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AMAP HUMAN HEALTH IN THE ARCTIC

Health effects associated with measured contaminants in the Arctic: short communication

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ABSTRACT

The Arctic Monitoring Assessment Program Human Health Assessment report 2021 presents a summary of the presence of environmental contaminants in human populations across the circumpolar Arctic and related health effects. Based on this report the objective of this paper is giving a short summary of the health effects related to the current level of persistent organic pollutants (POP) and metals. The overall key findings are as follows: i. metals and POP (polychlorinated biphenyls, per- and polyfluoroalkyl substances (PFAS)) in the Arctic have known adverse health impacts on humans especially on developing foetuses and children. Lifestyle, diet and nutrition and genetics influence the risk; ii. POP and metals negatively impact the brain and immune system, increasing the risk of childhood obesity, type 2 diabetes later in life and negatively affect foetal growth and development: iii. marine food omega-3 fatty acids can diminish adverse effects of high mercury exposure on cardiovascular and neurological outcomes; iv. the interaction of genetic, lifestyle, nutrition status and contaminants can influence the risk of cancer, metabolic disease, nervous system disorders, disruption of reproduction and foetal and child growth. Future investigations must focus on genetically and effect modifiers and mixtures of POP exposures to explore the effect of chemical interaction on health outcomes.

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Introduction

Environmental contaminants such as methylmercury (MeHg), polychlorinated biphenyls (PCB), and per- and polyfluoroalkyl substances (PFAS) are ubiquitous and persistent environmental chemicals with known or suspected toxic effects on developing foetuses, children and adults. In the circumpolar Arctic area, where the traditional diet mainly consists of fish and marine animals, research have shown high accumulation of these toxic compounds in the food web and humans. Foetuses and young children are most vulnerable to the exposure, and therefore much research is focused on prospective studies of pregnant women and child cohorts [1].

The work is based on the Arctic Monitoring and Assessment Programme (AMAP), one of six Working Groups of the Arctic Council [2]. The AMAP's members are the eight Arctic Council Member States (Canada, Denmark/Greenland/Faroe Islands, Finland, Iceland, Norway, Russian Federation, Sweden, the United States). AMAP's mandate is i. to monitor and assess the status of the Arctic region with respect to pollution and climate change issues; ii. to document levels and trends, pathways and processes, and effects on ecosystems and humans, and propose actions to reduce associated threats for consideration by governments; iii. to produce sound science-based, policy-relevant assessments and public outreach products to inform policy and decision-making processes. AMAP's work is directed by the Ministers of the Arctic Council and their Senior Arctic Officials, AMAP's work support international processes to reduce the global threats from contaminants and climate change. These include the United Nations Framework Convention on Climate Change, The United Nations Environment Programme (UNEP's) Stockholm Convention on Persistent Organic Pollutants and Minamata Convention on mercury, and the United Nation's Economic Commission for Europe (UN ECE) Convention on Long-range Transboundary Air Pollution [2]. This paper builds primarily on the Chapter 4 "Health effects associated with measured levels of contaminants in the Arctic" [3] in the 2021 AMAP Assessment of Human

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Health in the Arctic report [1]. The paper provides a summary of recent research on the detrimental effects caused by exposures to environmental contaminants in the Arctic. The summary of recent research is given in eight themes: neurobehavioral effects, immunological effects, reproductive effects, cardiovascular effects, endocrine effects, carcinogenic effects, genetic modifiers and effect modifiers followed by a conclusion [3].

Methods

The Arctic Monitoring and Assessment Programme (AMAP) is designed to deliver sound science-based information for use in policy- and decision-making. The AMAP assessment methodology is expert-based work activities being internationally coordinated, subject to rigorous peer-review and make use of the most up-to-date results from both monitoring and research. Previous AMAP assessments have documented that participation in external Quality assurance/quality control (QA/QC) program result in improved performance over time [4]. Hence, the exposure data in this paper are primarily from laboratories that are active participants in different QA/QC programs, particularly the AMAP Ring test [1]. The data for contaminants presented are reported in serum, plasma or whole blood on a wet weight basis. Comparisons made between populations or contaminants are descriptive, unless specified in text as statistically significant comparisons and provided with original reference citations which detail the statistical methods used.

This paper presents a short communication summary of health effects associated with measured contaminants in the Arctic given in detail in the Chapter 4, 2021 AMAP Human Health Assessment Report [1]. The 2021 AMAP health report, Chapter 4 [3], gives an update on the AMAP 2015 report on health effects associated with exposure to environmental contaminants especially the persistent organic pollutants (POP) such as lipophilic POP (PCB, organochlorine pesticides (OCP)) and the amphiphilic POP such as PFAS and metals (e.g. Cd, Cu, MeHg). The data are primarily based on epidemiologically studies of pregnant women, adult men and women, women of childbearing age, children and youth. These data have been collected as part of regional cross-sectional studies and ongoing cohort studies.

Results

Central nervous system/neurobehavioral effects

In the 2015 AMAP Human Health Assessment Report [5] on health effects related to contaminant exposure, the conclusions on the neurobehavioral effects were as follows: Effects associated with MeHg exposure are documented in humans at successively lower exposures and the developing brain is the most vulnerable organ system. Prenatal exposure to MeHg associates with detrimental effects on the developing brain. Cohort studies in the Faroe Islands demonstrated that children exposed in utero to MeHg exhibit decreased motor, attention span, verbal abilities, memory and other mental functions. Follow-up of these children to the age of 22 years indicates that these deficits appear to be permanent. Similarly, a study in Nunavik of child development at age 11 years showed that mercury (Hg) exposure associates with poorer early processing of visual information, lower estimated IQ, poorer comprehension and perceptual reasoning, poorer memory functions, and increased risk of attention problems, specifically attention-deficit hyperactivity disorder (ADHD) behaviour. Beneficial effects of seafood nutrients may mask some of the adverse effects of MeHg on neurodevelopment. Neurophysiological assessment of brain functions also indicates that postnatal exposure up to adolescence can cause harm. Thus, both pregnant women and children are at increased risk from MeHg exposure. Studies indicate that certain genetic factors may increase vulnerability to MeHg toxicity. Neurophysiological assessments of children from the Faroe Islands and Nunavik have not indicated clear associations regarding the effects of prenatal exposure to PCB.

Based on the latest findings on Neurobehavioral effects in the 2021 AMAP Human health Report [3] the data indicates that the extent to which postnatal MeHg exposure contributes to neurobehavioral delays is uncertain. Therefore, the prenatal exposure to MeHg could explain most of the neurodevelopmental deficits.

The neurobehavioral effects of prenatal exposures are often evaluated using the Strengths and Difficulties Questionnaire (SDQ) brief behavioural screenings [6,7] (Figure 1). Whereas neurophysiological assessments of children postnatal exposures often use the Neurobehavioral Evaluation System (NES) being a test battery that is composed of a set of perceptual-motor, memory, learning, reaction time, and attention tests widely used in the field of occupational health [8,9].

