seal consumption was only important for Hg, sample-collection timing at P1 for Co, and multivitamins and fish spread consumption for Se.

For the remaining elements, backward regression resulted in the following age and parity adjusted associations (data not shown): Pb, municipality ($10^{\beta} = 0.89$, p=0.010) with the highest mean (GM) blood levels in Finnmark (8.6 µg/L, CI 7.5-9.7), Troms (7.5 µg/L, CI 6.9-8.1), and Nordland (6.9 ug/L, CI 6.2-7.6); Cd(NS), interval ($10^{\beta} = 0.98$, p=0.035); Mo, municipality ($10^{\beta} = 0.92$, p=0.011) with Finnmark participants having the highest levels (GM) (0.81 µg/L, CI 0.7-0.9) followed by Troms (0.73 µg/L, CI 0.7-0.8)

and Nordland (0.69μg/L, CI 0.6-0.8); and for both Mn and Cu, pregnancy week (10^{β} = 1.02, p=0.002, and 10^{β} = 1.01, p<0.001 respectively). No predictors were evident for Zn.

4.0 Discussion

4.1 Grouping of the elements

Factors that may help to interpret and clarify the observed grouping of the blood concentration trends across the 3 collection periods for the 10 elements are explored below.

Group 1: Blood concentrations of Zn, Mn, Pb, As and Cd(NS) increased during pregnancy and from birth to 6 weeks postpartum. It is noteworthy that members of this group have the following common features: strong associations with erythrocytes; blood levels exceed those in plasma or serum[21, 22]; and the essential metals Zn and Mn are present in breast milk at substantial levels. [23-26] Other issues pertinent to their similar behaviour are: concentrations of calcium are high in breast milk[25]; Pb and Cd follow Ca in biological systems[27]; and Cd binds tightly to the Zn protein metallothionein.[27, 28] Presumably, the concentration increases for Group 1 from P1 to P2 are driven by the metabolic demand for Zn, Ca and Mn. Indeed, the interelement correlations observed for Mn, Zn, Pb and Cd(NS) support the various potential dependency issues mentioned. The % increases between P2 and P3 [9% (Mn), 30 % (Pb), 20 % (Zn), 25 % (Cd(NS)); Table S2, ESI†] likely reflect the reduction in the volume of maternal blood by 35 % between birth and 6 weeks postpartum.[4]

In terms of the suggestion that Group 1 elements are likely linked to the metabolic demand for Ca and Zn, it is known that bone serves as a pool of stored Ca to re-supply

body tissues during pregnancy and lactation.[29] It is well established that lead as Pb^{2+} can replace Ca^{2+} as they are of comparable ionic size, and that bone constitutes a long-term store (half-life ≥10 years) for Pb.[28, 30] By contrast, Zn does not have such a long-term storage. A small exchangeable pool (<10% of the body's Zn) links to the Zn provided in the diet and that stored in multiple tissues.[31] Exchange with RBC Zn is fast, liver (fast or slow) and very slow with skeletal muscle. The liver is also involved in the regulation of Mn.[26,32] As demonstrated recently for non-smoking women of reproductive age by Meltzer et al.[33], low iron status (as measured by serum ferritin) favours higher blood concentrations of Mn (also of Cd and Co; but not of Cu, Pb and Zn). Consequently, iron deficiency is another factor to be considered for some of the elements.

Group 2: Blood concentrations of Hg, Mo, Se and Cd(S) exhibit a minimum at P2. The lower concentrations at P2 reflects the pattern observed for proteins (*e.g.* for total protein or albumin[4]) and is to be expected from the 30 % expansion of the plasma volume during pregnancy. The increases observed between P2 and P3 constitute a reversal of this dilution factor: 30 % (Hg), 23 % (Mo), 19 % (Se) and 29 % (Cd) (Table S2). Consistent with this interpretation is that selenium is incorporated in proteins (non-specific substitution of selenomethionine for methionine;[34] and also occupies critical sites in selenoproteins and selenoenzymes.[35] Mercury ion (Hg^{2+}) and methylmercury ($HgCH_3^+$) are known to bind to proteins[36, 37], and molybdenum is an active component of oxidative enzymes and others.[38, 39] The P2 to P3 increase for Cd in smokers is also consistent with questionnaire information that some study subjects reverted to smoking postpartum (15/48 smoked at P3 *versus* 7/48 at P2). By contrast, the decrease for this metal from P1

to P2 presumably in part reflects the cessation of smoking by some of the smokers (36/48 at P1 and 41/48 at P2 were non-smokers).

Group 3: Cu and Co blood concentrations increase during pregnancy and decline during the 6 weeks postpartum period. Copper is an essential component of critical metalloenzymes needed for growth and development, and blood levels (mostly in serum) are regulated by the liver.[40, 41] Its peaking at birth in both serum[4] and whole blood (see Tables 3 and S2) reflects its importance. Since the size and geometric requirements of the divalent ions Zn^{2+} and Co^{2+} are comparable, the latter can replace Zn^{2+} at critical binding sites in proteins.[27] It seems probable that the demand for Zn is responsible for the rise of Co levels during pregnancy. As already alluded to, iron status can also be a confounder.[33] Vitamin B12, which contains one atom of Co, is present in concentrations of 0.3-1.0 μg/L in maternal serum during pregnancy.[4] Based on these circulating levels of vitamin B12, it is estimated that this Co source contributes 10 % or less of the observed blood concentrations of this metal. Co is not an essential nutrient on its own, and its compounds are known to be toxic.

4.2 Predictors of blood levels.

The magnitude of the observed concentrations of the elements As, Cd, Hg, Pb and Se are not unexpected. They reflect no unusual sources other than those expected from the consumption of seafood (As, Hg and Se), traditional foods harvested by hunting (Pb), smoking(Cd), and intake of multivitamins(Se). The concentration sequence Cd(S) > Cd(NS), and especially the much narrower concentration range for the latter (see Table 3), affirm that cigarette smoke is a major source of Cd.[42] Mercury bioaccumulates in fish, especially in piscivorous species.[43, 44] Use of leaded ammunition and contamination of

the bagged animals by lead shot pellets and/or their fragments are usually implicated as the major source of Pb.[45, 46] Smoking also appears to add to the body burden of lead[10], and this is reinforced by the association between Cd(S) and Pb concentrations observed in the current study. The most variable concentrations were observed for As, where the persons with the highest levels also had the highest fish intake. This is not surprising, since the total As levels reflect the recent consumption of seafood especially shell fish.[47, 48] Most of the whole blood arsenic is in the form of arsenobetaine, which is not considered toxic. It is excreted rapidly (half-life of hours).[48, 49] On the other hand, urinary inorganic arsenic (arsenate and arsenite) levels plus its metabolites constitute a measure of exposure to toxic forms of arsenic.[50, 51] Since fish are a good source of protein, they are also a good source of Se.[9, 52] It seems possible that outliers reflect clinical conditions, e.g., pathological bleeding during partus or the immediate post-partum period. Indeed at P2, the women with extreme levels of Mo, and the one individual with extreme Co and Mn concentrations, had significant pathological bleeding.

Correlations between Se an Hg are well documented, even among non-fish consumers.[52, 53] It is believed that Se acts as a detoxicant for Hg.[54, 55] The robust relationships between Hg, As and Se clearly reflect seafood as a common source. As already mentioned above the metabolic demands for Zn and Mn appear to coincide, and thus some association between these two essential metals seems reasonable.

The average total fish consumption in the current study (76 g/day) was almost double that (42g/d) reported recently for a southern urban area of Norway (n=119) as part of the Norwegian Mother and Child Study (MoBa).[9] In a 1997 national Norwegian survey, women (age 16-79) on average reported total fish intake of 58 g/d (49 g/d for the

16-49 age group). By Comparison, North Norwegian women (age 16-79) consumed 78g/d.[56] This difference in fish intake and species likely reflects the food culture and supply of fish in Northern Norway, compared to southern regions. Surprisingly our observed mean (AM) levels of Hg (1.5± 1.1 μg/L), As (2.1± 2.2 μg/L) and Se (86± 15 μg/L), were somewhat lower ($p \leq 0.02$) than found in the MoBa study (1.9±1.2, 2.6±2.2 and 107±21 μg/L, respectively for Hg, As, Se). This suggests that other factors are at play, such as fish species consumed or biased reporting. The low intake of certain species like freshwater fish, may also reflect restrictions issued by the health authorities,[57] as observed in the MoBa study.[9] The negative impact of Sámi affiliation on the blood concentrations of these 3 elements was unexpected, and probably reflects different diets. The relatively small sub-group proportion (21/211) of individuals with Sami affiliation is pertinent in this context. Misclassification of collected information seems less likely, although missing critical information is a possibility. Different dietary patterns have been identified to depend on ethnicity and residence (costal *versus* inland) in the SAMINOR studies.[58] Only 10 (6 of 21 Sami) of 211 women were from inland settlements and this limits any costal/inland comparisons. Further, we have no information on the prevalence of mercury-amalgam dental fillings in these women. Such factors are worthy of further investigation.

