Human exposure to pollutants and their health endpoints

The Arctic perspective

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Résumé : The most vulnerable period in a human life is before you are born and in early childhood. A number of reports and publications are now coming out of these studies and this chapter will go into details of some of the the most important studies and their defined health endpoints. Different epidemiological studies in the circumpolar area have shown associations between contaminants and different health outcomes. It is important to note that associations are not the same as causal relationships between exposure to a single substance (or a mix of substances) and an effect. When finding an association between a contaminant and an effect it is important to bear in mind the possibility that the studied substance are proxies for other substances in the mixture of contaminants to which the study population has been exposed – both harmful and beneficial. The effects reported are findings from different circumpolar communities. However, due to differences in genetic composition, socio-cultural practices, local food consumption patterns and exposure mixtures, a finding in one population should not be extrapolated to another population without careful investigation and comparative information.

Mots-clés : grossesse, naissance, santé environnementale, épidémiologie, arctique

1 The monitoring programs

The most comprehensive information we have about human exposure to contaminants in the Arctic has been collected, systematized, and presented in the different AMAP reports briefly described below.

Exposure to environmental contaminants through the traditional diet remains one of the risks to human health in the Arctic. Due to unique geographic and climatic characteristics, the Arctic has become a repository for contaminants transported long distances through the atmosphere and *via* ocean currents. These chemicals bioaccu-

mulate and biomagnify through Arctic food chains into the species that make up traditional food sources for many Arctic peoples. These Arctic populations traditionally rely on fish, terrestrial and marine mammals, as market foods are difficult to access or are not as nutrient-rich as traditional foods (Donaldson *et al.* 2010). Many of the marine mammals, some of which are top predators in the Arctic marine food Web, and some freshwater fish species tend to be the most highly contaminated with persistent, bioaccumulative chemicals. Biomonitoring studies are essential elements of the management of these risks, including the ability to analyze the risks and benefits for human populations which consume traditional food.

The AMAP 1998 report marked the first international, circumpolar report from the Arctic Monitoring and Assessment Programme (AMAP). Seven of the eight circumpolar countries (Canada, Denmark/Greenland/Faroe Islands, Iceland, Finland, Sweden, Norway, and Russia) contributed data to this report. Several polychlorinated biphenyls (PCBs), OCs, and metals were reported in different Arctic populations, both indigenous and non-indigenous.

The preliminary data identified in AMAP (1998) suggested that levels of POPs and methylmercury (MeHg) in breast milk and cord blood were two- to ten-fold higher than levels found south of the Arctic region. Despite worldwide risk management put in place for several POPs during the 1970s and 1980s, there seemed to be no evidence that levels in Arctic populations had decreased. Persistence, ubiquity and continued use in different parts of the globe contributed to continuous exposure levels for Arctic populations. This report was the first thorough report of human biomonitoring data for Arctic populations. While it could not provide temporal trends, it did provide the first Arctic-wide perspective (AMAP 2015).

Levels of hexachlorobenzene (HCB), mirex and three chlordane metabolites were markedly higher in Greenland and eastern Canadian Inuit maternal blood samples than in corresponding samples from the other participating countries. PCBs were highest in maternal blood samples from Greenland. Organochlorines such as β-hexachlorocyclohexane (β-HCH) and *p,p'*-dichlorodiphenyltrichloroethane (*p,p'*-DDT) were found to be higher in Russian populations than in populations examined from other countries, indicating potential uses in Russia or that these pesticides are being used on the food products consumed by these Arctic populations. Levels of *p,p'*-dichlorodiphenyldichloroethylene (*p,p'*-DDE) in Greenland and Russian populations were three to five times higher than those in other Arctic countries.

Greenland and Canada emerged as hotspots for metals, particularly mercury (Hg), lead (Pb) and cadmium (Cd). This exposure to Hg and Pb was attributed to specific traditional food consumption in these two populations in comparison with the food species consumed by populations in other parts of the Arctic; and smoking behavior was linked with levels of Cd.

Exposure levels found in the Arctic in this report were identified as being unacceptable. While temporal trends for Hg and Cd could not be determined from the data sets available, it was evident that Pb levels were decreasing in the Arctic in a similar

way as levels in the south, probably in response to the risk management action taken on Pb emissions, and the partial ban on lead shot.

The second AMAP human health assessment (AMAP, 2003) provided the first opportunity to compare contaminant levels over time, with the potential of multi-year data sets, especially in the Canadian and Greenlandic data sets for the maternal blood contaminant study. Data were submitted by all eight circumpolar countries. Fewer contaminants were reported in this report, but core contaminants of concern were consistently tested and reported in the Arctic countries, allowing for geographical comparison.

Levels of contaminants in blood samples from the populations living in the Arctic region again showed that certain POPs and Hg were high in Arctic people who consume certain traditional foods. Greenland Inuit mothers, in particular, were found to have levels of PCBs, HCB, total chlordanes and Hg higher than any other Arctic population. Russian non-indigenous populations had the highest levels of DDT and β-HCH; and elevated levels were also observed in Iceland and in the non-Caucasian, non-Dene/Métis, non-Inuit 'Others' group for the Canadian Arctic.

The third AMAP human health assessment report (AMAP, 2009) contained the first comparison of all Arctic regions in Russia as a part of the overall assessment. It provided some of the first trend data for particular OCs and metals. Data from Canada, Greenland, Iceland, Sweden, Finland and Russia showed that levels of contaminants such as PCBs, oxychlordane, and Hg were decreasing in a broad range of Arctic populations. It was apparent that the consumption of marine mammals as a part of a healthy traditional diet seemed to result in elevated contaminant levels in Inuit regions of Greenland and Canada.

A new set of contaminants were measured in the Arctic for this report. It was possible to report the levels of brominated flame retardants (BFRs) and perfluorinated compounds (PFCs) due to advances in detection techniques and methodologies. Levels of perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) were found throughout the Arctic and were elevated compared to other POPs. Polybrominated diphenyl ethers (PBDEs) were found at low levels across the Arctic, with the exception of high levels found in Alaska. Tetrabromobisphenol A (TBBPA) and hexabromocyclodecane (HBCD) had limited data but showed low blood levels. Concentrations of PFOS were significantly higher in consumers of fish and marine mammal meat in Nunavik, Canada. PBDEs were found to require more data before a source or trend could be identified. In general, more monitoring data were needed for the emerging contaminants, as some were very data-limited but anticipated to be of potential concern in the future.

Since the 2009 AMAP human health assessment, biomonitoring activities have continued in the eight Arctic countries. POPs and metals are still undergoing long-range transport to the Arctic, and are bioaccumulating and bioconcentrating within the Arctic food chains relied upon for a socially, economically, culturally and nutritionally beneficial traditional food supply. However, declines are beginning to be detected in certain Arctic populations, and public health interventions have been instituted ba-

sed on some of the biomonitoring results presented. Different contaminants are also being detected in the Arctic, indicating that new international risk management may be necessary. The use and production of PFCs started in the 1950s, increased during the 1970s, and continues today with PFCs still in demand in industrial and consumer applications (Nøst *et al.* 2014). Although PFCs do not bioaccumulate in fatty tissues, they are exhibiting similar behavior in terms of most other POPs, however the patterns for BFRs are slightly different. Further monitoring of BFRs is being pursued to identify their potential threat to Arctic populations.

2 Méthodological challenges

Since the first AMAP Human Health expert meeting in 1991, considerable efforts have been made to ensure the measurement of high quality human biomonitoring data for POPs and metals of concern to AMAP. The AMAP Human Health Assessment Group recommended in 2000 that a quality assessment (QA) program be established for POPs in human biological fluids (the AMAP Ring Test). The 2009 AMAP Human Health Assessment (AMAP 2009) described in detail the implementation and evolution of this external quality assessment scheme (EQAS), which has provided a means of comparing the quality of data produced by laboratories involved in the measurement of POPs in samples of human origin from Arctic countries (Weber 2002).