However, postnatal MeHg exposure appears to contribute, especially when it comes to visuospatial processing and memory. Further studies with better information on exposure profiles are needed to characterise the effects of postnatal MeHg exposure [11]. Associations between prenatal exposure to MeHg and neurobehavioral deficits were strengthened after fatty acid adjustment, suggesting that omega-3 fatty acids

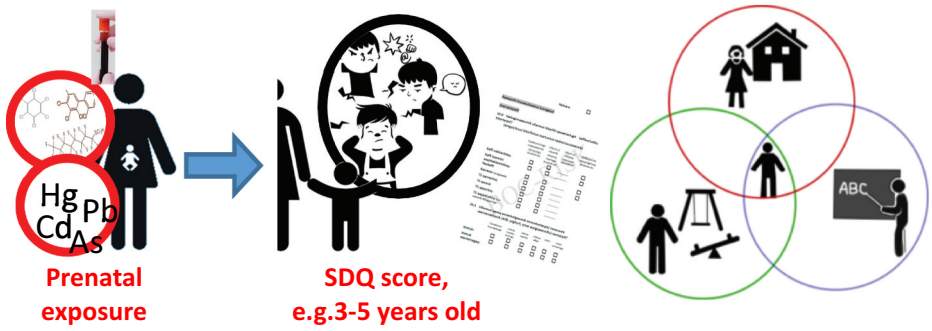


Figure 1. The strengths and difficulties questionnaire (SDQ) is a brief behavioural screenings questionnaire for children aged 2-17 years old [10] the parents answer a questionnaire based on their child's behaviour the last 6 months. SDQ include assessment of 1) Emotional symptoms; 2) Conduct problems; 3) Hyperactivity/inattention; 4) Peer relationship problems; 5) Pro-social behaviour. The SDQ scores 1) to 4) are added together to generate a total difficulties score. The prenatal exposure to contaminants can be measured in maternal blood and/or hair.

need to be included in analyses of similar studies to avoid underestimation of the effects of MeHg exposure [12]. This is in line with the findings in the Finish Kuopio Ischaemic Heart Disease Risk Factor Study, where higher serum long-chain omega-3 fatty acid concentrations were associated with better performance on neuropsychological tests of frontal lobe functioning in older men and women [13].

Prenatal exposure to PFAS and organochlorine compounds appear to have indications of a negative effect on child behaviour [6,7]. Whereas higher prenatal exposure to PCB153 and Dioxin-like compounds (dl-compounds) were not associated with parent-reported behavioural problems although the findings indicated that maternal dietary exposure to PCB-153 or dl-compounds during pregnancy was significantly associated with poorer expressive language skills in preschool girls (Figure 2) [14].

Association is not always causality and associations should be treated with caution in risk assessments. In a recent review, the significant and non-significant associations between maternal exposure to Hg and child development were studied in 73 publications. The median number of child development outcome variables in papers reporting significant ($n = 35$) and non-significant ($n = 38$) results was 4 versus 7, respectively. Authors often report health outcome variables based on their p-values rather than on stated primary research questions. Such a practice probably can skew the research evidence [15].

During the wintertime with reduced sunlight, there are a lack of sun in the Arctic, and this has been linked

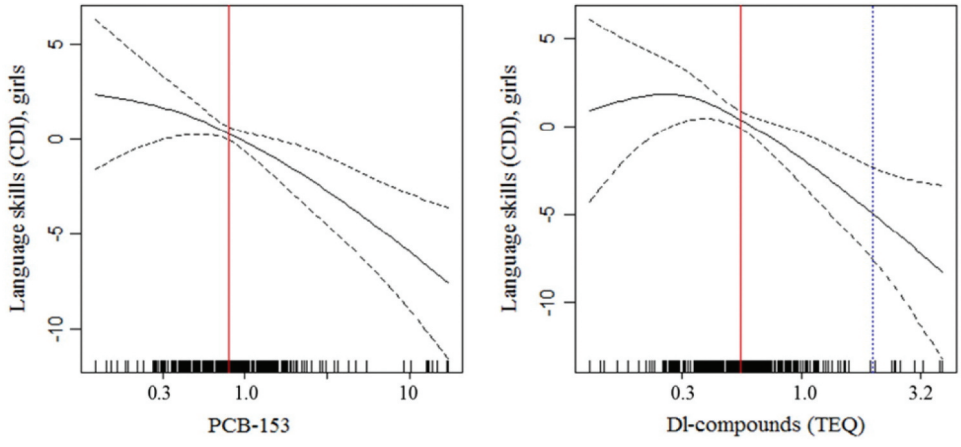


Figure 2. Dose-response associations for log10-scale of PCB-153 and dioxin-like compounds (Dl-compounds, calculated in toxic equivalents, TEQs) and expressive language score (CDI) in girls. Median values for PCB-153 and Dl-compound exposure are indicated by red solid vertical lines, and the tolerable weekly intake (TWI) for Dl-compounds is indicated by a blue dotted line. Models are adjusted for maternal energy intake, participation year, child's age at examination, maternal age, education, parity, pre-pregnancy BMI, household income, bilingualism, maternal folate supplement use, intake of docosahexaenoic acid (DHA)/n-3 fatty acids eicosapentaenoic acid (EPA) and MeHg during pregnancy and breastfeeding duration [14].

to vitamin D deficiency [16]. Mousavi and co-workers [17] reported an indication that environmental toxins may trigger further vitamin D deficiency. In a cross-sectional population-based study in the Faroe Islands [18] individual with autism spectrum disorder had significantly lower 25-hydroxyvitamin D3 (25(OH)D3) levels than their siblings without autism diagnosis, their parents and other healthy age- and gender-matched comparisons. There was a trend for males having lower 25 (OH)D3 than females. The study suggests that the low 25(OH)D3 levels in the autism spectrum disorder group might be an underlying pathogenic mechanism.

Immunological effects

Several studies in the circumpolar area indicate a negative impact on the immune system due to dietary exposure to environmental contaminants. In the AMAP 2015 assessment it was speculated that maternal transfer prenatally and postnatally of organochlorines especially dioxin-like PCB increases the susceptibility to infectious diseases of the child. Moreover, studies suggested that Faroese children with higher PCB and PFAS elicited a decreased effect of childhood vaccinations.

The latest findings on immunological effects in the 2021 AMAP Human health Report [3], the data indicated PFAS exposure at age 7 years was associated with a loss in diphtheria antibody concentration at age 13 years and a decrease in tetanus antibody concentration at age 5 years was associated with PFAS exposure in early infancy. While PFAS exposure may affect immune system function, these studies suggest that measles-mumps-rubella (MMR) vaccination might be a potential effect-modifier. MMR vaccination early in life may have a protective effect against allergy and asthma [19,20]. A recent review, including Arctic data, on epidemiologic data on vaccine response in relation to exposure to five principal perfluoroalkyl substances documented the immunosuppression of five principal PFAS across antibodies against multiple types of antigens: Diphtheria, Rubella, and Tetanus were more supportive of an association than for other antibodies, and support was greater for associations with PFOA, PFOS, and PFHxS, than for PFNA or PFDA. The data on any specific antibody were scarce. In general, studies evaluated were judged to have a low or moderate risk of bias (Figure 3) [21].

Data from Denmark indicate that prenatal exposure to POP appears to be associated with airway obstruction but not allergic sensitisation at 20 years of age [22,23]. However, in a Russian/Finnish study in Karelia, environmental chemicals did not explain the higher prevalence of atopy on the Finnish side [24].

Markers of inflammation were higher in Inuit compared to non-Inuit and increased with age and with the intake of Greenlandic food items high in POP [25].

In the Faroe Islands, the prevalence of inflammatory bowel disease is high. Interestingly, the excess risk in Faroese immigrants to Denmark disappeared over time, indicating a gene-environment interplay [26,27].