Interestingly, the quantity of unprocessed (fresh) fish consumed in the present study (40 g/d, including 19 g/d of fatty fish and fish spread; Table 2) is below the Norwegian national recommendation [300-450 g/week, including 200 g/week fatty fish (includes fish spread)[59]].

4.3 Biomonitoring issues

The observations and data analysis presented emphasize some important biomonitoring issues. The significant differences in concentrations across the 3 collection periods illustrate that when reporting elemental concentrations in maternal blood during pregnancy and post-partum, the months from conception need to be specified. Clearly physiological and metabolic changes during gestation and postpartum alter the concentration of essential and toxic elements. Further, any interpretation of unique sources such as industrial emissions of toxic elements must take into account maternal age, dietary habits and other life-style issues. Consequently, personal questionnaire information is essential when considering potential competing exposure sources such as consumption of traditional foods harvested and consumed, smoking habits, hobbies, and occupation. Breast feeding also needs to be specified as it has the potential of influencing the blood levels of Mn and Zn.

Other than for Pb, exceedances of health-related guidelines for toxic elements were not observed. Only one individual slightly exceeded the level of concern for Pb of 100 μg/L (0.48 μmol/L). Generally speaking, the levels of the toxic elements observed in our study were relatively low. Consequently they are not of clinical importance, and thus of no special concern for pregnant women, the unborn, females of reproductive age and children. Concentrations of Cu, Mn, Se and Zn in whole blood were within the ranges reported in the few studies available for pregnant women[2, 3, 9, 60] and women of reproductive age [33]; no comparative data appear to be available for Mo.

4.4 Study limitations

As pointed out in our recent paper on organochlorine plasma levels among this population[8], there is evidence that "study tiredness" (i.e., requests to participate in too

many studies) contributed to the low participation. This was difficult to overcome, even with vigorous promotion strategies. The consequence of this is that the study cohort is not as representative of the general population of Northern Norway as planned Another limitation is that this study group included a high proportion of "older" well-educated women, which may have influenced the dietary practices such as selection of healthier foods including fish.[56] The FFQ and the calculations of the consumption rates are based on self-reported data, standardized portions and food composition tables, which have a high degree of inherent uncertainty.[61] Null value or smallest amount imputation of missing information in the FFQ, may have resulted in underestimation and misclassification.[62] In addition, the dietary information has not yet been systematically analyzed. As already indicated, the small size of the Sámi sub-group also reduces the validity of the ethnic classification. These limitations lower the confidence in the regression analyses results for this subgroup.

The decision to analyze a subset of the study population has reduced the statistical power somewhat and thus places some restraint on the internal and external validity. However, the unavoidable low participation rate is likely a more severe limitation. Since an objective of this study was to detect patterns of change in the concentrations of the selected elements during gestational periods, external validity may be of less importance. On the other hand, the statistically different concentration patterns observed across the 2nd trimester and postpartum periods demonstrate the study's strengths.[7]

5 Conclusions

The observed blood concentration patterns of the 5 essential and 5 toxic elements measured are demonstrated to reflect established physiological and metabolic changes

that occur during gestation, at delivery and postpartum. This recognition emphasizes the importance in biomonitoring studies of reporting precise sampling times. Dietary information is also crucial, as consumption of certain items such as seafood can strongly influence the relative blood concentrations of selected elements. The observed levels of Cu, Mn, Se and Zn in whole blood were within the ranges reported in recent studies, while those of the toxic elements reflect no unusual sources other than those expected from the consumption of seafood (As, Hg), traditional foods harvested by hunting (Pb), smoking(Cd), and normal dietary sources (all). The observed levels of all 5 toxic elements were relatively low and thus are of no clinical importance. The blood concentrations of the essential elements appear to be normal.

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Table 1 Descriptive characteristics of the study population (n=211)

Variable	Mean (SD), Median, Min-Max; *or n(%)*
Age, years 2nd trimester	31.0 (4.8) 32.0; 18.0-44.0
< 25	*30 (14.2)*
26-30	*56 (26.5)*
31-35	*90 (42.7)*
>35	*35 (16.6)*
Parity, mean	0.9 (0.9) 1; 0-4
Para 0	*84 (39.8)*
Para 1	*78 (37.0)*
Para 2	*38 (18.0)*
Para 3	*9 (4.3)*
Para 4	*2 (0.9)*
Civil status, married/ live-in-partner,	*205 (97.2)*
Education, years,	15.9 (2.8) 16.0; 8-22
13-16, (n=206)	*82 (39.0)*
>16, (n=210)	*92 (43.8)*
Municipality,	
Nordland	*52 (24.6)*
Troms	*114 (54.0)*
Finnmark	*45 (21.3)*
Ethnic affiliation,	
Norwegian	*181 (85.8)*
Sami	*21 (10.0)*
Other	*9 (4.3)*
Income, household[a] > 600 000 NOK (n=197)	*117 (59.4)*
Smoking habits[b],	
Non-smoker	*163 (77.3)*
Smoker	*48 (22.7)*
Lactation P3, (n=179),	
No	*6 (3.4)*
Partially, substitute ≥1/d	*15 (8.3)*
Partially, seldom substitute	*13 (7.3)*
Exclusive	*145 (81.0)*

[a] Income classified as: <150 000, 150-300 000, 301-450 000, 451-600 000, 601 000-750 000, 750- 900 000 or >900 000 Norwegian Krones (NOK).
[b] Smoking either 6 months before pregnancy, and/or during pregnancy, and/or postpartum period

Table 2. Intake of supplements, fish and game

Variable		Mean (SD) or *n (%)*	Median	Min-max	Non-consumers *n (%)*
Supplementary intake last week					
Multi vitamins (n=203)	P1	*64 (31.5)*			
Multi vitamins (n=189)	P2	*42 (22.0)*			
Multi vitamins (n=203)	P3	*56 (27.6)*			
Omega-3[a] (n=208)	P1	*125 (60.1)*			
Omega-3[a] (n=194)	P2	*84 (43.3)*			
Omega-3[a] (n=208)	P3	*120 (57.7)*			
Fish intake (n=205), g/d					
Fatty fish[b]		10.6 (10.7)	8.0	0-66.0	*31 (15.1)*
Lean fish[c]		17.6 (17.7)	12.5	0-122.0	*16 (7.8)*
Other fish		1.1 (4.0)	0.0	0-41.0	*179 (87.3)*
Fish liver and roe		0.6 (0.9)	0.6	0-8.9	*78 (38.0)*
Fish products[d]		35.6 (21.7)	31.0	0-106.4	*4 (2.0)*
Fish spread[e]		8.4 (9.1)	5.1	0-48.0	*41 (20.0)*
Shellfish[f]		1.7 (1.6)	1.3	0-10.9	*35 (17.1)*
Total fish consumption[g]		75.6 (40.2)	68.0	10.2-251.9	*0*
Whale and seal		0.6 (0.8)	0.8	0-5.0	*98 (47.8)*
Game[h] (n=205), g/d		1.0 (3.2)	0.03	0-20.4	*97 (47.3)*

[a] Omega-3: supplements of cod-liver oil, other fish oil, or other omega-3 supplements

[b] Fatty fish= unprocessed cat-fish/flatfish/redfish, halibut, salmon,/trout, herring, mackerel; >4 % fat.

[c] Lean fish= unprocessed cod/ saithe/haddock/pollack, tuna, fresh-water fish; < than 4 % fat

[d] Fish products= fish cake/balls, fried fish, gratin and other processed fish products

[e] Fish spread= spread of crab, salmon/trout, mackerel, herring/anchovy/sardine, fish liver, caviar and other fish spread.