Since its inception in 2001, the scope of the AMAP Ring Test has changed to add or remove different POPs, with a substantial revision occurring in 2007 to add more POPs and also to modify the scoring system. The scheme now considers 37 analytes (11 pesticides, eight PBDEs, nine PCBs, six PFCs, total lipids, cholesterol and triglycerides). Several international EQAS already exist for metals in biological fluids, as well as a number of national schemes. Participation in the AMAP Ring Test by both AMAP and non-AMAP countries has fluctuated over the years. Currently, 32 laboratories are registered participants.

It is important for AMAP to present spatial and temporal trends of exposure with confidence and to demonstrate that the trends are not influenced unduly by analytical uncertainty. The AMAP Ring Test has thus established criteria for good (within 20% of target) and acceptable (within 40% of target) EQAS performance. Although fluctuations in individual performance are expected, the proportion of laboratories showing excellent or good performance generally increased between 2001 and 2007, often with pronounced improvements for some analytes (AMAP 2009). Ongoing participation in the AMAP Ring Test (or another suitable intercomparison program) is therefore highly encouraged, as this seems to have provided impetus for participating laboratories to examine and refine analytical procedures and organizational protocols necessary for meeting performance targets. All laboratories submitting data to this assessment were active participants in a QA/QC program.

We can now explore how contaminant levels are changing with time, with indications of differences between populations, geographical areas, and traditional practices. In doing so, insight is obtained about how international risk management efforts, dietary shifts, and risk communication interventions from public health officers and other officials may be affecting Arctic residents' exposure. For several Arctic countries,

there are now almost 20 years of biomonitoring data available to assess changes in contaminant concentrations.

3 The studies

This section will describe some of the most important ongoing trend and effect studies in the Arctic. More details are available in the recently released AMAP Human Health Assessment Report (AMAP 2015). The Arctic studies have the overall aim to provide compatible data independent of geographical or socioeconomic/cultural differences, which is still only partly fulfilled.

3.1 The MISA study of Northern Norway

The Northern Norway mother-and-child contaminant cohort study – the MISA study – is a cross-sectional study with longitudinal aspects aimed at establishing a new northern Norway mother-and-child contaminant cohort study. The MISA database is considered suitable for exploring associations between contaminant exposure and diet, enhancing understanding of the interplay between physiological changes that occur in mothers and contaminant pharmacokinetics (including transfer to the infant before and after birth), and conducting prospective health studies of the children (Hansen *et al.*, 2010 ; 2011 ; Veyhe *et al.*, 2012).

3.2 The Tromsø Study

The Tromsø Study is a population-based health survey initiated in 1974 to investigate the reasons for high mortality due to cardiovascular disease in northern Norway. Six surveys have been undertaken since 1974 and the health research topics included have increased. A total of 40,051 people have participated in at least one survey and 15,157 have participated in three or more surveys. The Tromsø Study was also used to explore changes in POP concentrations from 1979 to 2007 on an individual basis with a repeat measurement design. Serum samples were obtained from the freezer archive for 54 men who participated in all of the survey points : 1979, 1986, 1994, 2001, and 2007. The archived serum samples were analysed for PCBs, chlorinated pesticides, and per-and polyfluoroalkyl substances (PFASs).

The trends observed between 1979 and 2007 probably reflect the overall trends in the use and emission of the different POPs, together with compound-specific persistency, bioaccumulation potential and long-range transport. Study design and population characteristics must also be considered in monitoring studies. The Tromsø Study has increased knowledge of intra-individual variation in POP concentrations with respect to time and exposure history, which is essential for understanding past exposure and predicting future exposure. These findings have important implications for future studies of exposure and vulnerable groups (Nøst *et al.*, 2013 ; 2014).

3.3 Northern Finland 1966 Birth Cohort

There is information on the individuals born into the Northern Finland 1966 Birth Cohort in the provinces of Oulu and Lapland since the 24th gestational week as well as on their mothers and, to a lesser extent, fathers. A total of 12,058 live-born chil-

dren were born into the cohort (around 96% of all eligible) and 11,665 were alive in 1997. Data were collected by questionnaire, from hospital records and various registers and databases (social benefits, medication reimbursement, hospital discharges and deaths, community wealth), as well as by interview and clinical examination at birth, age 1 year and 14 years, and at age 31 years when a comprehensive follow-up was conducted on each subject's well-being, social standing and health. In 1997, all members of the cohort who lived in the provinces of Oulu and Lapland (n=7191) or who had moved to the capital region (n=1272) completed a questionnaire and underwent a health examination. Those living in other parts of the country (n=2164) or abroad (n=695) were also sent the questionnaire. In total, 8676 people returned the questionnaire, making a response percentage of about 77%. About 71% attended the health examination. Selected blood samples (n=250) from the 1997 sampling were analyzed for toxic and essential elements to establish levels in persons born and living for the last five years in the eastern and western part of Lapland (AMAP 2016).

3.4 The Chukotka studies

Data were collected in 2001–2003 in Chukotka (Russia) on PCB and DDT contamination of different local foods (and indoor materials). Exposure of indigenous people was evaluated by comparing pollutant levels in foods with levels in human blood in people living in coastal and inland regions (Dudarev *et al.*, 2012).

Levels of persistent toxic substances (PTS) in blood from 17 mothers and cord blood from the corresponding 17 babies born in the Chukotka coastal area in 2001–2002 were compared with PTS levels in blood sampled from the same women and their five-year old children in 2007 with the aim of examining the influence of breastfeeding on maternal POPs serum levels and the link between children's POPs blood levels and the frequency of infectious diseases (Dudarev *et al.* 2010 ; 2012).

In the period 2001–2002 126 indigenous pregnant women (68 coastal and 58 inland) were interviewed and gave blood samples in the Chukotka delivery departments. Births with adverse outcomes were observed in almost every fourth woman (23%) : premature births (22 cases) partially accompanied by low birth weight (13 cases), stillbirths (3 cases), and congenital malformations (3 cases – a heart defect and two multiple defects, one stillborn).

3.5 The Kola Lapland study 2001–2006

Interviews and blood samples of 4359 residents of Kola Lapland in Murmansk Oblast in 2006 (2736 rural and 1623 urban, including Sami – 694, Komi – 910, Nenets – 80) showed that risk of Type 2 diabetes (overweight/obesity, enhanced blood pressure, sedentary lifestyle, malnutrition, alcohol abuse) was 3–7 times lower in indigenous residents than non-indigenous residents. Among Sami people of the remote villages signs of diabetes were absent. Elevated levels of blood glucose were found mainly in large settlements. By all criteria of predisposition to diabetes mellitus, indigenous residents in remote villages demonstrate minimum risk levels, and this appears to reflect their traditional diet based on local foods, a physically active lifestyle, and minimal consumption of high carbohydrate foods (Dudarev *et al.*, 2012a).

3.6 The Nunavik Child Development Study

The primary objective of the Nunavik Child Development Study (NCDS) was to document the growth, neurobehavioral and cardiac effects of pre- and postnatal exposure to OCs with endocrine-disruptive properties, as well as to Hg and Pb. A secondary aim was to test whether nutritional variables, such as prenatal polyunsaturated fatty acid (PUFA) intake, breastfeeding, and childhood vitamin deficiency, mediate and/or mitigate the effects of environmental contaminants on health and development. The NCDS was made possible by the *Nunavik Cord Blood Monitoring Program,* through which exposure to environmental contaminants was determined from cord blood samples obtained from Nunavik infants born between 1994 and 2001 (Muckle *et al.*, 1998; Dallaire *et al.*, 2003).

3.7 The Inuit Cohort : Canada

The Nunavik Health Survey Qanuippitaa was conducted between 30 August and 1 October 2004 on the scientific research vessel CCGS *Amundsen.* The research group visited the 14 communities of Nunavik (www.qanuippitaa.com) and recruited 917 participants. Samples were analyzed for POPs that had also been determined during the 1992 Santé Québec Health Survey. Plasma concentrations of new halogenated hydrocarbons such as PBDEs, PFOS, hydroxy-PCBs, methyl-sulfone PCBs and chlorophenols were also determined.