The INUENDO birth cohort including mother-child pairs from Greenland and Ukraine found limited evidence to support a link between prenatal exposure to environmental chemical contaminants and childhood asthma and eczema [28].

In summary, all the mentioned associations between contaminant exposure and the functions of the immune system demonstrate the need for further mechanistic studies to find causal explanations. Furthermore, explorations are needed of the windows of vulnerability pre- and postnatal, and identification of the most immunotoxic substances.

Reproductive effects

Health, exposure and birth outcome for pregnant women. The 2021 AMAP Human Health Assessment Chapter 4 [3] reports a further transition from traditional to imported food in Greenlandic pregnant women, a high smoking frequency, higher BMI and regional age differences for planned breastfeeding. The negative effect of POP exposure on foetal growth was reported by the significantly inversely association between serum perfluorooctanoic acid (PFOA) level and foetal growth indices, whereas gestation age was positively associated in the Greenlandic Inuit ACCEPT cohort pregnant women (Figure 4) [29]. Foetal growth is also affected by prenatal exposure to heavy metals, such as Cadmium (Cd) and Cupper (Cu) [30]. The lipophilic mixture of serum POP of pregnant ACCEPT women elicited hormone-disrupting effect interfering with the oestrogenic (ER) and androgenic receptor activity, affecting foetal development and growth as suggested in Greenlandic pregnant women (personal communication Eva C. Bonefeld-Jørgensen) as well as serum PFAS mixtures disruption of ER function affecting foetal growth indices (FGI) in Danish pregnant women [31].

Studies in Inuit and European cohorts report that phthalate, PFAS, and organochlorine chemical groups may independently be associated with impaired foetal growth [32]. Serum 25(OH)D concentrations in cord blood associate positively with infant length but not with birth weight and head circumference [33]. The possible long-term effects of late-pregnancy D hypovitaminosis deserve attention.

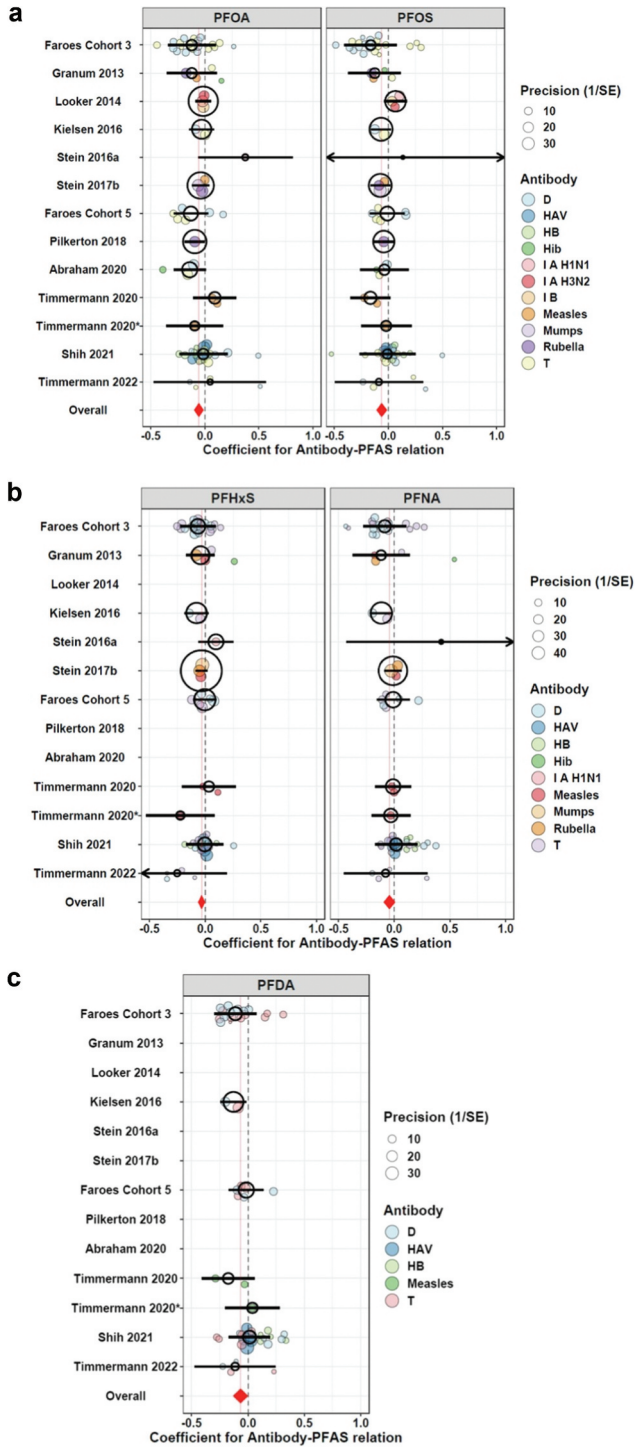


Figure 3. Forest plots of coefficients for antibody-PFAS relationship from a systematic review and meta-analysis of epidemiologic data on vaccine response [21]. a) PFOA and PFOS; b) PFHxS and PFNA, c) PFDA. The red diamond at the bottom of each figure is centered horizontally on the summary association from a univariate multilevel meta-regression model and its width marks the 95% confidence interval. The model was fitted with all antibody types treated as one. The units for the x-axis are difference in ln transformed antibody concentration per doubling of serum PFAS concentration. The y-axis indicates each study. The individual observations reported by the original studies are represented by a colored circle and are antibody-specific; the precision legend applies to these colored circles. For descriptive purposes only the results of each study are also summarized using a fixed-effect method that accounts for the correlation of results within-study. This study-specific summary is drawn as an open circle with a 95% confidence interval; the size of the open circles is shown at 50% of 1/(standard error) [21].

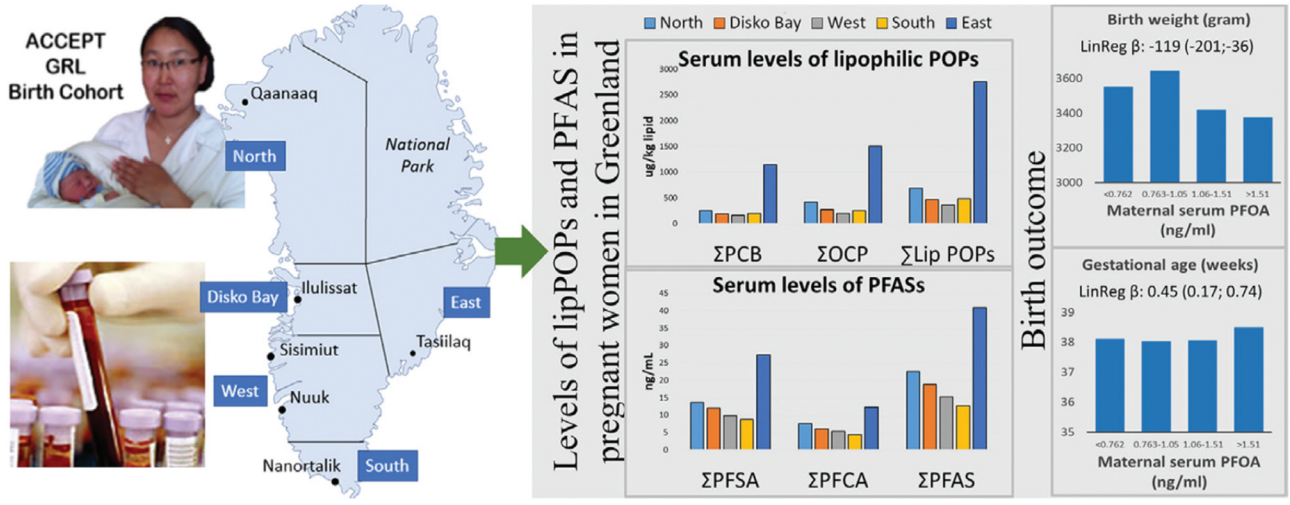


Figure 4. The serum levels of lipophilic POPs and PFAS among Greenlandic pregnant women sampled 2010-2015 and birth outcome illustrated by foetal growth indices and gestational age at birth. Maternal PFOA serum level was inversely associated with birth weight but positively with gestational age [29].