[f] Shellfish= prawn/ shell, crab (brown meat)

[g] Total fish including unprocessed and processed fish, fish spread and shellfish

[h] Game= reindeer, grouse and moose

Table 3 Concentrations (µg/L[a]) of As, Cd, Co, Cu, Hg, Mn, Mo, Pb, Se, and Zn in maternal blood samples from Northern Norway

	2nd trimester (P1)					3 days postpartum (P2)					6 weeks postpartum (P3)				
		Concentration (µg/L[a])					Concentration (µg/L[a])					Concentration (µg/L[a])			
Compound[b]	n[c]	GM[d]	AM[e]	SD	Min-max	n[c]	GM[d]	AM[e]	SD	Min-max	n[c]	GM[d]	AM[e]	SD	Min- max
As	211	1.4	2.1	2.2	0.1-12.8	211	1.8	2.4	2.1	0.1-17.1	211	3.7	6.4	9.4	0.1-80.9
Cd (*Smoker*)	48	0.26	0.41	0.50	0.05-2.74	48	0.23	0.33	0.40	0.08-2.42	48	0.32	0.43	0.48	0.09-3.06
Cd (*Non- smoker*)	163	0.15	0.17	0.09	0.04-0.59	163	0.17	0.19	0.08	0.05-0.45	163	0.23	0.25	0.11	0.07-0.78
Co	211	0.10	0.13	0.11	0.02-0.60	211	0.29	0.31	0.11	0.07-0.63	211	0.21	0.25	0.15	0.07-0.96
Cu[a] (mg/L)	211	1.65	1.67	0.25	1.11-2.69	211	1.78	1.80	0.25	1.12-2.84	211	1.09	1.10	0.14	0.64-1.54
Hg	211	1.2	1.5	1.1	0.1-6.6	211	1.0	1.2	0.7	0.2-3.7	211	1.5	1.8	1.0	0.2-6.4
Mn	211	10.7	11.3	4.0	3.8-37.8	211	15.8	16.5	5.1	6.6-43.1	211	17.3	18.1	5.5	7.6-41.3
Mo	211	0.7	0.8	0.3	0.2-1.9	209	0.6	0.7	0.3	0.2-2.0	211	0.8	0.9	0.2	0.3-1.6
Pb	210	7.5	8.2	4.0	2.2-41.1	211	9.2	9.9	4.1	3.7-29.0	211	13.2	14.2	6.2	4.0-52.6
Se	211	85	86	15	58-170	211	72	73	15	43-143	210	89	90	17	53-152
Zn[a] (mg/L)	211	5.11	5.18	0.84	2.73-9.00	211	5.48	5.59	1.09	2.92-9.82	211	6.81	6.89	1.03	3.93-11.74

[a] Concentrations of Cu and Zn are reported in mg/L, [b] As, arsenic; Cd, cadmium; Co, cobalt; Cu, copper; Hg, mercury; Mn, manganese; Mo, molybdenum; Pb, lead; Se, selenium; and Zn, zinc. [c] A number (N) of outliers were omitted from the following data sets (N, collection period, element): 1, P1, Pb; 2, P2, Mo; 1, P3, Se (see text); [d] GM= Geometric mean; [e] AM= Arithmetic mean

Table 4 Fractional change in Co, Hg, As and Se concentrations per unit change in predictors at P1, in a multivariable linear regression model.

	Co (n=211)			Hg (n=205[b])			As (n=205[b])			Se (n=198)		
	Ratio[a]	CI	p	Ratio[a]	CI	p	Ratio[a]	CI	p	Ratio[a]	CI	p
Age (10 years)	1.12	0.91-1.38	0.302	1.51	1.26-1.82	<.001	1.26	1-1.62	0.059	1.05	1-1.10	0.063
Parity (0-multipara)	1.39	1.14-1.70	0.002	0.83	0.69-0.99	0.047	1.00	0.79-1.27	0.991	0.96	0.92-1.01	0.086
Sami affiliation (no -yes)	0.66	0.48-0.91	0.010	0.66	0.50-0.88	0.005	0.61	0.42-0.88	0.008			
Interval P1 (weeks)	1.04	1.01-1.06	0.006									
Multivitamin P1 (no -yes)										1.09	1.04-1.14	<0.001
Fatty fish (10 g/d)				1.12	1.02-1.23	0.019	1.18	1.02-1.32	0.013			
Lean fish (10 g/d)				1.10	1.05-1.18	0.001	1.10	1.02-1.18	0.007	1.02	1.01-1.02	0.001
Shellfish (10 g/d)				2.63	1.51-4.47	0.001	3.55	1.74-7.24	0.001	1.29	1.15-1.48	<0.001
Whale/seal (10 g/d)				3.16	1.12-8.91	0.030						
Fish spread (10 g/d)										1.02	1.01-1.05	0.026
R^2			0.12			0.36			0.25			0.25
F			6.799			15.946			10.999			10.581
p (overall)			<0.001			<0.001			<0.001			<0.001

[a] Corresponds to 10^{β}, with β the regression coefficient.

[b] 5 Individuals were excluded due to non-reporting of fish intake in the FFQ, and 1 was excluded because the questionnaire was not filled out.

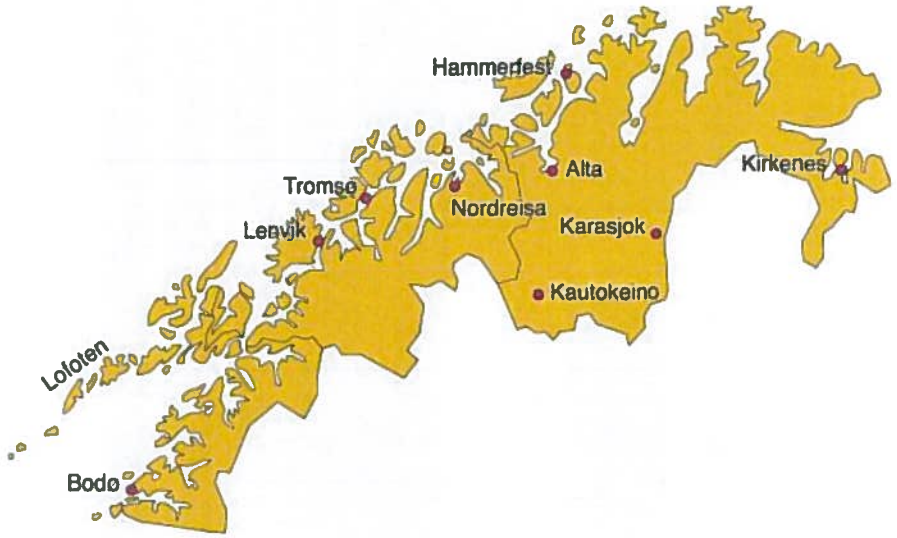


Fig 1: Map of study area

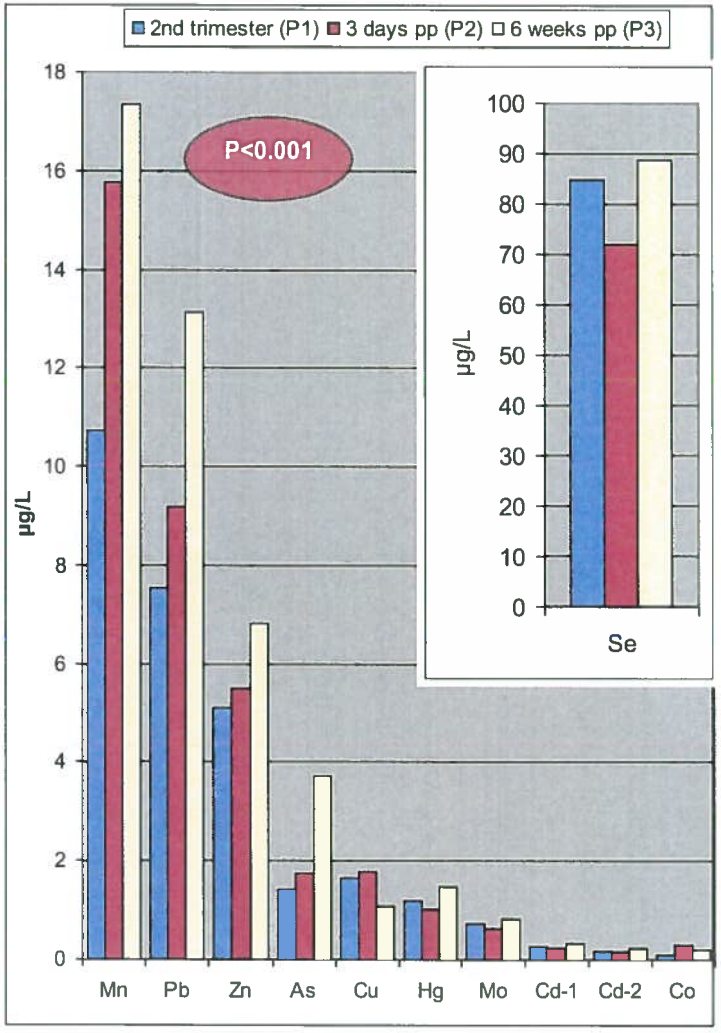


Fig. 2 Geomean concentrations of As, Cd-1 (smokers), Cd-2 (non-smokers), Co, Cu, Hg, Mn, Mo, Pb, Se and Zn (µg/L, except for Cu and Zn reported in mg/L) for the collection periods P1, P2 and P3. The p-value refers to trends across the three collection periods and between any two, with the exception of P2/P1 for As (p=0.002).