The Inuit Health Survey (2007–2008) was a comprehensive study that included the measurement of dietary intake of contaminants, contaminant body burden, as well as other determinants of health and their relationship with health outcomes of the participants. It was the first time that such a complete set of data was collected in the Arctic. Of the 2595 individuals that participated in IHS, 2172 provided blood samples. The body burden of several metals (e.g. Cd, Pb) and POPs (e.g. PCBs, DDT, DDE, toxaphene, chlordane, PBDEs) were measured for Inuit participants (n=2172) from 36 communities in Nunavut, Nunatsiavut, and the Inuvialuit Settlement Region, in Canada (Laird *et al.*, 2013).

3.8 INUENDO

The INUENDO project :_ Biopersistent OCs in diet and human fertility _was supported by the European Union FP5 (www.inuendo.dk) (Bonde *et al.*, 2008). The cohort was established in 2002–2004 and involved about 1400 pregnant women from Greenland, Poland and Ukraine, as well as studies on about 600 previous pregnant fishermen's wives and fishermen.

The study included measurement of PCB153 and p,p'_-_DDE and bioeffect markers of serum legacy POP-induced estrogen- and androgen-receptor transactivity and epidemiological cross-sectional studies on male and female reproductive health on these individuals in relation to the measured exposures.

3.9 CLEAR

The CLEAR project : Climate Change, Environmental Contaminants and Reproductive health is supported by the European Union FP7 (www.inuendo.dk/clear). In

addition to modelling the effects of climate change on contaminant distribution to the environment, the project includes a series of cross-sectional studies on male and female reproductive health combined with a follow-up study on childhood growth and development at 6–9 years of age in a cohort of about 1400 mothers, fathers and offspring from Greenland, Poland and Ukraine. The original INUENDO cohort was established in 2002–2004 and a follow-up on the children was undertaken in 2010–2012.

3.10 Cohorts in the Faroe Island

A cohort of 1022 singleton births was assembled in the Faroe Islands during a 21-month period in 1986 and 1987 (Grandjean *et al.*, 1992). Frequent whale meat dinners during pregnancy, frequent consumption of fish (to a much lesser degree) and increased parity or age were associated with high Hg concentrations in cord blood and maternal hair. Mercury concentrations in cord blood correlated moderately with blood-selenium. Lead concentrations in cord blood were low (median, 82 nmol/L). Because the effects of fetal childhood exposure to MeHg are persistent, detailed examination of children with prenatal exposure to this neurotoxicant were perfomed at age 7 years (1993–1994). A total of 917 of the children (90.3%) completed the examinations. Past medical history, current health status and social factors were recorded on a self-administered form. The physical examination included a functional neurological examination with emphasis on motor coordination and perceptual-motor performance. The main emphasis was placed on detailed neurophysiological and neuropsychological tests that had been selected on the basis of a range of considerations (Grandjean *et al.*, 1997 ; 2012a).

The findings from the first cohort suggested that exposure assessment should encompass several lipophilic pollutants in addition to MeHg. A follow-up cohort was therefore established during a 12-month period in 1994–1995 and included 182 singleton term births from consecutive births at the National Hospital in Tórshavn, Faroe Islands. Relevant obstetric data were obtained by standardized procedures and supplemented by a brief nutrition questionnaire.

New insight into health risks caused by environmental pollutants and changing exposure patterns in the Faroes lead to the formation of Cohort 3 from 656 consecutive births in Tórshavn between November 1997 and March 2000. Following dietary recommendations from the Faroese health authorities, MeHg exposure had now decreased thus allowing better characterization of possible effects of PCBs and other persistent contaminants. Additional attention was turned to the perfluorinated compounds (PFCs), as they have been documented as contaminants of marine food chains with possible toxicity to the immune system. The most recent cohort was born during an 18-month period between October 2007 and April 2009. The total of mother-child pairs included was 475 (73% of the eligible population). Blood was taken from the cord, and blood, hair, and milk were obtained from the mother (AMAP 2016).

4 Effects discussed in the different studies, single compouds or combined effects

4.1 Neurological effects

Mercury : The cohort studies in the Faroe Islands have demonstrated that children exposed to methylmercury (MeHg) *in utero* exhibit decreased motor function, attention span, verbal abilities, memory, and other mental functions (Grandjean *et al.*, 1997). The effects are dose-dependent : the greater the mercury (Hg) exposure, the greater the effect. A follow-up of these children at ages 14 and 22 years showed the deficits appear to be permanent (Debes *et al.*, 2006). Overall, a doubling of the prenatal Hg exposure of a child resulted in a developmental delay of one to two months at the age of 7 years ; the age when the child is expected to enter school. This delay corresponds to about 1.5 IQ points (Grandjean and Herz 2011).

In the Nunavik Child Development Study (NCDS) the children were followed up at age 11 years. The results show that Hg was associated with : poorer early processing of visual information ; alteration of attentional mechanisms modulating processing of sensory information ; lower estimated IQ ; poorer comprehension and perceptual reasoning ; poorer immediate memory and recollection of information stored into memory ; and increased risk of attention problems and attention deficit hyperactivity disorder (ADHD) behavior.

In the Nunavik study, prenatal Hg was related to poorer IQ after adjustment for exposure to the other contaminants assessed, to docosahexaenoic acid (DHA) and selenium, and to the other potentially confounding variables. The Hg effect became stronger when cord DHA was also considered, indicating that the beneficial effect of prenatal DHA statistically suppresses the adverse effects of prenatal Hg exposure. Verbal comprehension and perceptual reasoning were indices most sensitive to prenatal Hg exposure.

Some of the adverse effects of MeHg on neurodevelopment may be masked by beneficial effects of seafood nutrients (Budtz-Jorgensen *et al.*, 2007). On the other hand, the benefits from seafood nutrients may be consumed or cancelled by the Hg toxicity. Thus, full benefit from fish and seafood diets requires that MeHg exposure is minimized. Given the continued development of the nervous system after birth, postnatal exposure to MeHg is also likely to cause adverse effects. Neurophysiological assessment of brain function supports the notion that postnatal exposure up to the teenage years can cause harm (Murata *et al.*, 2004). Thus, both pregnant women and children should be considered populations at increased risk (Grandjean 2013).

Adverse effects may also include aspects of brain function other than cognitive achievement. In the NCDS (Nunavik 2005–2010), exposure to contaminants was measured at birth and at school age. An assessment of child behavior (n=279 ; mean age = 11.3 years) was obtained from the child's classroom teacher on the Teacher Report Form (TRF) from the Child Behavior Checklist, and the Disruptive Behavior Disorders Rating Scale (DBD). Cord blood Hg concentrations were associated with higher TRF symptom scores for attention problems and DBD scores consistent with ADHD. This appears to be the first study to identify an association between prena-

tal MeHg and ADHD symptomatology in childhood (Boucher *et al.* 2012). Likewise, cross-sectional evidence links MeHg exposure to autism spectrum disorder (Geier *et al.*, 2012). However, the evidence available is limited and so conclusions regarding autism or ADHD must be drawn with caution.

Mercury may also negatively affect other aspects of human neurological health. Some research suggests that MeHg neurotoxicity may spur the development of degenerative diseases of the nervous system, such as Parkinson's disease (Petersen *et al.*, 2008).

Effects associated with MeHg exposure have been documented in humans at lower and lower exposures. This tendency reflects the use of better study design, larger groups of subjects examined, more sensitive methodology and better control of confounding factors that may influence study outcome. From the evidence available, it is clear that the developing brain is the most vulnerable organ system. Given the complexity of brain development and the difficulties in determining detailed functions, especially in small children, it is likely that future studies will continue to identify effects at lower exposures than those considered safe today.

Lead and mixed metal exposures : Few studies have examined the effects of mixed metal exposures in humans. In one of the Faroese birth cohorts the effect of prenatal lead (Pb) exposure in the presence of similar molar-level exposure to MeHg was evaluated (Yorifuji *et al.*, 2011). A cohort of 1022 singleton births was assembled during 1986–1987 and Pb was measured in cord blood. A total of 896 cohort subjects participated in a clinical examination at age 7 years and 808 subjects in a follow up at age 14 years. The association between cord-blood Pb concentration and cognitive deficits (attention/working memory, language, visuospatial, and memory) using multiple regression models was evaluated. Overall, the Pb concentration showed no clear pattern of association. However, in subjects with a low MeHg exposure, Pb-associated adverse effects on cognitive function were observed. Some interaction terms between Pb and MeHg suggested that the combined effect of the exposures was less than additive.