Exposure and female fertility and male reproduction parameters. In the AMAP Human Health assessment 2015 [5] it was reported that PCB153 exposure level was inversely related sperm mobility in Greenlandic men but not to sperm count and morphology [5]. The studies given in the 2021 AMAP Human Health Assessment report [3] on phthalates and POP show no consistent exposure effect on female fertility and/or male reproduction parameters. There are indications that environmental exposure to PFAS may impair female fecundity (i.e. delaying time taken to conceive), although, the results do not provide consistent evidence to support this hypothesis.

Exposure to a mixture of organochlorines and phthalates can adversely affect parameters of male reproductive health and di(2- ethylhexyl) phthalate (DEHP) metabolites, less for diisononyl phthalate (DINP) metabolites, elicit weak anti-androgenic action but have no major effect on semen quality or reproductive hormones [34]. However, high peri-pubertal serum 2,3,7,8-tetrachlorodibenzodioxin (TCDD) concentrations and polychlorinated dibenzodioxins (PCDD) toxic equivalents (TEQs) were associated with lower semen quality such as sperm concentration, total sperm count, and total motile sperm count. In addition, semen samples of men with high exposure to organochlorines at age 14 years and in adulthood were associated with sperm chromosomal disomy, suggesting impacts of POP on testicular maturation and function [35].

In highly exposed fertile Faroese men, the serum PCB concentration was associated with a higher androgen/oestrogen ratio and associated with higher total testosterone and elevated sex hormone-binding globulin levels but no association with semen quality parameters. PCB and perfluorooctane sulphonic acid (PFOS) are positively associated with luteinising hormone and might suggest an interfering effect on Leydig cells and testosterone synthesis [36]. More research is needed on PCB- and PFAS-associated hormonal effects.

Exposure of women in Denmark and Finland to PFOA and PFOS shows differences in cord blood levels between countries, being highest in Denmark but with no statistically significant association between cord blood PFOA and PFOS levels and congenital cryptorchidism [37]. Future research on PFAS exposure and diseases in male organs in the Arctic populations might help identifying whether there are possible health effects of PFAS exposure on Inuit male organs.

Maternal exposure to sumPCB, DDE and MeHg was associated with an increase in the ratio of male to female live births [38].

Hazard quotient (HQ) profiles used as a risk assessment tool for PFOS and PFOA serum levels in three European populations demonstrated that the HQ approach could help interpret human biomonitoring data and thus serve as an important tool in further risk assessment [39].

In overall, the high level of POP and heavy metals in maternal blood requires further dietary recommendations to encourage increased intake of foods from the lower levels of the marine food chain, such as fish. The continued high frequency of tobacco smoking during pregnancy is of concern and the relation to lower serum iron levels, which can affect oxygen transport, might affect foetus development and growth being in accordance with foetal growth and maternal smoking are inversely related [29,40,41].

Cardiovascular effects

Fish consumption and long-chain omega-3 polyunsaturated fatty acid (omega-3 PUFA) intake have been shown to protect for cardiovascular disease. However, consumption of some fish also leads to a higher exposure to environmental contaminants, which may have adverse effects on health, including cardiovascular disease [3]. In Finnish studies, hair Hg was not associated with sudden cardiac death. However, the associations of total long-chain omega-3 PUFAs with higher maximum rate of oxygen consumption were stronger among men with lower hair Hg levels. Higher serum long-chain omega-3 PUFA concentrations were associated with lower resting heart rate in middle-aged men from eastern Finland, which may partially explain the potential cardio-protective effect of fish intake [42,43].

The beneficial effect on myocardial infarctions of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in the traditional Inuit diet is diminished by the adverse effects of MeHg. Therefore, promoting the increased consumption of fish species with high EPA +DHA concentrations and low MeHg may help prevent myocardial infarctions among the Inuit [44,45].

No significant associations were observed between PCB, OCP and blood pressure among Greenlanders. A recent prospective study of Inuit in Greenland showed no association between blood Hg and risk of developing cardiovascular diseases [46].

Endocrine effects

The persistent organic pollutants including PCB, OCP and the amphiphilic PFAS are endocrine disrupters with the potential to interfere with the homoeostasis of endogenous hormones, such as thyroid-, androgen-, and oestrogen-hormones [47–50] (Figure 5). Exposure during foetal and neonatal development is especially critical and can disrupt normal development and risk of diseases later in life. In Greenlandic and European men, POP (PCB153, p,p´-DDE) exposure seems to affect gonadotropin and steroid hormone-binding globulin levels [5].

Thyroid homeostasis effects. The PFAS can disrupt thyroid hormone homoeostasis in humans. A recent review in 2020 on exposure to PFAS and foetal and maternal thyroid status included fifteen original publications from global cohorts on PFAS concentrations and thyroid hormones (TH) in pregnant women and/or infants [52]. The conclusion of this review stated a mainly positive relationship between maternal PFAS concentrations and thyroid stimulating hormone (TSH) levels, and suggestion of an inverse association with thyroxine (T4) and/or triiodothyronine (T3) levels, whereas associations of infant TH with PFAS concentrations were less consistent.

In Alaska Indigenous People, exposure to PFAS associated with and modified circulating thyroid hormone concentrations. The effects of PFAS exposure on thyroid hormone homoeostasis may differ between sexes [53]. Individual polybrominated diphenyl ethers (PBDEs) were reported to modify thyroid homoeostasis in Alaska Inuit. Another study in Alaska Inuit observed a positive association between penta-BDE congeners and concentration of TSH and free T3, and negative relation between PBDE153 and T3 level [54].

To examine POP exposure and effects on hormones and FGI the following were measured in Danish nulliparous pregnant women during 1st trimester: maternal thyroids, androgens and oestrogens, lipophilic POP and PFAS serum levels. Lipophilic POP inversely associated with androgen and oestrogen levels but no strong association with thyroids. Whereas positively association were seen between PFAS level and thyroid and androgen hormone levels. Thyroid-peroxidase-antibody (TPO-Ab) and oestradiol level associated with higher birth weight and length in sons, whereas the opposite was observed for daughters, TPO-Ab being inversely associated with birth weight and length. Mediation analyses suggested that TPO-Ab mediates the association of PFAS with FGI [55].