Supplementary Data Depository

Table S1 Limit of detection (LOD) and detection frequencies above LOD of As, Cd, Co, Cu, Hg, Mn, Mo, Pb, Se and Zn in maternal whole blood samples from Northern Norway

Compound[a]	LOD[b] µg/L[c]	2nd trimester (P1)		3 days postpartum (P2)		6 weeks postpartum (P3)	
		n[d]	% detected >LOD	n[d]	% detected >LOD	n[d]	% detected >LOD
As	0.19	211	98.6	211	99.5	211	99.1
Cd	0.02	211	100	211	100	211	100
Co	0.03	211	97.6	211	100	211	100
Cu	0.002	211	100	211	100	211	100
Hg	0.15	211	99.1	211	100	211	100
Mn	0.11	211	100	211	100	211	100
Mo	0.12	211	100	209	100	211	100
Pb	0.26	210	100	211	100	211	100
Se	0.93	211	100	211	100	210	100
Zn	0.01	211	100	211	100	211	100

[a] See footnote b, Table 3 of the text for the full names of the elements

[b] LOD= Limit of detection. All levels below the LOD were set to LOD/√2. LOD for all three periods were similar. [c] Measured in µg/L, except for Cu and Zn reported in mg/L

[d] Variation in n is due to exclusion of some single concentrations (see footnote c in Table 3 of the text).

Table S2 Changes in concentrations of As, Cd, Co, Cu, Hg, Mn, Mo, Pb, Se and Zn across the collection periods P1 (2nd trimester), P2 (3 days postpartum) and P3 (6 weeks postpartum)

		Geomean concentrations (µg/L[a])			
		Time periods			
Compound[b]	Estimates of change[c,d,e,f,g]	P1/P3	P2/P3	P2/P1	p[h]
As	β	-0.415	-0.327	0.089	
	p	**<0.001**	**<0.001**	**0.002**	**<0.001**
	Ratio	0.39	0.47	1.23	
Cd (Smokers)	β	-0.089	-0.148	-0.060	
	p	**0.001**	**<0.001**	**0.010**	**<0.001**
	Ratio	0.82	0.71	0.87	
Cd (Non-smokers)	β	0.181	-0.124	0.057	
	p	**<0.001**	**<0.001**	**<0.001**	**<0.001**
	Ratio	0.66	0.75	1.14	
Co	β	-0.327	0.137	0.463	
	p	**<0.001**	**<0.001**	**<0.001**	**<0.001**
	Ratio	0.47	1.37	2.90	
Cu	β	0.179	0.212	0.033	
	p	**<0.001**	**<0.001**	**<0.001**	**<0.001**
	Ratio	1.51	1.63	1.08	
Hg	β	-0.105	-0.158	-0.053	
	p	**<0.001**	**<0.001**	**<0.001**	**<0.001**
	Ratio	0.79	0.70	0.89	
Mn	β	-0.208	-0.042	0.167	
	p	**<0.001**	**<0.001**	**<0.001**	**<0.001**
	Ratio	0.62	0.91	1.47	
Mo	β	-0.044	-0.112	-0.068	
	p	**<0.001**	**<0.001**	**<0.001**	**<0.001**
	Ratio	0.90	0.77	0.85	
Pb	β	-0.240	-0.156	0.085	
	p	**<0.001**	**<0.001**	**<0.001**	**<0.001**
	Ratio	0.58	0.70	1.22	
Se	β	-0.019	-0.091	-0.072	
	p	**<0.001**	**<0.001**	**<0.001**	**<0.001**
	Ratio	0.96	0.81	0.85	
Zn	β	-0.125	-0.095	0.030	
	p	**<0.001**	**<0.001**	**<0.001**	**<0.001**
	Ratio	0.75	0.80	1.07	

[a] Measured in µg/L, except for Cu and Zn reported in mg/L; [b] See footnote b, Table 3 of the text for the full names of the elements [c]Analysis was by the linear mixed model; [d] Regression coefficient (β); [e] p-Value refers to the change across the 2 periods ; [f] The ratio corresponds to 10^{β}; [g] In the text, ratios are reported as % change $[(10^{\beta}-1)*100]$; [h] p-Value refers to the change across the 3 periods.

Table S3. Predicators of Elemental Blood Levels [Univariate Analysis(log scale); p≥0.05 , non-significant (n.s); not observed (No)]