Persistent organic pollutants : Grandjean *et al.* (2012a) analyzed banked cord blood from a Faroese birth cohort to determine the possible neurotoxic impact of prenatal exposure to polychlorinated biphenyls (PCBs). The subjects were born in 1986–1987, and 917 cohort members completed a series of neuropsychological tests at age 7 years. Major PCB congeners (PCB118, PCB138, PCB153, PCB180), the calculated total PCB concentration, and the PCB exposure estimated in a structural equation model showed weak associations with test deficits, with statistically significant negative associations only with the Boston Naming test. Likewise, neither hexachlorobenzene (HCB) nor *p,p'*-dichlorodiphenyldichloroethylene (*p,p'*-DDE) showed clear links with neurobehavioral deficits. Thus, these associations were much weaker than those associated with cord-blood Hg concentration, and adjustment for Hg substantially attenuated the regression coefficients for PCB exposure. When the outcomes were merged into motor and verbally mediated functions in a structural equation model, the PCB effects remained weak and virtually disappeared after adjusting for MeHg exposure, while Hg remained statistically significant. Thus, in the presence of elevated MeHg exposure, PCB neurotoxicity may be difficult to detect, and PCB exposure does not

explain the MeHg neurotoxicity previously reported in this cohort (Grandjean *et al.*, 2012a).

Immunological effects : certain environmental pollutants can adversely affect the development of the immune system (Dewailly *et al.*, 1993 ; Weisglas-Kuperus *et al.*, 1995 ; 2000 ; Chao *et al.*, 1997 ; Dewailly *et al.*, 2000 ; Vine *et al.*, 2001 ; ten Tusscher *et al.*, 2003 ; Jusko *et al.*, 2010).

The high incidence of infectious diseases – particularly meningitis, broncopulmonary infections, and middle ear infections – in young children from Nunavik has been known for many years (Dufour 1988). In view of the immunotoxic properties displayed by some organochlorines (OCs), in particular following perinatal exposure, it has been hypothesized that part of the high infection incidence among Inuit infants could be related to the relatively high maternal body burden of these contaminants, and their partial transfer to newborns during breastfeeding. To test this hypothesis, three epidemiological studies have been conducted during the past 20 years in Arctic Quebec to investigate the relationship between pre- or postnatal OC exposure, immune status, and the occurrence of infectious diseases among Inuit infants. Results in three different groups of Inuit children indicated that prenatal exposure to OCs increases susceptibility to infectious diseases, and in particular to otitis media (Dewailly *et al.*, 2000 ; Dallaire *et al.*, 2004 ; 2006). Although potential confounding factors were considered in the statistical analyses, residual confounding is still a possibility.

The Faroese studies are the first to provide epidemiological data on human immunotoxicity – as reflected by a reduction in serum antibody production after routine childhood immunizations – in relation to developmental exposures to environmental chemicals (Heilmann *et al.* ; 2006 ; 2010 ; Grandjean *et al.*, 2012b). The studies showed that developmental and perinatal exposure to PCBs and PFCs from marine food and other sources may inhibit immune function, as indicated by deficient serum concentrations of antibodies against childhood vaccines. Results from the Faroe Islands show that the risk of having an antibody concentration below 0.1 IU/mL at age 7 years increased at higher levels of exposure to PCBs and PFCs. The results suggest that PFCs have an even stronger negative effect than PCBs on serum-antibody concentrations (Heilmann *et al.*, 2006 ; 2010 ; Grandjean *et al.*, 2012b). For PCBs, a doubling of the serum concentration at age 18 months was associated with a decline of 20% in the antibody level at age 7 years. After the completion of breastfeeding and associated transfer of PCBs, the child at age 18 months has an average serum-PCB concentration similar to that of the mother (Heilmann *et al.* ; 2010), after which the concentration declines as the body lipid compartment continues to expand. For PFCs, the recent accumulation was found to be the most important predictor of immunotoxicity : A doubling in serum-PFC concentration measured at age 5 years was linked to a decrease of up to 50% in the antibody concentration at age 7 years ($p<0.001$). Due to the long half-life of PFCs (Olsen *et al.*, 2007), serum concentrations at early school age are expected to be relatively stable.

In conclusion, elevated exposure to PCBs and PFCs in Faroese children was associated with reduced humoral immune response to routine childhood immunizations (Heilmann *et al.*, 2006 ; 2010 ; Grandjean *et al.*, 2012b). These findings suggest a de-

creased effect of childhood vaccines and may reflect a more general immune system deficit. The clinical implications of insufficient antibody production emphasize the need to prevent immunotoxicant exposure and assessment of risk related to exposure to these contaminants

5 Reproductive effects

In 1992, Carlsen and co-workers published a combined analysis of results from 61 papers published between 1939 and 1991 and showed a significant decline in sperm count over the 50-year period. A detailed reanalysis of the results found that this conclusion was supported by the underlying studies (Swan *et al.*, 1997 ; 2000). Following the 1992 publication, many researchers retrospectively analyzed their historical data for temporal trends, some finding a decline and others not.

The causes of decreased semen quality are not clear, but it is feasible that many cases may have been caused by exposure to environmental factors *in utero*, during adolescence or in adulthood (Joensen *et al.*, 2008) ; probably also influenced by different genetic susceptibility.

The median sperm concentration of fertile men in a semen quality study conducted in Greenland in 2004 was 53 million/mL, with a median sperm cell volume of 3.2 mL, a total sperm count of 186 million and a median motility of 60% (Toft *et al.*, 2004). No regional difference was found in sperm count, but sperm cell motility differed among regions. In a following study, Toft *et al.* (2006) found that sperm concentration was not impaired by increasing serum PCB153 or *p,p'*-DDE levels in Greenlanders. Also, that there was no association between the proportion of morphologically normal sperm and either PCB153 or *p,p'*-DDE concentration in blood. However, sperm motility was inversely related to PCB153 concentration in this population.

In a recent study on testicular function in the Faroe Islands, Halling *et al.* (2013) found sperm concentrations for Faroese men to be lower than for Danish men (crude median 40 vs 48 million/mL, $p<0.0005$). However, because semen volume was higher in the Faroese men, the total sperm counts did not differ (159 vs 151 million, $p=0.2$). Similarly, there was no overall difference between the two populations in terms of sperm motility or morphology. Recent data have shown sperm count to be low in young men from several European countries, but slightly higher than among the Danes (Jorgensen *et al.*, 2002 ; Punab *et al.*, 2002 ; Richthoff *et al.*, 2002). This indicates that semen quality for both Danish and Faroese men seems to be low compared to men from other European countries.

The reason for low testicular function in the Faroese young men is unclear, but could be due to high exposure to persistent organic pollutants (POPs). Studies have shown associations between high PCB levels and low semen quality, and since PCBs and *p,p'*-DDE have the potential to interfere with sex hormone functions, it could be assumed that these compounds can affect the function of the testicles (Elzanaty *et al.*, 2006). Some reports on the effect of POPs on male reproduction in humans indicate weak negative effects on sperm motility (Hauser *et al.*, 2002 ; Richthoff *et al.*, 2003 ; Elzanaty *et al.*, 2006). Among the Faroese men the present study found the percentage of motile

cells to be significantly lower compared to Danish men, indicating that increased exposure to endocrine disruptors may be one explanation for the difference.

Serum steroid hormone-binding globulin (SHBG) levels for the Faroese men were much higher than for the Danes. One explanation could be the high PCB levels among the Faroese. Grandjean *et al.* (2012c) reported that SHBG increased at higher PCB exposure, both prenatally and later in life. Because PCBs are known to affect a number of liver functions it may be that PCB-induced hepatic SHBG synthesis could play a role, although this remains to be confirmed (Grandjean *et al.*, 2012c).