A background exposed maternal population from northern Norway also indicated that PFAS exposure can modify thyroid hormone homoeostasis, and changes in maternal thyroid hormones that might have significant consequences for foetal health [56]. In three European mother-child cohorts early life exposure to PCB153 and p,p'-DDE affected newborn TSH (thyrotropin) levels. Higher exposure levels were associated with 12–15% lower TSH levels [57]. Maternal urinary concentrations of DEHP were associated with increased risk of ADHD in a northern Norway case-control study of clinical ADHD. Elucidation of the mechanisms linking phthalates to ADHD needs further research. In addition, iodine deficiency among pregnant women in northern Norway (MISA cohort) influences maternal thyroid homoeostasis and is therefore a risk factor for foetal and infant development. An array of exposure and factors can thus disrupt the thyroid hormone system [58].

In contrast to humans, the relationship between POP exposure and TH or vitamins in pilot whales seems to have minor effects on TH level and vitamin concentrations. Future research might establish the mechanism differences between humans and pilot whales [59].

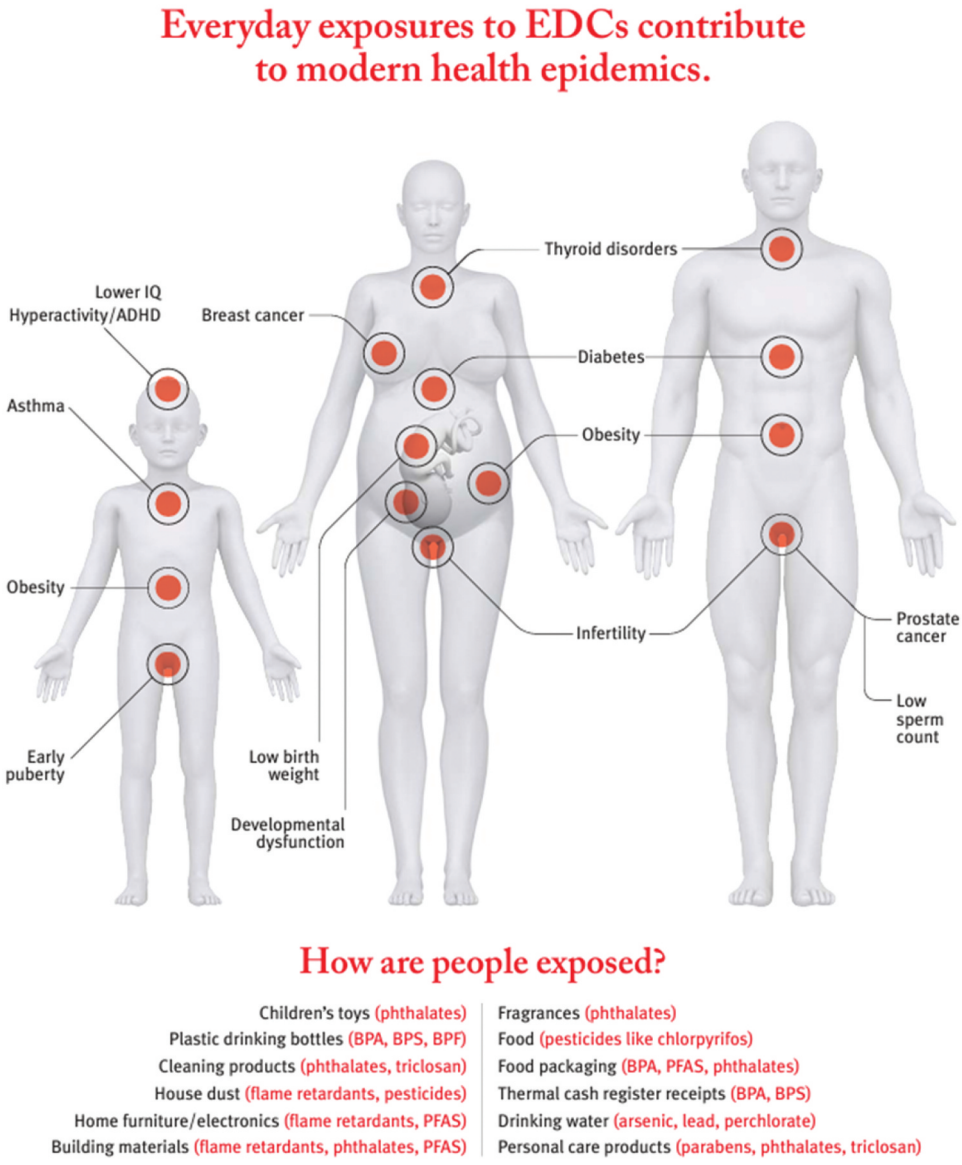


Figure 5. The potential adverse health effect of the endocrine disruption (EDC). EDCs are chemicals disrupting the function of natural endogenous hormones increasing the risk for health problems. https://www.env-health.org/wp-content/uploads/2019/03/EDCs-Infographics-22.2.20192-Low-Doses-Matter.pdf [51].

POP, body weight and risk of diabetes. Though not consistent, several studies suggest an association between POP exposure and body weight [60] Childhood obesity might have several risk outcomes as child and grown up [60–63] (Figure 6). A follow-up study of Greenlandic, Polish and Ukrainian populations showed no clear association between pregnancy PCB153 and p,p'-DDE levels and child body mass index (BMI), either for postnatal exposure to p,p'-DDE and PCB153 or for BMI at the age of 5–9 years [65]. In contrast, a cohort study on Faroese children supported a role for maternal exposure to PCB and DDE, and childhood obesity epidemic. Girls whose mothers have a high pre-pregnancy BMI seem most affected (Figure 7) [66]. In support, maternal exposure to endocrine disrupter such as hexachlorobenzene (HCB), PFOS and PFOA associated with increased BMI and/or overweight in preschool Faroese children [67]. Another Faroese study on pregnant women and their offspring found associations with gestational diabetes and offspring birth size related to environmental pollutants and/or pollutant group. Birth size measures appear independent of gestational diabetes occurrence [68]. In support, a Crete pregnancy cohort reported women with high PCB levels in early pregnancy had a higher risk for gestational diabetes [69]. A study on pregnant Norwegian and Swedish women found positive associations between maternal serum PFAS concentrations

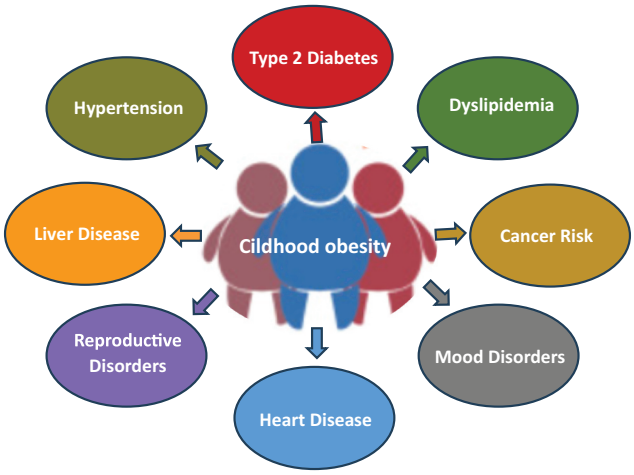


Figure 6. The risk of childhood obesity on health outcomes. Obesity in childhood is one of the most challenging public health issues in the twenty-first century. Childhood obesity has important consequences for health and wellbeing both during childhood and in later adult life. The rising prevalence of childhood obesity poses a major public health challenge in both developed and developing countries by increasing the burden of chronic noncommunicable diseases increasing the risk of morbidity. Childhood obesity is a complex condition that has many contributing factors e.g. intake of more calories than needed for growth, genetics, family/maternal and environment factors, social determinants of health [60–64].

and child overweight/obesity at 5 years of age, particularly among Norwegian participants [70]. In contrast, in a low-exposed Danish population, childhood serum concentrations of PCB, DDE, and HCB were not associated with subsequent weight gain [71]. In a study on three European birth cohorts, perinatal exposure to dioxin and dioxin-like compounds associated with increased early infant growth, and increased BMI in school age girls [72]. Studies in larger sample sizes are required to confirm these sex-specific effects.