Independent Variable	As p; β	Cd (S)[a] p; β	Cd (NS)[a] p; β	Co p; β	Cu p; β	Hg p; β	Mn p; β	Mo p; β	Pb p; β	Se p; β	Zn p; β
Age (year)	P1: .003; .016 P2: .002; .016 P3: n.s	P1: n.s P2: n.s P3: n.s	P1: n.s P2: n.s P3: .030; .006	P1: .047; .009 P2: .006; .006 P3: n.s	P1: n.s P2: n.s P3: n.s	P1: <.001; .021 P2: <.001; .016 P3: <.001; .015	P1: n.s P2: n.s P3: n.s	P1: n.s P2: n.s P3: n.s	P1: n.s P2: n.s P3: n.s	P1: .012; .003 P2: .n.s P3:<.001; .004	P1: n.s P2: n.s P3: n.s
Parity (0-MP)	P1: n.s P2: n.s P3: n.s	P1: n.s P2: n.s P3: n.s	P1: n.s P2: n.s P3: n.s	P1: .001; .148 P2:<0.001; .083 P3: n.s	P1: n.s P2: n.s P3: n.s	P1: n.s P2: n.s P3: n.s	P1: n.s P2: n.s P3: n.s	P1: n.s P2: n.s P3: n.s	P1: n.s P2: n.s P3: n.s	P1: n.s P2: n.s P3: .019; -.026	P1: n.s P2: .034; .026 P3: .028; .020
Education (Year)	P1: n.s P2: n.s P3: n.s	P1: n.s P2: .032; -.034 P3: .044; -.030	P1: n.s P2: n.s P3: n.s	P1: n.s P2: n.s P3: .037; .012	P1: n.s P2: n.s P3: n.s	P1: .001; .026 P2: .001; .020 P3: .010; .016	P1: n.s P2: n.s P3: n.s	P1: n.s P2: n.s P3: n.s	P1: n.s P2: n.s P3: n.s	P1: .004; .005 P2: .008; .005 P3: .006; .005	P1: n.s P2: n.s P3: .026; -.004
Income >600 000 (0-1)	P1: .018; .135 P2: n.s P3: n.s	P1: n.s P2: n.s P3: n.s	P1: n.s P2: n.s P3: n.s	P1: n.s P2: n.s P3: n.s	P1: n.s P2: n.s P3: n.s	P1: .001; .156 P2: .002; .115 P3: <.001; .134	P1: n.s P2: n.s P3: n.s	P1: n.s P2: n.s P3: n.s	P1: n.s P2: n.s P3: n.s	P1: n.s P2: n.s P3: .024; .025	P1: n.s P2: n.s P3: n.s
Smoking (0-1)	P1: n.s P2: .010; -.149 P3: .001; -.245	No	No	P1: n.s P2: n.s P3: n.s	P1: n.s P2: n.s P3: n.s	P1: .013; -.130 P2: .016; -.100 P3: .045; -.085	P1: n.s P2: n.s P3: n.s	P1: n.s P2: n.s P3: n.s	P1: n.s P2: n.s P3: n.s	P1: n.s P2: n.s P3: n.s	P1: n.s P2: n.s P3: n.s
Alcohol as wine weekly intake (0-1)	P1: n.s P2: n.s P3: n.s	P1: n.s P2: n.s P3: n.s	P1: n.s P2: n.s P3: n.s	P1: n.s P2: n.s P3: n.s	P1: n.s P2: n.s P3: n.s	P1: .003; .168 P2: n.s P3: n.s	P1: n.s P2: n.s P3: n.s	P1: n.s P2: n.s P3: n.s	P1: n.s P2: n.s P3: n.s	P1: .007; .032 P2: .017; .036 P3: .018; .033	P1: n.s P2: n.s P3: n.s
Muncl-pality F-T-N	P1: n.s P2: n.s P3: n.s	P1: n.s P2: n.s P3: n.s	P1: n.s P2: n.s P3: n.s	P1: n.s P2: n.s P3: n.s	P1: n.s P2: n.s P3: n.s	P1: n.s P2: n.s P3: n.s	P1: n.s P2: n.s P3: n.s	P1: .017; -.035 P2: n.s P3: .006; -.035	P1: .012; -.047 P2: n.s P3: n.s	P1: n.s P2: n.s P3: n.s	P1: n.s P2: n.s P3: n.s
Sámi affiliation (0-1)	P1: .015; -.216 P2: n.s P3: n.s	P1: n.s P2: n.s P3: n.s	P1: .045; .105 P2: n.s P3: .034; .098	P1: .030; -.159 P2: n.s P3: n.s	P1: .036; .030 P2: n.s P3: n.s	P1: .009; -.192 P2: n.s P3: n.s	P1: n.s P2: n.s P3: n.s	P1: n.s P2: n.s P3: n.s	P1: n.s P2: .027; .084 P3: .005; .108	P1: n.s P2: n.s P3: n.s	P1: n.s P2: n.s P3: n.s
Vitamin Suppl. (0-1)	P1: n.s P2: n.s P3: n.s	P1: n.s P2: n.s P3: n.s	P1: n.s P2: n.s P3: n.s	P1: n.s P2: .047; -.057 P3: n.s	P1: n.s P2: n.s P3: n.s	P1: n.s P2: n.s P3: n.s	P1: n.s P2: n.s P3: n.s	P1: n.s P2: n.s P3: n.s	P1: n.s P2: n.s P3: n.s	P1: .001; .034 P2: n.s P3: .006; .034	P1: n.s P2: n.s P3: n.s
Omega Suppl. (0-1)	P1: n.s P2: n.s P3: .007; .163	P1: .040; -.230 P2: n.s P3: n.s	P1: n.s P2: n.s P3: n.s	P1: n.s P2: n.s P3: n.s	P1: n.s P2: n.s P3: n.s	P1: n.s P2: n.s P3: .010; .092	P1: n.s P2: n.s P3: n.s	P1: n.s P2: n.s P3: n.s	P1: n.s P2: n.s P3: n.s	P1: .003; .030 P2: .006; .034 P3:<.001; .048	P1: n.s P2: n.s P3: n.s
Fish, total[b]	P1:<.001; .038 P2: .009;.016 P3:<.001; .038	P1: n.s P2: n.s P3: n.s	P1: n.s P2: n.s P3: n.s	P1: n.s P2: n.s P3: n.s	P1: n.s P2: n.s P3: n.s	P1:<.001; .032 P2:<.001; .025 P3:<.001; .026	P1: n.s P2: n.s P3: n.s	P1: n.s P2: n.s P3: n.s	P1: n.s P2: n.s P3: n.s	P1:<.001; .005 P2: .014; .004 P3: .001; .004	P1: n.s P2: n.s P3: n.s
Fatty fish[b]	P1:<.001; .123 P2: .006; .062 P3:<.001; .130	No	No	No	No	P1:<.001; .109 P2:<.001; .085 P3:<.001; .092	No	No	No	P1:<.001; .020 P2: .013; .014 P3:<.001; .021	No
Lean fish[b]	P1:<.001; .070 P2: n.s P3:<.001; .070	No	No	No	No	P1:<.001; .066 P2:<.001; .051 P3:<.001; .055	No	No	No	P1: .003; .008 P2: n.s P3: .037; .007	No
Shellfish[b]	P1:<.001; .773 P2:<.001; .648 P3:<.001; .789	No	No	No	No	P1:<.001; .689 P2:<.001; .576 P3:<.001; .601	No	No	No	P1:<.001; .148 P2:<.001; .156 P3:<.001;.161	No
Fish spread[b]	P1: .030; .065 P2: n.s P3: n.s	No	No	No	No	P1: .005; .070 P2: .005; .055 P3: n.s	No	No	No	P1: .001; .018 P2: .011; .017 P3: .006; .017	No
Processed fish[b]	P1: .004; .036 P2: n.s	No	No	No	No	P1: .027; .023 P2: .044; .017	No	No	No	P1: n.s P2: n.s	No

	P3: n.s					P3: .014; .020				P3: n.s	
Whale/ seal[b]	P1: n.s P2: .019; .702 P3: n.s	No	No	No	No	P1: .002; .828 P2: .013; .535 P3: .042; .446	No	No	No	P1: n.s P2: n.s P3: n.s	No
Game[b]	P1: n.s P2: n.s P3: n.s	P1: n.s P2: n.s P3: n.s	P1: n.s P2: n.s P3: n.s	P1: .036;-.148 P2: n.s P3: n.s	P1: n.s P2: n.s P3: n.s	P1: n.s P2: n.s P3: n.s	P1: n.s P2: n.s P3: n.s	P1: n.s P2: n.s P6: .036; .058	P1: n.s P2: n.s P3: n.s	P1: n.s P2: n.s P3: n.s	P1: n.s P2: n.s P3: n.s
Interval (weeks)	P1: n.s P2: n.s P3: n.s	P1: .044; -.010 P2: n.s P3: n.s	P1: .045; .008 P2: n.s P3: n.s	P1: .015;.014 P2: .012;.007 P3: n.s	P1: .004; .001 P2: n.s P3: .018;-.005	P1: n.s P2: n.s P3: n.s	P1: .008; .003 P2: n.s P3: n.s	P1: .n.s P2: .005; .009 P3: n.s	P1: n.s P2: n.s P3: n.s	P1: n.s P2: n.s P3: n.s	P1: n.s P2: n.s P3: n.s
Lactation[c] **P3 (0-1)**	P3: n.s	P3: n.s	P3: n.s	P3: n.s	P3: n.s	P3: n.s	P3: .024; -.067	P3: n.s	P3: n.s	P3: n.s	P3: n.s
Independent Variable	**As p; β**	**Cd (S)**[a] **p; β**	**Cd (NS)**[a] **p; β**	**Co p; β**	**Cu p; β**	**Hg p; β**	**Mn p; β**	**Mo p; β**	**Pb p; β**	**Se p; β**	**Zn p; β**

[a] S= smokers; NS= non-smokers

[b] β estimates are expressed here in units of 10 g/d

[c] Lactation: No breastfeeding or daily substitute (n=21) *versus* exclusive breastfeeding, including those whom seldom were given a substitute (n=158)

APPENDIX I

Basis for Paper I

Questionnaires

ENVIRONMENT & REPRODUCTIVE HEALTH STUDY

This questionnaire is part of the Medical Research Council environment and reproductive health study. We would like to request that you take the time to answer the questionnaire with the assistance of trained interviewer. We thank you in advance for your participation.

If you have questions or need more information, please do not hesitate to call .

Clinic Name: .....
Clinic address: .....
Town/Province: .....
Interview date (date/month/year): .....
Interviewer: .....

Patient name: .....

Patient Hospital Code .....

Patient Study Code .....

Delivery date: .....

Name of Doctor or Sister attending: .....

Was cord blood collected: .....Yes.....No.....

If no, please explain .....

SECTON A: MATERNAL INFORMATION

Name of Doctor attending: .....
Clinic Name: .....
Fill-in date:.....

1. Maternal name

   Year of birth..... File number:.....

2. Area: Nha Trang Dien Khan

   House number..... Street/village ..... Section of town.....

Telephone…… Name of household leader/keeper (for locating purpouses)…….

3. Occupation…….. Husbands occupation……..
4. Economic status: Poor middle class affluent
5. Maternal weight in pregnancy …….kg before delivery: ……kg

   Maternal height: ……cm…

6. Pregnancy history

   Number of normal deliveries……..

   Number of early deliveries…….

   Previous spontaneous abortions 1. trimester: (if available)……..

   Previous spontaneous abortions 2. trimester (if available)…….

   Number of children…….

7. Previous deliveries

   For each child: Year, gestational age (weeks), birth weight, duration of breast feeding (months), special problems

8. **History of disease**: yes/no.
   Diabetes, Heart disease, thyroid gland, other……..

Medication of mother (if daily: ……

……

Disease during first tri-mester:

1st pregnancy: flu, rubella, toxoplasmosis, other …….

2nd pregnancy: flu, rubella, toxoplasmosis, other .....

Current pregnancy: flu, rubella, toxoplasmosis, other .....