5.1 Cardiovascular effects

Mercury : possible cardiovascular effects of Hg have recently emerged in the scientific literature (Roman *et al.*, 2011). A growing body of evidence suggests that MeHg exposure can increase risk of adverse cardiovascular impacts in exposed populations. The link between MeHg and acute myocardial infarction or sudden cardiac death is still debated in low Hg exposed populations (Mozaffarian *et al.*, 2011 ; Virtanen *et al.*, 2012).

Contradictory results have been reported on Hg exposure and the risk of hypertension (Mozaffarian *et al.*, 2012). In Nunavik adults, a retrospective analysis of the 1992 survey reported no association between Hg and high blood pressure (Valera *et al.*, 2013). Based on the 2004 data, however, Hg was associated with increased blood pressure and pulse pressure (Valera *et al.*, 2008 ; 2009). In the Faroe Islands, high blood pressure was found to be associated with Hg exposure among male whale hunters (Choi *et al.*, 2009). In Greenland, no association was found between Hg exposure and high blood pressure (Nielsen *et al.*, 2012). Associations between Hg exposure and blood pressure were also studied in children. Associations were reported between prenatal Hg exposure and lower systolic blood pressure in 7-year-old Faroese children (Sorensen *et al.*, 1999) and for lower diastolic blood pressure in the Seychelles (Thurston *et al.*, 2007). In Nunavik children, no association was found between blood pressure and either cord blood or contemporary Hg exposure at age 11 years (Valera *et al.*, 2012).

Heart rate variability has also been studied in Arctic populations. An association was reported between Hg exposure and decreased heart rate variability in adults from Nunavik (Valera *et al.*, 2008). Similar results were reported among James Bay Cree adults (Valera *et al.*, 2011). In children from Nunavik, cord blood Hg concentrations were not related to heart rate variability parameters at age 11 years, but child blood Hg levels were associated with decreased overall heart rate variability parameters, and these associations remained significant after adjusting for cord blood Hg, *n*-3 polyunsaturated fatty acids (PUFA) and selenium. In Faroese children, cord Hg concentrations were related to hear rate vartiabiloity at age 7 years as well as 14 years, and hair Hg at age 7 years was associated with a low frequency variation coefficient (Grandjean *et al.*, 2004).

The predictive value of heart rate variability parameters in healthy children and risk of chronic diseases is unknown. Nevertheless, results from the Faroese and Nunavik cohorts provide evidence that Hg exposure during childhood is related to changes in cardiac autonomic activity at school age.

Endocrine effects : environmental chemicals have significant impacts on biological systems. Exposure during early stages of fetal and neonatal development is especially critical and can disrupt the normal pattern of development and thus dramatically alter disease susceptibility in later life. Endocrine-disrupting chemicals are those that interfere with the body's endocrine system and so result in adverse developmental, reproductive, neurological, cardiovascular, metabolic and immune effects in humans. An endocrine-disrupting chemical is defined as 'an exogenous substance or mixture, that alters the function(s) of the endocrine system, and consequently causes adverse health effects in an intact organism or its progeny or \textsubscript{-population' (Schug *et al.*, 2011). Thus they are compounds that can mimic, interfere with or block the function of endogenous hormones and thereby disrupt the normal hormone homeostasis of the body. Growing evidence shows that endocrine-disrupting chemicals may also modulate the activity and/or expression of steroidogenic enzymes, having the ability to convert circulating precursors into active hormones as well as to affect hormone metabolism and transport through the body (Yang *et al.*, 2006 ; Schug *et al.*, 2011).

5.2 Impact on the hypothalamo-pituitary-gonadal axis

Exposure to POPs may have a negative impact on reproductive function *via* impact on the hypothalamo-pituitary-gonadal axis. A study of reproductive hormones in men from Greenland and three European cohorts (Swedish fishermen, Warsaw Poland, Kharkiv Ukraine) *(Bonde* et al.*, 2008)* reported significant variations in associations between exposure to PCB153 and *p,p'*-DDE and the outcomes. For the Kharkiv group, statistically significant positive associations were found between levels of both PCB153 and *p,p'*-DDE and steroid hormone-binding globulin, as well as luteinizing hormone, while for the Greenlandic Inuit men there was a positive association between PCB153 exposure and luteinizing hormone. In the pooled data set from all four centers, there was a positive association between *p,p'*-DDE and FSH levels ($\beta = 1.1$ IU/L ; 95% CI : 1.0–1.1 IU/L), whereas the association between PCB153 and SHBG was of borderline statistical significance ($\beta = 0.90$ nmol/L ; 95% CI : -0.04 to 1.9 nmol/L). The authors concluded that gonadotropin levels and SHBG seem to be affected by POPs exposure, but that the pattern of endocrine response is the subject of considerable geographic variation (Giwercman *et al.*, 2006).

Studying differences between men living south and north of the Arctic Circle in Norway, Haugen *et al.* (2011) found no geographical differences in either mean levels of PCB153 (50 vs 59 ng/g lipid ; p=0.27) or sperm parameters. However, mean levels of *p,p'*-DDE were higher in the south than the north (81 vs. 66 ng/g lipid ; p=0.02), as were levels of total and free testosterone. Moreover, FSH levels were lowest in the south. A strong relationship was observed between PCB153 and SHBG levels. The regional differences observed for *p,p'*-DDE, testosterone and FSH were not reflected in semen quality.

In the Faroe Islands, where PCB exposure is elevated, Grandjean *et al.* (2012c) studied the possible endocrine disruption of PCBs on 438 adolescent boys from a birth cohort by measuring PCB and *p,p'*-DDE levels in cord blood and serum from clinical examination at age 14 years. Higher prenatal PCB exposure was associated with

lower serum concentrations of both luteinizing hormone and testosterone. In addition, SHBG was positively associated with both prenatal and concurrent PCB exposure. The PCB–SHBG association was robust to covariate adjustment. In a structural equation model, a doubling in prenatal PCB exposure was associated with a decrease in luteinizing hormone of 6% (p=0.03). Prenatal exposure to PCB and DDE showed weak, non-significant inverse associations with testicular size and Tanner stage. DDE was highly correlated with PCB and showed slightly weaker associations with the hormone profile. The findings suggest that delayed puberty with low serum-LH concentrations associated with developmental exposure to non-dioxin-like PCBs may be due to a central hypothalamo-pituitary mechanism.

5.3 Impact on the hypothalamo-pituitary-thyroid axis

Dallaire et al (2008) investigated the potential impact of transplacental exposure to PCBs and HCB on thyroid hormone concentrations in neonates from two remote coastal populations in Canada ; one in Nunavik (n=410) and one on the Lower North Shore of the St. Lawrence River (n=260). Both populations were exposed to OCs through seafood consumption. Cord blood samples were analyzed for thyroid parameters (TSH ; free T4, fT4 ; total T3, tT3) and contaminants. PCB153 was not associated with thyroid hormone and TSH levels in either population. Prenatal exposure to HCB was positively associated with fT4 levels at birth in both populations (Nunavik, $\beta = 0.12$, $p = 0.04$; St. Lawrence, $\beta = 0.19$, $p < 0.01$), whereas thyroxine-binding globulin concentrations were negatively associated with PCB153 concentrations ($\beta =$ -0.13, $p = 0.05$) in the St. Lawrence cohort. Thus OC levels were not associated with a reduction in thyroid hormones in neonates from the two populations. Essential nutrients derived from seafood such as iodine may have prevented the negative effects of OCs on thyroid function during fetal development. Dallaire *et al.* (2009) studied the relationship between exposure to potential thyroid hormone-disrupting toxicants and thyroid hormone status in pregnant Inuit women from Nunavik and their infants within the first year of life. In pregnant women, they found a positive association between hydroxylated metabolites of PCBs and total triiodothyronine (T(3)) concentrations ($\beta = 0.57$, $p = 0.02$). In umbilical cord blood, PCB153 concentrations were negatively associated with thyroxine-binding globulin levels ($\beta =$ -0.26, p=0.01). In a subsample analysis, a negative relationship was also found between maternal pentachlorophenol levels and cord free thyroxine (fT(4)) concentrations in neonates ($\beta =$ -0.59, p=0.02). No association was observed between contaminants and thyroid hormones at 7 months of age. The authors concluded that there is little evidence that the environmental contaminants analyzed in their study affect thyroid hormone status in Inuit mothers and their infants. The possibility that pentachlorophenol may decrease thyroxine levels in neonates requires further investigation.