Previous studies have indicated a potential influence of POP on Type 2 diabetes pathogenesis [5]. Further findings in a Faroese birth cohort suggest that, for 5-years-old girls, exposure to POP prenatally may play a role in later development of metabolic diseases by affecting the level of insulin [73]. Although in contradiction to other reports, a study on comparison with balanced food intake, participants with main intake of Greenlandic traditional food positively associated with Type 2 diabetes, impaired fasting glucose and fasting plasma glucose, and negatively associated with β-cell function. Imported meat seemed best in relation to glucose intolerance, with lowest fasting plasma glucose and lowest risk for impaired fasting glucose and Type 2 diabetes [74]. Further studies are needed to confirm these Greenlandic data with simultaneously measurement of serum POP levels.

Metals, omega-3 PUFA and risk of diabetes. Another study in Greenlandic Inuit found a weak but statistically significant association between whole blood Hg and both impaired fasting glycaemia and Type 2 diabetes, but no associations with measures of underlying disturbances in glucose homoeostasis [75]. A review showed that increased total Hg exposure may increase risk of diabetes and metabolic syndrome, but lack of consistency in the epidemiological evidence made it impossible to identify a causal relationship. Studies in non-Arctic populations support the findings on the relation between POP exposure and risk of Type 2 diabetes [76].

Higher serum Zn levels in Finnish men were associated with higher risk of Type 2 diabetes, partly explained by effects of Zn on BMI and insulin sensitivity [77]. Moreover, studies in Finnish men showed that serum long-chain omega-3 PUFA concentrations were associated with long-term lower risk of Type 2 diabetes [78]. A Norwegian study found a possible role of bromine (Br), Cd, chromium (Cr), iron (Fe), nickel (Ni), silver (Ag) and zinc (Zn) in the development of Type 2 diabetes [79].

A recessive genetic model used in a small and isolated Greenlandic population identified a genetic risk in TBC1D4 gene variants with loss-of-gene-function. The findings give new insights into the genetics of Type 2 diabetes and support the existence of high-effect genetic risk factors in isolated populations such as Greenlanders [80,81].

Lifestyle, diet and exposure to POP. The levels and trends of for example PFAS differ between countries and populations as illustrated by data from five international birth cohorts from Greenland, Denmark (two cohorts), Norway and China (Figure 8). The concentrations and composition of serum PFAS were similar for the Danish ABC cohort women and the Norwegian MISA cohort women but were otherwise different across cohorts, being higher in the Chinese SBE and Greenlandic ACCEPT birth cohort. The different exposure profiles might relate to differences in local PFAS production (e.g. in China) and in lifestyle and diet, and might as well affect health outcome implications [82].

A study on elderly in Europe found regulatory and individual efforts to reduce chemical exposures might reduce the burden and costs of diabetes, indicating the need for further worldwide regulations. New results from pharmacokinetic analysis suggest that a third factor e.g. high intake of animal foods could explain both higher levels of POP in the body and higher incidence of Type 2 diabetes. BMI alone is not enough to describe the diet confounding. Pharmacokinetics of the studied compounds including analysis of food consumption could help address causality between POP and Type 2 diabetes [83].

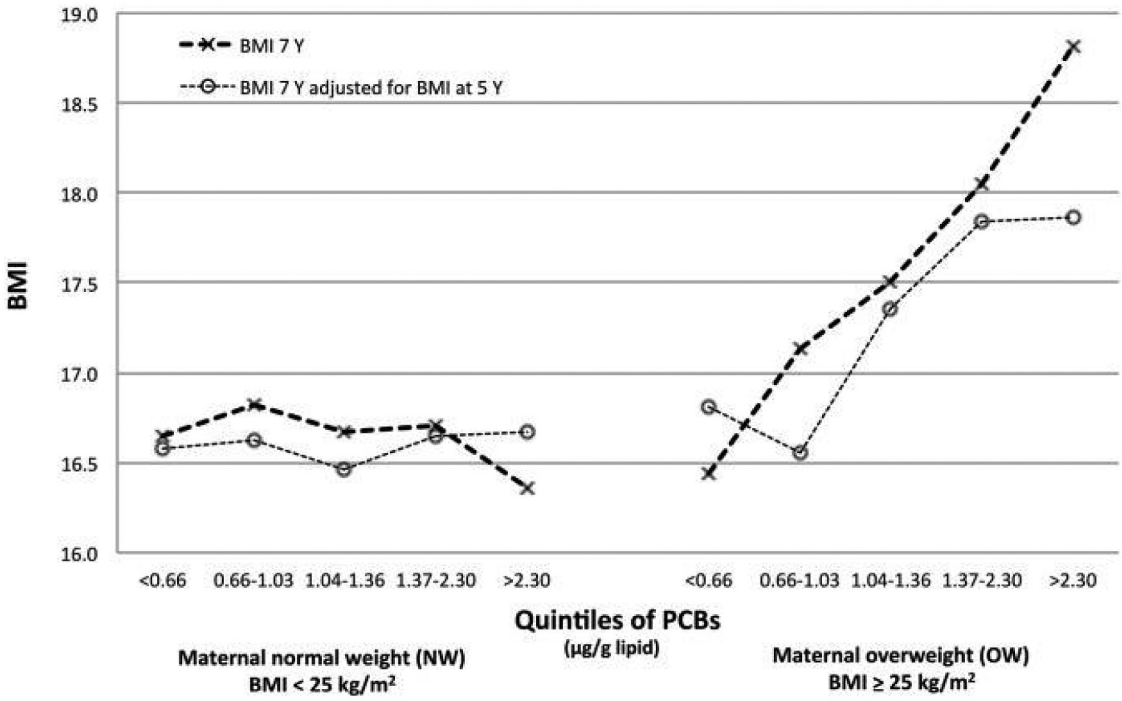


Figure 7. Interaction between prenatal polychlorinated biphenyl (PCB) exposure, maternal Body Mass Index (BMI) and BMI in girl-child at 7 years of age. The associations between prenatal PCB exposure in quintiles and BMI in 7-y-old girls, and BMI in 7-y-old girls is adjusted for BMI at 5 y of age according to maternal prepregnancy BMI [faroese cohort 1996–2001 ($n = 259$)]. Values were adjusted for maternal parity and age by using multiple linear regression. *P*-trend for BMI at 7 y of age: NW, $p = 0.60$; OW, $p = 0.003$; *P*-trend for BMI at 7 y of age adjusted for BMI at 5 y of age: NW, $p = 0.73$; OW, $p = 0.001$ [66].

Effects and mechanisms. Risk assessment must include mixtures exposures since nobody are exposed only to one chemical and predictive concentration addition concept assessment can be used [84] and/or in support using real-life POP mixture exposure upon extraction from human serum and test in cell cultures of effects on endogenous hormone receptors (Figure 9) [31,50,85–87].