SECTION B: INFORMATION ABOUT THE NEWBORN CHILD

1. **Birth weight of baby: .....kg.....**
2. **Birth length of baby: .....cm**
3. **Caput circumference of baby: .....cm**
4. **Gestation age of baby (based on Naegele term):**
5. **APGAR score (any sign of asphyxia?) .....**
6. **Gender of baby .....**
7. **Congenital malformations (visible at birth) .....**
8. **Any delivery complications, if yes, what kind (section Caesarean, forceps, vacuum, retentio placenta)**

   .....

   .....

9. **Any other medical observations or conditions**

   .....

   .....

SECTION
A1: BACKGROUND DETAILS

Patient study code.....

In this section we would like to obtain a few background details about yourself.

1. What is your first name ..... middle name .... surname? .....

2. Current address if you have stayed here more than one year (address)?

.....

.....

4. Your contact address?.....
5. What is your present contact telephone number .....
7. When were you born? (please give day, month and year)
Day .....
Month .....
Year .....
8. How many children do you already have:
.....
9. How many daughters do you have: number: ..... ages: .....
10. How many sons do you have: number: .....ages .....
11. What is your nationality? .....
3. How would you describe your place of residence (please circle one answer only)

1. Urban (city)
2. Rural (farming community)
3. Peri urban (close to the city)
4. Close to industrial site: (please specify)
.....
5. Don't Know

3b. How long have you lived at your present home address?

Years .....
Months .....

12. Where do you get your drinking water from **most** of the time? (please circle)

1. Indoor tap (municipality distribution)
2. Rainwater tank
3. Open well
4. Borehole Depth in meters.....
5. River/stream
6. Other (please specify)

Address of water source (if they do not have their own:.....

SECTION C: SOCIAL AND ENVIRONMENTAL ASPECTS

In this section we will ask some questions relating to you and other people living in your home.

1. Marital status: (please circle)
    1. Married
    2. Divorced
    3. Single
    4. Living together
    5. Widowed

2. How many people live in this house?
    1. Males older than 15 years
    2. Women (including yourself) older than 15 years
    3. Children aged 15 years or younger

3. What is your highest educational qualification?
…….. .....
4. Do you have permanent job: (please circle)
1. YES
2. NO

If yes, what type (seasonal or continuous) please underline
1. Occupation/Position……..
2. Seasonal
3. Permanent
4. Leader/employer
5. employee

5. For how many years have you held your current job?
……
6. What does your husband/partner do at work? ……
……
7. Where does he work?
…….. ……
8. What is the highest education qualification of your husband/partner?
…….. .....
9. How many years has he held his current job?
……
10. If maintaining or repairing your home, do you or handyman use lead-containing materials (paints, solders etc.?
1. Yes
2. No
3. Don't know

11. What is the total monthly income in your family?
.....
12. Describe the hobbies of people living in the house (for instance car repairs, pottery, welding, etc).
……
……
……
13. What is your opinion on air quality in your area? (please circle)
1. Good
2. Bad
3. I don't know

14. Are there any sources of environmental pollution around your home?
1. Yes
2. No
3. If yes specify source
……
……

15. How far is your home from the nearest main road? Km
16 Do you use pesticides for insect control (flies, bugs, cockroaches, mosquitoes, in your

home?)

1. Yes
2. No
3. do not know

17. If yes, are these pesticides used in: (please circle)

1. Kitchen
2. Living room
3. Bedroom
4. Others, please specify

.....

18. What are the names of the pesticides do you use?

.....

19. How often do you use the pesticides?

1. ...times a week
2. ...times a month

20. Where do you store these pesticides? .....

21. Do you grow your own food? (leaf vegetables, "fruit" vegetables, root vegetables, rice, fruits)

1. Yes
2. No

If yes specify.....

22 Do you use pesticides in your garden or field?

1. Yes
2. No

If yes please specify which pesticide?

.....

23. Do you or a member of your household fish?

1. Yes
2. No

Where do you fish? Please name the location .....

Please name the fish type .....

24. If yes do you consume this fish?

1. Yes
2. No

SECTION E: HEALTH

In this section some information about your health status is requested.

1. Are you well at present?

1. Yes
2. No
3. Don't know

2. If you are not well, what are the problems?

.....

.....

3. Do you suffer from any of the following? (circle correct answers please)

1. Diabetes

Since when / How long ……..
Are you on medication for this condition? YES NO
2. Thyroid gland
Since when / How long ……..
Are you on medication for this condition? YES NO
3. Liver disease
Since when / How long
Are you on medication for this condition? YES NO

4. Heart disease
Since when / How long
Are you on medication for this condition? YES NO
5. High blood pressure
Since when / How long
Are you on medication for this condition? YES NO
6. Infectious/parasite disease, if yes please tick:
TB (tuberculosis)
Pneumonia
Virus hepatitis
If other please specify ……..
7. Cancer YES NO
If yes, please specify organ…….
If yes, did you receive treatment:……..
Please specify type of treatment…….

9. Are there any hereditary diseases in family (for example high blood pressure, lung disease, etc.?)
If yes, please specify ……..
Difficult question to answer

8. Do you suffer from any other illnesses (for example skin condition etc):
1. Yes
2. No
If yes, please specify)…....

10. Have you ever treated diseases yourself (please circle)?
1. Yes
If yes, please specify……..
2. No
3. Don't know

11. Are you taking any prescription medication at present? (please circle)
1. Yes:
If yes, what medication are you taking, please specify:
……..
……
2. No
3. Don't know

12. Are you taking any special remedies during your pregnancy?

If yes, please specify .....
.....

SECTION F: DIET AND LIFESTYLE

1. Please answer questions about your usual diet before and during pregnancy:

Table 1

Frequency of consumption of food (including all types of cooking: raw, boiled, fried, smoked, salted, dried, pickled, etc.) before / during pregnancy.

Type of foodstuff	Unit	Quantity per meal **before**	Quantity per meal **during**	How many times a week **before**	How many times a week **during**	How many times a month **before**	How many times a month **during**	Seldom or never **before**	Seldom or never **during**	Food locally **yes/no**
Meat products										
Beef	100g									
Pork	100g									
Lamb	100g									
Chicken	100g									
Other types of meat and birds	100g									
Tinned meat	100g									
Sausage	100g									
Lap sung (chinese) sausage	100g									
Ham and other smoked meat products	100g									
Cut'bird eggs	Number									
Duck eggs	Number									
Chicken Eggs	Number									
Fish Please tell 5-7 kinds of fish that you often eat:										
	100g									
	100g									
	100g									
	100g									
	100g									
	100g									

Tinned fish	100g									
Snails and shell	**Tell 1-2 kind that you eat most frequently:**									
Shrimps										
Crabs										
Vegetables										
Vegetables for soup. Tell 5-6 types of vegetable for soup that you eat the most frequently										
	100g									
	100g									
	100g									
	100g									
	100g									
Raw/boiled/fried/salted/ pickled vegetables. Tell 5-6 types of vegetable for soup that you eat the most frequently										
	100g									
	100g									
	100g									
	100g									
	100g									
Fruits. Tell 5-6 types of fruits that you eat the most frequently										
	100g									
	100g									
	100g									
	100g									
	100g									
Dairy products										
Milk	Litre									
Sour milk products	Litre									
Butter	G									
Cheese	G									
Cereal and cereal product										

Tell two kinds of beans you eat most frequently										
Bean ???	100g									
Bean??	100g									
Soya milk	Litre									
Soya curd	100g									
Peanut	100g									
Corn/maize										
Other										
Oil	ml									
Pork grease	ml									
Noodle soup	Bowl									
Instant noodle	Packet									
Fried noodle	100g									
Bread (pariserloaf)	Number									
Boiled Rice	bowl									
Raw rice. Tell where you bought your rice during and before pregnancy. **Rice produced by yourself or not? Yes/no**										
Sugar										
Tinned Fruit juice										
Soft drinks										
Bottled water										
Non food item,										
Specify										

2. How many cups of coffee do you drink?
   1 Number of cups Daily
   2 Weekly
   3 Never
3. How many cups of tea do you drink?
   I. Daily
   2 Weekly?
   3 Never
4. How many bottles of beer do you drink?
   1. Daily
   2 Weekly?
   3. None

5. How many bottles of wine do you drink?
    1. Daily
    2 Weekly?
    3. None
6. How many glasses of vodka or other strong alcohol do you drink?
    1. Daily
    2 Weekly?
    3. None
7. Do you smoke?
    1. Yes
    2. No
8. If yes, for how many years have you smoked regularly?
9. At what age did you start to smoke regularly?
10. What do you smoke? (please circle)
    cigarettes, self-rolled cigarettes, water pipe, pipe, cigars
11. How many cigarettes do you smoke daily?
12. If you do not smoke, did you smoke earlier? Yes No
13. At what age did you start to smoke regularly? ***The question is by mistake the same as number 9.***
14. At what age did you quit smoking?
15. Within the last 6 months, did you take any drugs that influenced on your mood?
    1. Yes
    2. No
    3. Refuse to answer
16. Do you have any hobby?
    1. Yes
    2. No
    3. If yes, what?