Audet-Delage *et al.* (2013) studied whether exposure to POPs might decrease the circulating concentrations of T4 bound to transthyretin (TTR) in Inuit women of reproductive age in Nunavik Canada. Hydroxylated PCBs, pentachlorophenol and PFOS compete with T4 binding sites on TTR. The data suggested that circulating levels of TTR-binding compounds were not high enough to affect TTR-mediated thyroid

hormone transport. However, the authors suggested that the possibility of increased delivery of these compounds to the developing brain requires further investigation.

In a study on the relationship between exposure to POPs and anti-thyroid peroxidase antibody (TPOAb), Schell *et al.* (2009) assessed thyroid dysfunction of 115 young adults of the Akwesasne Mohawk Nation tribe. Overall, 18 participants (15.4%) had TPOAb levels above the normal laboratory reference range (23% of females, 9% of males). Among participants who were breast fed (n=47), those with an elevated TPOAb level had significantly higher levels of all PCB groupings, with the exception of levels of non-persistent PCBs which did not differ significantly. Levels of *p,p'*-DDE were also significantly elevated, while HCB and Mirex were not higher among those with elevated TPOAb. Also, after stratifying by breast-feeding status, participants who were breast fed showed significant, positive relationships between TPOAb levels and all PCB groupings, except groups comprising non-persistent PCBs, and with *p,p'*-DDE, HCB, and Mirex. No effects were evident among non-breast-fed young adults.

Bloom *et al.* (2014) observed an association between POPs and thyroid hormones in aging residents of upper Hudson River communities (48 women, 66 men, aged 55–74). The POPs included 39 PCBs, DDT and DDE and nine PBDEs. Among women, DDT+DDE increased T4 by 0.34 μg/dL (p=0.04) and T3 by 2.78 ng/dL (p=0.05). Also in women, ΣPCBs in conjunction with PBDEs elicited increases of 24.39–80.85 ng/dL T3 (p<0.05), and ΣPCBs in conjunction with DDT+DDE elicited increases of 0.18–0.31 μg/dL T4 (p<0.05). For men, estrogenic PCBs were associated with a 19.82 ng/dL T3 decrease (p=0.003), and the sum of estrogenic PCBs in conjunction with DDT+DDE elicited an 18.02 ng/dL T3 decrease (p=0.04). The authors suggested that the influence of POPs on thyroid hormones in aging populations may have clinical implications and merits further investigation.

5.4 Persistent organic pollutants and Type 2 diabetes

Several descriptive epidemiology studies suggest that certain POPs can contribute to the development of Type 2 diabetes (Carpenter *et al.*, 2002; Patel *et al.*, 2010). Although many POPs have now been banned, exposure continues for the most persistent, such as the PCBs and the pesticide metabolite *p,p'*-DDE. Other persistent environmental chemicals still in current use are suspected to be diabetogenic, for example the brominated flame retardants and perfluorinated compounds. Most of the recent epidemiological evidence is from cross-sectional case-control studies, where increased serum POP concentrations were found to be a major determinant of diabetes (Everett and Matheson 2010) and metabolic syndrome (Lee *et al.*, 2007). Genetic predisposition to Type 2 diabetes seems to play a role, but most genetic variants so far identified are associated with β-cell function and account for no more than about 10% of the risk. Thus it is very likely that POP exposure may trigger gene–environment interactions with effects on insulin resistance and/or secretion.

In the Faroe Islands, 713 septuagenarians with a high POP exposure owing to a traditional diet (including pilot whale blubber), were examined for indicators of glucose metabolism in subjects free of Type 2 diabetes and pre-diabetes (impaired fasting

glycaemia) (Grandjean et al, 2011). Results showed that the fasting insulin concentration decreased by about 8% for each doubling of the serum concentration of PCBs, and that a similar increase occurred in the fasting glucose level. Along with higher PCB exposure in subjects with Type 2 diabetes and impaired fasting glycaemia, the results suggest that PCB-induced β-cell deficiency may be involved in the disease pathogenesis. Impaired insulin secretion appears to constitute an important part of the Type 2 diabetes pathogenesis associated with exposure to persistent lipophilic food contaminants).

Individuals with vitamin D levels below 50 nmol/L doubled their risk of newly diagnosed Type 2 diabetes. Thus, in elderly subjects, vitamin D may provide protection against Type 2 diabetes (Dalgard *et al.*, 2011). The high prevalence of low vitamin D levels among the elderly Faroese population (19% with <25 nmol/L) reflects the low skin synthesis during most months of the year, which is caused by limited sun exposure and insufficient intake of marine diet (Dalgard *et al.*, 2010).

5.5 Carcinogenic effects

Throughout the 20th century, the cancer patterns of the Inuit population have been characterized by a high risk of Epstein-Barr virus (EBV)-associated carcinomas of the nasopharynx and salivary glands, and a lower risk of tumors common in Caucasian populations, including cancer of the breast, prostate, testis, and hemopoietic system. Both genetic and environmental factors seem to be responsible for this pattern. Over the past 50 years, Inuit societies have undergone major changes in lifestyle and living conditions. The incidence of traditional Inuit cancers (nasopharynx and salivary glands cancer) has remained relatively constant, whereas the incidence of lifestyle-associated cancers, especially cancer of the lung, breast, stomach and colorectal has increased considerably following changes in lifestyle (smoking, alcohol), diet, and reproductive factors (Friborg and Melbye 2008).

A comparison of cancer incidence patterns between residents of Inuit Nunangat and the rest of Canada showed the age-standardized incidence rate for all cancer sites (1998–2007) to be 14% lower for the Inuit Nunangat male population and 29% higher for the female population compared to the rest of Canada (Carriere *et al.*, 2012). Cancers of the nasopharynx, lung and bronchus, colorectal, stomach (males), and kidney and renal pelvis (females) were elevated in the Inuit Nunangat population compared to the rest of Canada, whereas prostate and female breast cancers were lower. As well as higher smoking prevalence within Inuit Nunangat, distinct socioeconomic characteristics between the respective populations (including housing and income) may have contributed to the incidence differentials (Carriere *et al.*, 2012).

Some cancer incidence in Greenland is several times higher compared to Denmark, such as nasopharyngeal, esophagus, biliary, ventricle, cervical, lung, liver, pancreas and colorectal cancer, respectively (AMAP 2015).

A study showed that the indigenous coastal Chukchi and Inuit living in Chukotka (Russia) were at higher risk of death from cancer during 1961–1990 than the Russian population nationally, with age-standardized cancer mortality among men twice that of Russia in general, and among women 3.5 times higher. The difference is due to the

particularly high mortality from esophageal cancer and lung cancer in the indigenous people of coastal Chukotka. The mortality data from this study correspond to the pattern of incidence reported among other indigenous people of the Russian Arctic (Dudarev *et al.*, 2012a). The incidence of colorectal cancer is currently higher in Alaskan Inuit than in Caucasians living in the United States (Friborg and Melbye 2008). Cancer is now the leading cause of death among Alaska Native people, and cancer mortality rates in Alaska are significantly higher than in the mainland United States (Lanier *et al.*, 2008).

5.6 Lung cancer

The incidence of lung cancer has increased remarkably in all Inuit populations over the past 40 years. Lung cancer now constitutes about 20% of all cancers in Inuit (Friborg and Melbye 2008). In fact, lung cancer incidence in circumpolar Inuit is among the highest in the world, for men and women. The age-standardized incidence rate of lung and bronchus cancer during 1998–2007 of male Inuit from Nunangat was 113 per 100,000 which is double that for the rest of Canada (50.6 per 100,000) (Carriere *et al.*, 2012). Greenland Inuit have double the standardized incidence rate of lung cancer in Denmark. The smoking pattern among Inuit, possibly combined with co-factors related to environment and diet, are believed to be the relevant causal factors (AMAP 2015). Although modern housing conditions have decreased exposure to fumes from lamps and open fires for cooking, many Inuit still spend substantial periods out on the land, cooking on open stoves inside tents. Marijuana smoking in 85% of adults (of Nunavik, Canada) might also play a role in the high incidence of lung cancer (AMAP 2016).