As already stated, POP are endocrine-disrupting chemicals that can elicit xeno-oestrogenic activity. Environmental xeno-oestrogens can downregulate placental ABCG2 protein expression (efflux transporters in the placenta) depending on gestational age [89].

Carcinogenic effects

Cancer is an increasing public health concern, especially lung and colorectal cancer, among some Indigenous People including Inuit in the Arctic. Compared to the world average, Inuit are at extreme high risk for lung and colorectal cancer, and some rare cancers, such as nasopharyngeal cancer [90]. A significant increase in cancer incidence in Greenland was observed, with nearly the same incidence level as for the other Nordic countries (Figure 10). Environmental contaminants such as POP and heavy metals are potentially carcinogenic due to genotoxicity and inducement of oxidative stress. The reported studies show that exposure to environmental contaminants such as lipophilic POP, amphiphilic PFAS and phthalates plays a role in the increase of cancer incidence in the circumpolar region [91].

Breast cancer in the Arctic Greenland is increasing e.g. the last 10 years with 0.9%, nearly reaching the incidence for the Nordic countries of which most countries have decreasing incidence over the last 10 years (Figure 11). The possible biological mechanism of lipophilic POP on breast cancer may relate to their hormone disruptive property, while PFAS seem to influence breast cancer risk through other pathways such as promotion of cell proliferation through accelerating the transition from G0/G1 phase to S phase of the cell cycle and stimulating migration and invasion of normal breast epithelial cells. In vitro studies suggest that the possible mechanisms of carcinogenicity of PFAS were to induce oxidative stress, inhibit hepatocyte nuclear factor 4 alpha (HNF4α), and stimulate expression of proto-oncogenes in liver cells [49,93–95].

A study on a non-Inuit population suggested the anti-oestrogenic effect of Cd might play a role in breast cancer development. An in vitro study showed that Cd induced the transformation of normal lung cells to malignant cells via oxidative stress and anti-apoptosis [97].

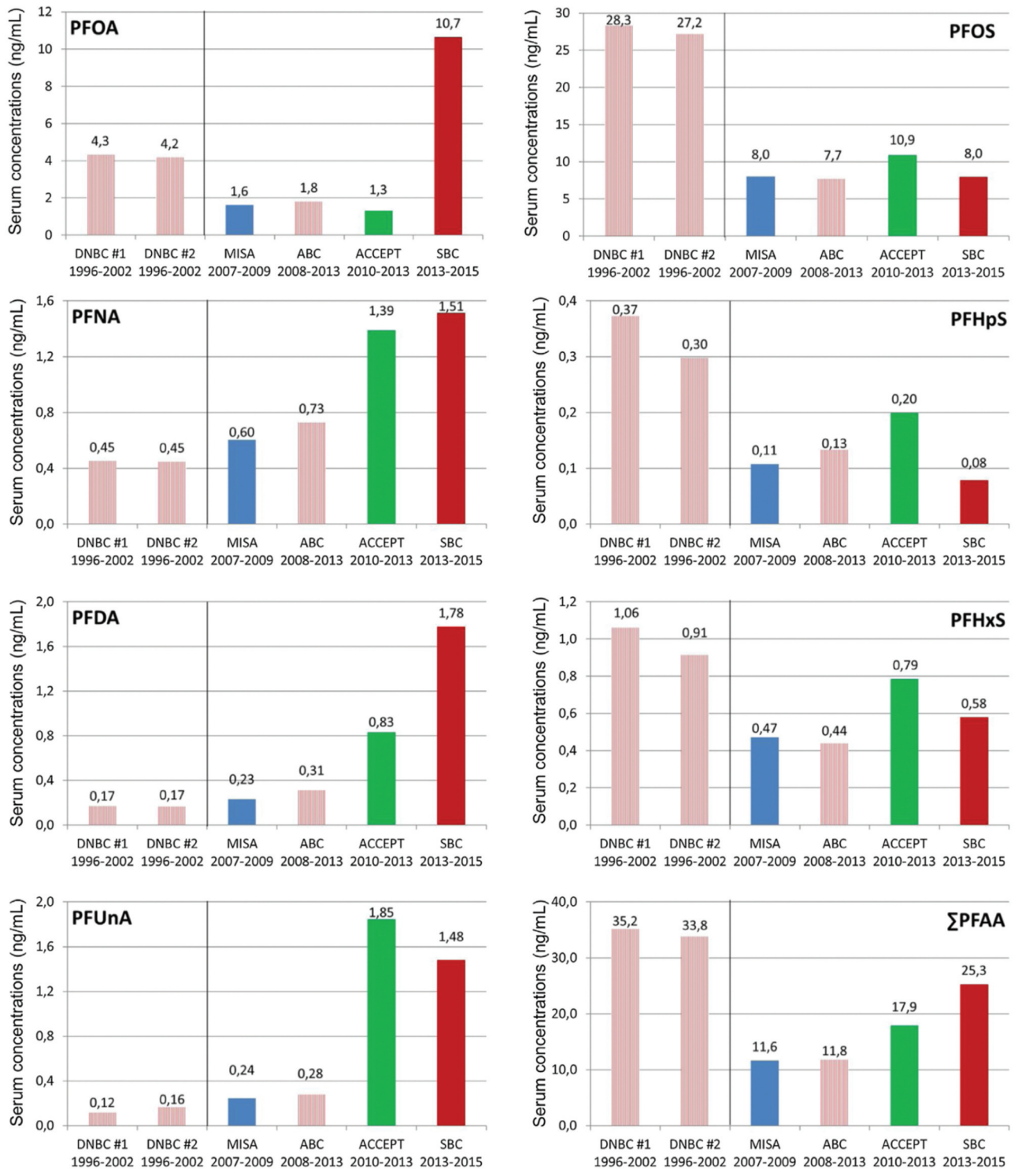


Figure 8. Geometric mean concentrations (ng/mL) of perfluoroalkyl acids in maternal serum from the danish national birth cohort (DNBC #1, $n = 1594$ and DNBC #2, $n = 545$, sampled earlier than the other cohorts [1996–2002]), the Northern Norwegian mother-child cohort (MISA, $n = 391$), the aarhus birth cohort (ABCB, $n = 1533$),the Greenlandic birth cohort (ACCEPT, $n = 207$), and the Shanghai birth cohort (SBC, $n = 448$) upon adjustment for age and parity. _∑PFAA is the total concentration of all seven congeners (PFHxS, PFHpS, PFOS, PFOA, PFNA, PFDA, and PFUnA). Pink bars = Denmark; blue bars = Norway; green bar = greenland; red bar = China [82].