17 How many times you visited this clinic during pregnancy:.....

END OF QUESTIONNAIRE,
THANK YOU for answering the questions, your assistance is highly appreciated.

QUESTIONAIRES

Investigator: _____

Hospital: _____

Date: _____/ _____/ _____

A.- INFORMATIONS OF THE MOTHER:

1. Name : _____
2. Year of birth (age): _____
3. Adress : Nha Trang ف Diên Khánh ف
4. Number _____ street _____ ward _____ village _____
5. Occupation : _____ husband's occupation: _____
6. Economic status: Poor ف Intermediaire ف Rich ف
7. Physic status: Height_____ Cm, Weight: _____ Kg, non-pregnan weight (if available):_____kg

8. **Obstetric history:**

PARA	No of birth	No of preterm-delivery	No of abortion		No of living infant.
			1st trimestre	2nd trimestre	

Previous delivery:

	Year	Gestional age (weeks)	Birth weight (kg)	Breast feeding duration (months)	*Special problems
1					
2					
3					

**Delivery complications, malformation of the baby.*

9. **Medical history:**

Major illnesses : فdiabetes/ فcardiovascular diseases/ ف thyroid dysfunction ف other

Medication (if daily) : _____

Illnesses in 1st triemester of previous pregnant periods:

ف influenzae/ ف rubella / ف toxoplasmosis / ف other (what?)

Illnesses in 1st triemester of current pregnant period:

ف influenzae/ ف rubella / ف toxoplasmosis / ف other (what?)

10. Foods and Nutrition

Sources of water: ف well / ف tape water / ف other

Sources of drinking water: ف well / ف tape water / ف other

Sources of foods

Rice : ف from market / ف self cultivated / ف other

Meat : ف from market / ف self cultivated / ف other

Fish : ف from market / ف self cultivated / ف other

Vegtables : ف from market / ف self cultivated / ف other

B. - INFORMATIONS OF THE BABY

1. Date of birth _____/_____/_____ (dd/mm/yy)
2. APGAR score : [ ]

Birth weigth (gram)	Birth length (cm)	Gestational age (week)	Caput circonference (cm)	Gender (M/F)	Congenital malformations (visible at birth)

Other notes: _____

_____

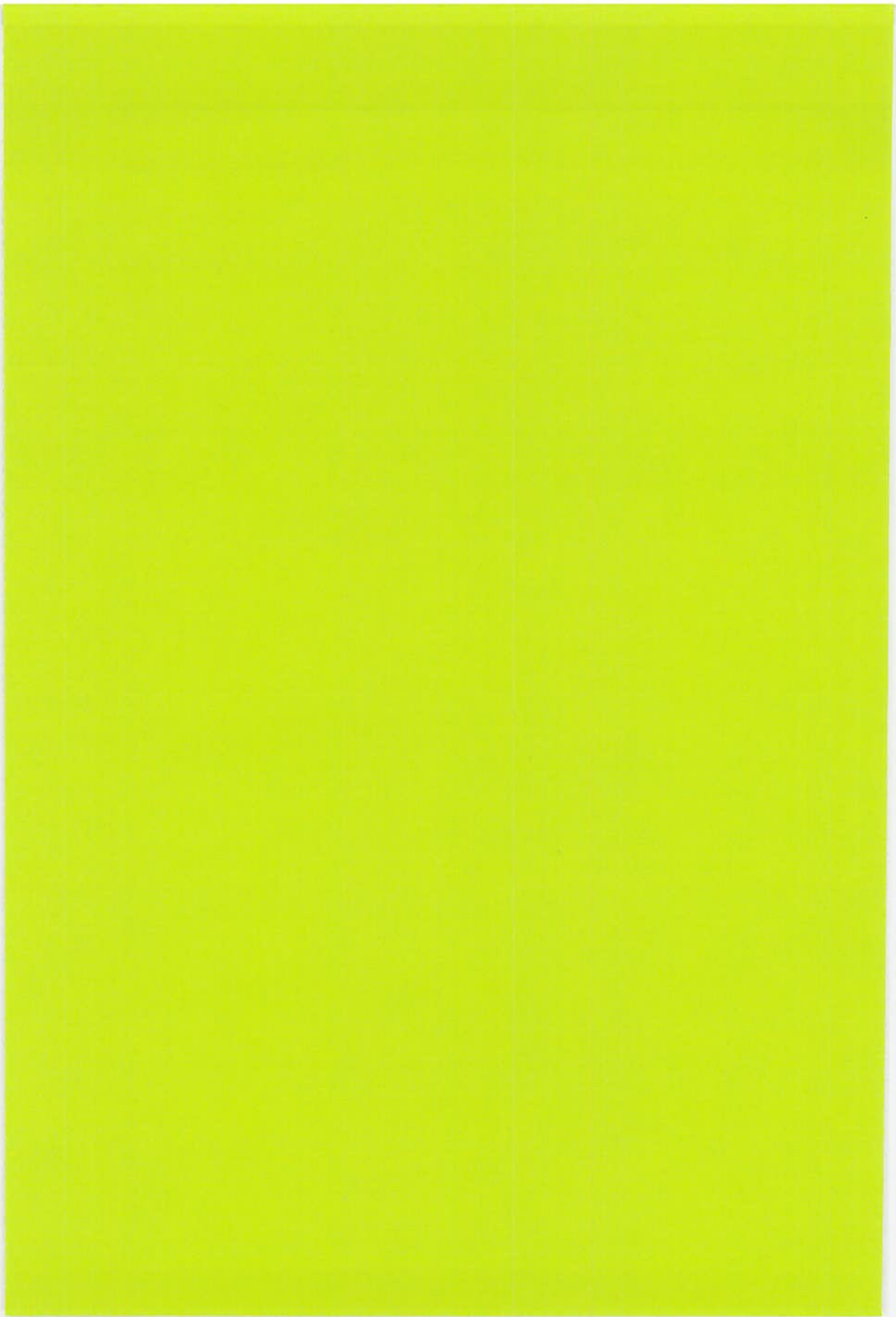
APPENDIX II

Basis for Paper II & III

Invitation letter

Questionnaires

Enquiry



Til deg som er gravid

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

Til deg som vil delta

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

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

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

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

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

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

På forhånd takk og vel møtt!

Vennlig hilsen
Solrunn Hansen
Prosjektleder / Jordmor

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

Forespørsel om deltakelse i forskningsprosjekt

Miljøgifter i svangerskapet og i ammeperioden

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

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

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

Hensikten er å:

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

Forespørsel om å delta sendes til alle gravide som:

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

Frivillig deltagelse

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

Hvis du blir med, spør vi deg om:

1. Spørreskjema:

- Å svare på et spørreskjema i første halvdel av svangerskapet

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

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

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

3. At vi av ditt nyfødte barn kan få:

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

4. Morsmelkundersøkelsen:

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

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

5. Ditt samtykke:

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

6. Innhenting av opplysninger:

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

7. Tillatelse til å koble innsamlede opplysninger om deg:

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

8. Kontakte deg senere for å:

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

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

Din sikkerhet og tilbakemelding

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

Godkjenninger

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

Ansvarlig

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

Påmelding, samtykke

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

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

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

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

Vennlig hilsen

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

Merete Eggesbø (sign.),
Prosjektleder Mørsmelksundersøkelsen/ 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 (DDMMÅÅÅÅ):

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: _____

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

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

Dato dag mnd

Preparatnavn:
(Ikke skriv her →)

Dato dag mnd

Preparatnavn:
(Ikke skriv her →)

Dato dag mnd

Preparatnavn:
(Ikke skriv her →)

Dato dag mnd

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

Dato ..... dag | | mnd | |

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

Dato ..... dag | | mnd | |

Preparatnavn: .....

(Ikke skriv her →) | | |

Angi mengde

☐ 1 stk ☐ 2 stk ☐ 3 stk

Dato ..... dag | | mnd | |

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

Dato ..... dag | | mnd | |

Preparatnavn: .....

(Ikke skriv her →) | | |

Dato ..... dag | | mnd | |

Preparatnavn: .....

(Ikke skriv her →) | | |

Dato ..... dag | | mnd | |

Preparatnavn: .....

(Ikke skriv her →) | | |

Dato ..... dag | | mnd | |

Preparatnavn: .....