A cross-sectional study of Alaska Natives has demonstrated the importance of genetic variation in *CYP2A6* on the regulation of tobacco consumption behavior, procarcinogen exposure and metabolism in both light smokers and smokeless tobacco users (Zhu *et al.*, 2013).

5.7 Breast cancer

Breast cancer is the most common cancer for women in the western world. The established risk factors include genetic inheritance, for example mutations in the *BRCA-1* and *BRCA-2* genes (Ferla *et al.*, 2007), lifelong exposure to estrogens (early menarche and late menopause increases risk), obesity after menopause, alcohol, smoking and high fat intake. Although breast cancer risk is influenced by genetics and reproductive history, the known risk factors explain less than a third of all cases and more than 70% of women diagnosed with breast cancer have no inherited or sporadic cancer. Risk is thought to be modified by lifestyle and environmental exposure (Madigan *et al.*, 1995). Although still lower, incidence is now approaching incidences recorded in Western populations (Friborg *et al.*, 2003) and today about 12 to 15 women are diagnosed every year in Greenland. From 1988 to 1997, the age-adjusted incidence rate for women in Greenland was 46.4 per 100,000. For comparison, the rate in the United States was 124 per 100,000 for 2001 to 2008 and in Denmark about 100 per 100,000 in 2010 (Fredslund and Bonefeld-Jørgensen 2012). The age-adjusted incidence rate for breast cancer in Inuit Nunangat was lower than for the rest of Canada (45 vs

81 per 100,000) (Carriere *et al.*, 2012). Although there is no significant difference in breast cancer rate between Alaska Native women and U.S. white women, a significant increase in Alaska Native women was reported during 1974–2003 (Day *et al.*, 2010).

Breast cancer incidence in the Arctic increased between 1969 and 2003 (Fredslund and Bonefeld-Jørgensen 2012). The enormous transition in health conditions and lifestyle in the Arctic might be contributing to the known risk factors. Previous data suggest that exposure to POPs including PFCs might contribute to breast cancer risk. PCBs have been associated with effects relevant breast cancer development such as estrogenic, tumor promotion (Moysich *et al.*, 2002). Rat studies showed that PFCs cause a significant increase in mammary fibroadenomas (Sibinski, 1987). Bonefeld-Jørgensen *et al.* (2011) evaluated the association between serum levels of POPs/PFCs in 31 cases of breast cancer in Greenlandic Inuit and 115 controls during 2000–2003 to establish whether the combined POP-related effect on nuclear hormone receptors affects risk. Serum levels of POPs, PFCs, some metals and the combined serum POP-related effect on ER-, AR- and AhR-transactivity were determined. For the very first time a significant association between serum PFC levels and the risk of BC was observed. The breast cancer cases also showed a significantly higher concentration of PCBs at the highest quartile. Also, for the combined serum legacy POP-induced agonistic AR transactivity a significant association with breast cancer risk was found, and cases elicited a higher frequency of samples with significant POP-related hormone-like agonistic ER transactivity. The level of serum POPs, particularly PFCs, might be a risk factor in the development of breast cancer in Inuit. Hormone disruption by the combined serum POP-related xenoestrogenic and xenoandrogenic activities may contribute to the risk of developing breast cancer in Inuit (Bonefeld-Jørgensen *et al.*, 2011).

5.8 Ovarian cancer and prostate cancer

The etiology of ovarian cancer is not fully understood. Previous results support the hypothesis of long-term elevated estrogen concentrations as etiologically important for this disease (Spillman *et al.*, 2010). For Arctic populations, the age-standard incidence rate of ovarian cancer among Alaska Native women was significantly lower than for U.S. white women (5.2 vs.10.5 per 100,000) in 1999–2003.

Risk of prostate cancer in Inuit is 10–20% of the risk in the respective national white population (Friborg *et al.*, 2003; Snyder *et al.*, 2006). A recent study showed that the age-standard incidence rate for prostate cancer during 1998–2007 was lower in the Inuit Nunangat population than in the rest of Canada (17 vs. 85 per 100,000) (Carriere *et al.*, 2012).

5.9 Pancreatic cancer

A comprehensive meta-analysis has suggested that tobacco smoking, obesity, Type 2 diabetes mellitus and chronic pancreatitis are risk factors for pancreatic cancer. Kirkegaard (2012) reported that the age-standardized incidence rate for pancreatic cancer is 138% higher in Greenland Inuit than in Denmark. This could be partly explained by a higher prevalence of smoking and Type 2 diabetes.

5.10 Genetic polymorphisms and contaminants in the Arctic

The Indigenous Arctic population is of Asian descent, and their genetic background is different from that of the Caucasian populations. Relatively little is known about the specific genetic polymorphisms in genes involved in the activation and detoxification mechanisms of environmental contaminants in Inuit and their relation to health risk. The Greenlandic Inuit are highly exposed to legacy POPs such as PCBs and OC pesticides, and an elucidation of gene-environment interactions in relation to health risks is needed.

Ghisari *et al.* (2013) compared the genotype and allele frequencies of the cytochrome P450 CYP1A1 Ile462Val (rs1048943), CYP1B1 Leu432Val (rs1056836) and catechol-*O*-methyltransferase COMT Val158Met (rs4680) in Greenlandic Inuit (n=254) and Europeans (n=262) and explored the possible relation between the genotypes and serum levels of POPs. The genotype and allele frequency distributions of the three genetic polymorphisms differed significantly between the Inuit and Europeans. For Inuit, the genotype distribution was more similar to those reported for Asian populations. A significant difference in serum PCB153 and *p,p'*-DDE levels between Inuit and Europeans was found, and for Inuit associations were also found between POP levels and genotypes for *CYP1A1*, *CYP1B1* and *COMT*. Thus, the data provide new information on gene polymorphisms in Greenlandic Inuit that might support evaluation of susceptibility to environmental contaminants and warrant further studies (Ghisari *et al.*, 2013).

Ghisari *et al.* (2014) investigated the main effect of polymorphisms in genes involved in xenobiotic metabolism and estrogen biosynthesis, *CYP1A1*, *CYP1B1*, *COMT* and *CYP17*, *CYP19* and the *BRCA1* founder mutation in relation to breast cancer risk, and possible interactions between the gene polymorphisms and serum POP levels on breast cancer risk in Greenlandic Inuit women. They found that the *BRCA1* founder mutation and polymorphisms in *CYP1A1* and *CYP17* can increase breast cancer risk among Inuit women and that risk increases with higher serum levels of PFOS and PFOA. Serum PFAS levels were a consistent risk factor for breast cancer, but inter-individual polymorphic differences might cause variations in sensitivity to the PFAS/POP exposure.

6 Genetics in relation to lifestyle factors in artic populations

Nicotine, the psychoactive ingredient in tobacco, is metabolically inactivated by *CYP-2A6* to cotinine. *CYP2A6* also activates procarcinogenic tobacco-specific nitrosamines (TSNA). Genetic variation in *CYP2A6* is known to alter smoking quantity and lung cancer risk in heavy smokers. A study by Zhu *et al.* (2013) aimed to investigate how *CYP2A6* activity influences tobacco consumption and procarcinogen levels in light smokers and smokeless tobacco users. Cigarette smokers (n=141), commercial smokeless tobacco users (n=73) and iqmik (mixture of tobacco and ash) users (n=20) were recruited in a cross-sectional study of Alaska Native people. The participants' *CYP2A6* activity was measured by both endophenotype and genotype, and their tobacco and procarcinogen exposure biomarker levels were also measured. Smokers, smokeless tobacco users and iqmik users with lower *CYP2A6* activity had lower urinary

total nicotine equivalents and (methylnitrosamino)-1-(3)pyridyl-1-butanol (NNAL) levels (a biomarker of TSNA exposure). Levels of N-nitrosonornicotine (NNN), a TSNA metabolically bioactivated by *CYP2A6*, were higher in smokers with lower *CYP2A6* activities. Light smokers and smokeless tobacco users with lower *CYP2A6* activity reduce their tobacco consumption in ways (such as inhaling less deeply) that are not reflected by self-report indicators. Tobacco users with lower *CYP2A6* activity are exposed to lower procarcinogen levels (lower NNAL levels) and have lower procarcinogen bioactivation (as indicated by the higher urinary NNN levels suggesting reduced clearance), which is consistent with a lower risk of developing smoking-related cancers. This study demonstrates the importance of *CYP2A6* in the regulation of tobacco consumption behaviors, procarcinogen exposure and metabolism in light smokers and smokeless tobacco users (Zhu *et al.*, 2013).

6.1 Epigenetics

The placenta is central to successful reproductive outcomes. Its functions can be influenced by the environment encountered throughout pregnancy, thereby altering the genetic programming needed to allow sustained pregnancy and appropriate fetal development. This altered programming may result from epigenetic alterations related to environmental contaminant exposure. Epigenetic alterations are now being linked to several important reproductive outcomes, including early pregnancy loss, intrauterine growth restriction, congenital syndromes, preterm birth, and preeclampsia. As research continues to enhance understanding of the molecular processes including epigenetic regulation that influence pregnancy, it will be critical to specifically examine how the environment, broadly defined, may play a role in altering these critical functions (Robins *et al.*, 2011).

Rusiecki *et al.* (2008) analyzed the relationship between plasma POP concentrations and global DNA methylation (percent 5-methylcytosine) in DNA extracted from blood samples from 70 Greenlandic Inuit and used pyrosequencing to estimate global DNA methylation *via* Alu and LINE-1 assays of bisulfite-treated DNA to evaluate the correlations between plasma POP concentrations and global DNA methylation. This first study investigating environmental exposure to POPs and DNA methylation levels in an Arctic population has shown that global methylation levels are inversely associated with blood plasma levels for several POPs and merit further investigation.

6.2 Genetic predisposition and methylmercury neurotoxicity

Cognitive consequences at school age associated with prenatal MeHg exposure may need to take into account nutritional and socio-demographic cofactors as well as relevant genetic polymorphisms. Julvez *et al.* (2013) selected a subsample (n=1311) of the Avon Longitudinal Study of Parents and Children (Bristol, UK) and measured Hg concentrations in freeze-dried umbilical cord tissue as a measure of MeHg exposure. In this population with low MeHg exposure, associations between MeHg exposure and adverse neuropsychological outcomes were equivocal. Assessment of several relevant genes suggests possible genetic predisposition to MeHg neurotoxicity in a substantial proportion of the population.

6.3 Effect modifiers

Most environmental research on the effects of chemicals focuses on single exposures. However, exposure to mixtures of chemicals is ubiquitous in real life (Bellinger 2009). Certain chemical substances may target the same organ and induce similar effects in an additive or non-additive way (Carpenter *et al.*, 2002). Recent studies suggest a synergistic effect of metal mixtures with neuropsychological outcomes (Kim *et al.*, 2009) or kidney disease (Navas-Acien *et al.*, 2009). However, studies that examine the effects of chemical mixtures remain limited in humans, and even in experimental animal studies (Carpenter *et al.*, 2002).

Methylmercury, a worldwide contaminant of seafood, can cause adverse effects on the developing nervous system. However, long-chain n-3 PUFAs in seafood provide beneficial effects on brain development. Negative confounding is likely to result in underestimation of both Hg toxicity and nutrient benefits unless mutual adjustment is included in the analysis. In the Faroe Islands cohort studies, associations between prenatal exposure to MeHg and neurobehavioral deficits at school age were strengthened after fatty acid adjustment, thus suggesting that n-3 fatty acids should be included in similar studies to avoid underestimating associations with MeHg exposure (Choi *et al.*, 2014).

Yorifuji *et al.* (2011) examined the effects of prenatal Pb exposure on cognitive deficits in the presence of a similar molar concentration of a neurotoxic co-pollutant (MeHg) in 7- and 14-year-olds born in the Faroe Islands. Their analyses of the total cohort and those of cohort members without interaction terms among lower co-pollutant exposure categories showed equivocal results. When the subjects were restricted to a lower co-pollutant category, and statistical interaction terms were entered within the category, adverse effects of prenatal Pb exposure on cognitive function in childhood were observed, especially on attention, learning and memory. In the Faroe Islands it has been suggested that another co-pollutant, the PCBs, may affect human brain development through maternal ingestion of contaminated pilot whale blubber.

7 The challenge of climate change

7.1 Combined effects of climate warming, anthropogenic contaminants and zoonotic disease

A change in temperature may directly affect community infrastructure and community food and water security. The combined effects of climate warming, anthropogenic contaminants, and zoonotic diseases on rural food and water security also represent a significant risk to the safety of rural subsistence food and water supplies. Many circumpolar communities, particularly remote and small communities, will need to develop monitoring and adaptation strategies to deal with these interacting risks.

— The warming climate has resulted in changes in ocean and atmospheric contaminant transport, which may have increased the movement of anthropogenic contaminants and Hg from lower latitudes to the Arctic (Kallenborn *et al.*, 2012). Warmer water in freshwater lakes, tundra ponds and streams may re-

sult in greater bacterial methylation of Hg, and Hg released from thawing permafrost.
— Climate-mediated changes in the transport of anthropogenic contaminants to the circumpolar region may result in higher exposure in subsistence wildlife which could increase the risk of immunosuppression, and active zoonotic infection in these animals. This could result in risk to human consumers of infection and toxic effects from contaminant exposure (Fisk *et al.*, 2005).
— The warming climate is enabling southern plant, insect and animal species to expand their ranges further north, in some cases, into Arctic regions. These species may bring new zoonotic diseases with them. Higher winter temperatures in the Arctic may increase the winter survival of infected animals, raising the risk of hunter/consumer exposure. The warming climate may drive changes in the forage resources of subsistence species, and thus in the range, health and abundance of those subsistence species. The ecosystem changes could also impact on existing and newly emerging zoonotic pathogens of subsistence species (www.IPCC.CH/report).

8 Final remarks

A summary of known or predicted health endpoints for persistent toxic substances is shown in Box 1. Contaminants are still being transported to and recycled in the Arctic, and levels in certain populations demonstrate that biomonitoring of contaminants of concern should continue. Looking towards the future, it is possible that climate change may affect contaminant exposure in the Arctic (Carrie *et al.*, 2010), and may release contaminants currently held in soil, permafrost or ice. Even so, few differences have yet been seen in the food chain. Changes in food-Web structure, feeding habits and diet can affect concentrations of contaminants in biota and humans.

Despite global action through the Stockholm Convention to reduce the production and use of POPs, contaminants are still being transported to and recycled within the Arctic environment (www.IPCC.CH/report ; http ://chm.pops.int/). In addition to long-range transport as a source of contaminants to the Arctic, there is evidence that global warming may affect the cycling of contaminants within the Arctic environment (Carrie *et al.*, 2010), with the potential for release of contaminants currently held in soil, permafrost or ice, although few changes have been seen in the Arctic food chain to date. Nevertheless, changes in the structure and dynamics of the Arctic food Web, especially in relation to species forming part of the traditional diet, could have implications for contaminant levels in Arctic populations, with associated impacts on human health. Although time series data sets indicate a current decline in concentration for most POPs in Arctic biota, particularly PCBs and DDT, and contaminants such as PBDEs and PFOS that, prior to 2000 appeared to be increasing now appear to show either no trends or a decrease (AMAP 2015). The potential implications for human health highlight the clear need to continue biomonitoring contaminants of concern. Further biomonitoring will also aid in measuring the success of international risk management strategies for reducing risk for all Arctic and vulnerable populations. The ongoing cohort studies will continuously add more evidence and knowledge about environmental contaminants and effects on human health and development in

the coming years. The precautious principle must be the central issue to protect the health of the coming generations in the Arctic.

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