(Ikke skriv her →) | | |

Dato ..... dag | | mnd | |

Preparatnavn: .....

(Ikke skriv her →) | | |

Dato ..... dag | | mnd | |

Preparatnavn: .....

(Ikke skriv her →) | | |

Takk for hjelpen!

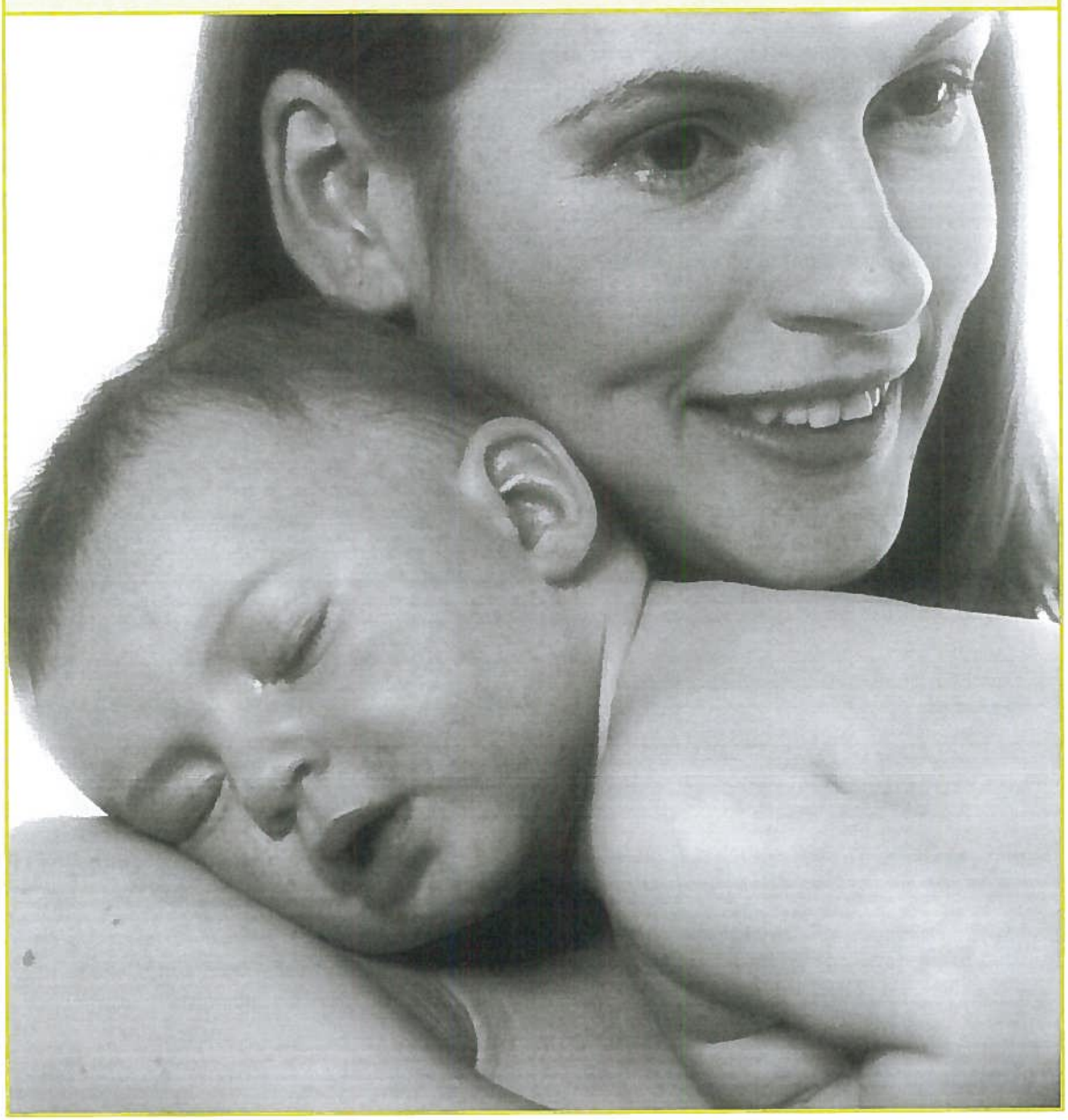
2007
KONFIDENSIELT

MILJØGIFTER I SVANGERSKAPET OG I AMMEPERIODEN

ID-nr:

Universitetet i Tromsø

Romssa universitehta



Universitetet i Tromsø — Romssa universitehta

MILJØGIFTER I SVANGERSKAPET OG I AMMEPERIODEN

Vi ber deg fylle ut spørreskjemaet så nøye som mulig.

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

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

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

Dato for utfylling av spørreskjema: dag mnd år

Dato ..... | | | |

SOSIALE FORHOLD

Hva er ditt postnummer? .....

Hva er ditt fødselsår: .....

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

Hvor mange personer er det i ditt hushold? Voksne Barn

Hvor høy er den samlede bruttoinntekten i ditt hushold?

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

Hva er ditt yrke?

..... *(Ikke skriv her →)*

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

..... *(Ikke skriv her →)*

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

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

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

- ☐ Nei
- ☐ Delvis sykemeldt
- ☐ Fullt sykemeldt

Hvordan er du sykemeldt?

- ☐ Sykemeldt korttids
- ☐ Sykemeldt langtids

OPPVEKST

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

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

FAMILIE- OG SPRÅKBAKGRUNN

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

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

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

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

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

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

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

SVANGERSKAPET

Var dette svangerskapet planlagt?

☐ Ja ☐ Nei

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

Antall mnd. ☐☐

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

☐ Ja ☐ Nei

Dersom JA, hva var årsaken?

.....

Hvilken behandling fikk du da?

.....

MORSMELK SOM BABY

Ammet din mor deg da du var baby?

☐ Ja ☐ Nei

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

Totalt antall mnd. med morsmelk ☐☐ Vet ikke ☐

SELVOPPLEVD HELSE

Oppfatter du din helse som:

☐ Meget god ☐ God ☐ Dårlig ☐ Meget dårlig

VEKT

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

Hva var din egen fødselsvekt som nyfødt baby?

(Gram) ☐☐☐☐ Vet ikke ☐

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

☐ Ja ☐ Nei Antall ganger ☐☐

FYSISK AKTIVITET

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

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

RØYK OG ALKOHOL

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

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

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

	Antall pr dag	Antall pr 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 o.l.)*	☐	☐	☐	☐	☐	☐	☐
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 o.l.)*	☐	☐	☐	☐	☐	☐
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 *(lør 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 *(lør 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 *(lør 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 *(lør 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 *(lør 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 *(lør 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 reslen av året	☐	☐	☐	☐	☐
Voksen vinter *(lør siste året)*	☐	☐	☐	☐	☐
Voksen resten av året *(lør siste året)*	☐	☐	☐	☐	☐

BARNEFAR

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

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

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

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

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

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

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

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

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

ANGÅENDE SPØRSMÅLENE

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

☐ Ja ☐ Nei

Andre kommentarer:

Takk for hjelpen!

Navn _____

ID ☐

Fødseldato for barnet ☐

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

Kontroll miljøgiftsprosjektet 6 uker etter fødselen

Dato ☐

Uker etter fødselen ☐

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

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

Ammestatus for prosjekt-barnet ved miljøgiftskontrollen 6 uker etter fødselen

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

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

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

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

Barnet var ☐ uker

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

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

Dato for utfylling av skjema ☐

Eventuelle kommentarer skrives på baksiden av arket

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

Tusen takk for hjelpen!

Navn _____

ID [ ]

Fødseldato for barnet [ ]

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

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

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

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

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

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Tusen takk for hjelpen!

Universitetet i Tromsø
Romssa universitehta

Forskningsprosjektet
Miljøgifter i svangerskapet og i ammeperioden

Tromsø, den 21. oktober 2009

Kjære NN

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

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

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

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

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

Igjen mange takk for hjelpen, og vi beklager bryderiet.

Med vennlig hilsen

Solrunn Hansen
prosjektkoordinator

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

ISM SKRIFTSERIE - FØR UTGITT:

1. Bidrag til belysning av medisinske og sosiale forhold i Finnmark fylke, med særlig vekt på forholdene blant finskættede i Sør-Varanger kommune.
Av Anders Forsdahl, 1976. (nytt opplag 1990)

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Av Anders Forsdahl, 1977.

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Av Jan-Ivar Kvamme og Trond Haider, 1979.

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Av Jan-Ivar Kvamme, 1980.

6. Til professor Knut Westlund på hans 60-års dag, 1983.

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Av Jan-Ivar Kvamme, Bernt Nesje og Anders Forsdahl, 1983.

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