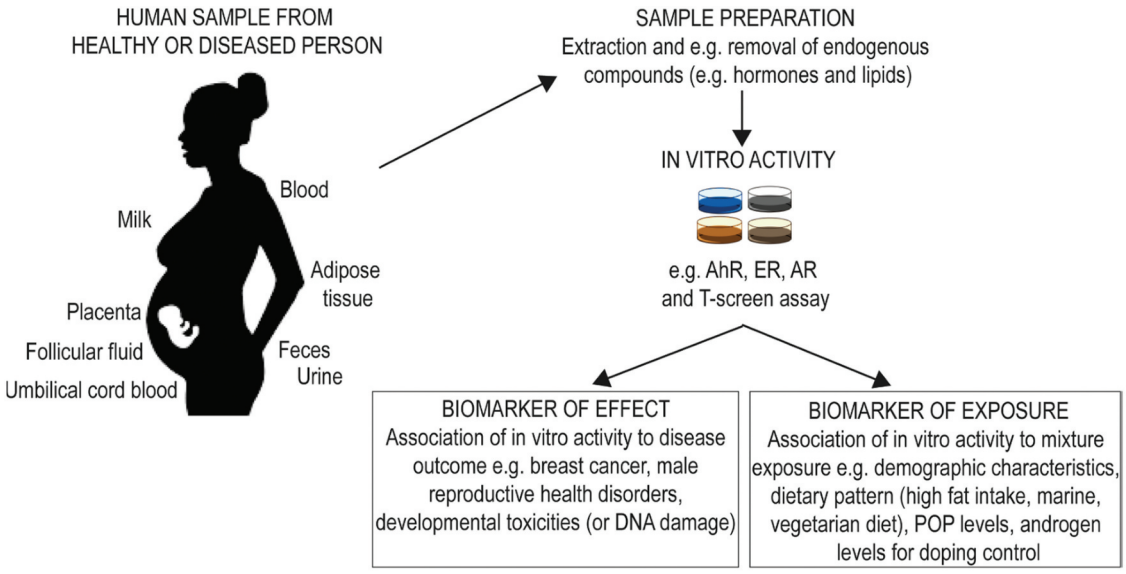
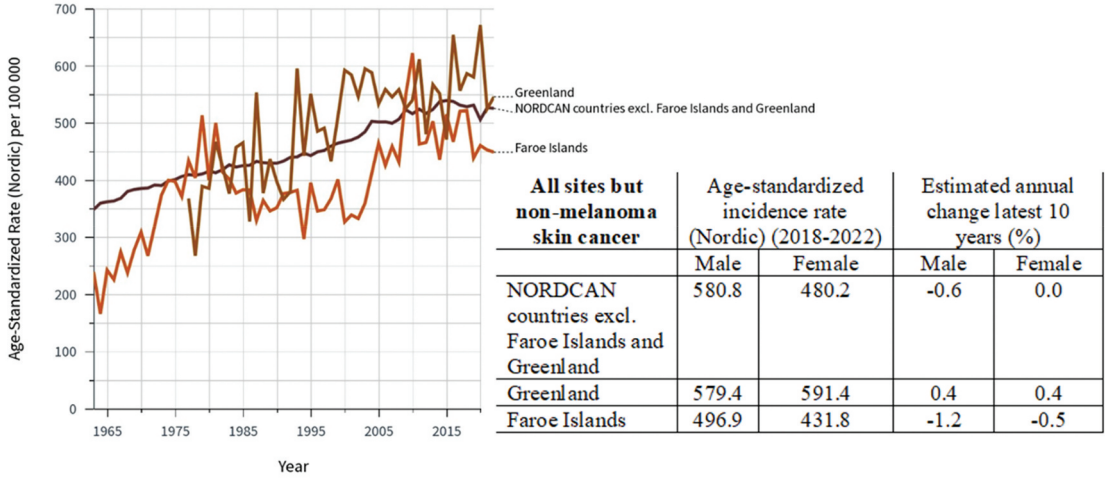


Figure 9. Approaches for linking chemical exposures to health outcomes by using ex vivo extraction for determining *in vitro cell culture* activities measuring the real life mixture effects of chemicals. Relevant biological samples of human body fluids, tissues or secretions are selected from the cohorts of interest. The biological sample is typically undergoing an extraction and fractionation procedure to isolate a specific group of chemicals such as lipophilic POPs or PFAS free from endogenous hormones. The measured *in vitro cell culture* activities including aryl hydrocarbon receptor (AhR), oestrogen receptor (ER), androgen receptor (AR) and thyroid hormone function (T-screen) can be used as a biomarker of effect by association with the disease outcome [47,50,86,88].



All sites but non-melanoma skin cancer	Age-standardized incidence rate (Nordic) (2018-2022)		Estimated annual change latest 10 years (%)	
	Male	Female	Male	Female
NORDCAN countries excl. Faroe Islands and Greenland	580.8	480.2	-0.6	0.0
Greenland	579.4	591.4	0.4	0.4
Faroe Islands	496.9	431.8	-1.2	-0.5

Figure 10. Age-standardized rate of all site cancer per 100 000, incidence, both sexes. Non-melanoma skin cancer not included. NORDCAN rate (NORDIC) per 100 000, incidence. NORDCAN iarc-https://gco.iarc.who.int (date version 9.4-07.2024) [92].

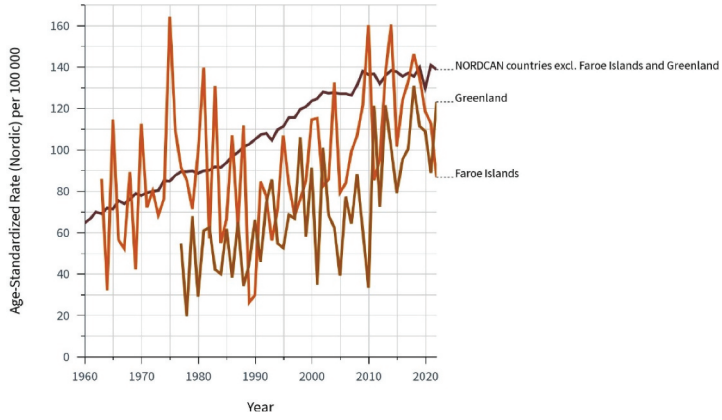
No data on environmental exposure and prostate cancer in the Arctic were available after 2015. Lipophilic POP such as PCB and organochlorine pesticides were observed to play a role in the aetiology of prostate cancer in the non-Inuit populations of northern European countries [3].

Contaminants may interact with microorganisms to influence cancer development. The hepatitis B virus (HBV) linked chronic inflammation and hepatocellular carcinoma in Alaska Natives might be stimulated by elevated body levels of dioxins [3].

A US study indicated that cold environments (north of 36.5°N) were associated with higher cancer incidence in females compared to south of this latitude. The combined effect of environmental contaminant exposure and cold environment in terms of the increasing trend of cancer incidence in Arctic regions merits further studies [3].

Genetic and effect modifiers

Interaction between genotypes and environmental exposures play a role in cancer risk. Genetic variants



Breast cancer (female)	Age-standardized incidence rate (Nordic) (2018-2022)	Estimated annual change latest 10 years (%)
NORDCAN countries excl. Faroe Islands and Greenland	136.8	0.1
Greenland	111.8	0.9
Faroe Islands	118.7	-3.2
Iceland	139.2	-0.8
Denmark	144.7	-0.4
Norway	133.8	1.4
Sweden	129.9	-0.1
Finland	143.5	-0.1

Figure 11. Breast cancer for females only. Age-standardized rate (NORDIC) per 1000 000, incidence. NORDCAN iarc-https://gco.iarc.who.int (date version 9.4-07.2024) [96].

can increase the susceptibility to POP exposures. As reported for Greenlandic Inuit, exposure to POP (PFOS, PFOA) and mutation in BRCA1 and polymorphisms in the metabolic genes *CYP1A1* and *CYP17* can increase the risk of breast cancer. Genetic variation in *CYP2A6* was shown related to lung cancer risk in heavy smokers. In addition, heterogeneity in relevant genes suggest genetic predisposition to MeHg neurotoxicity [5].

In multifactorial diseases such as cancer, environmental variables and gene variants shape the risk per population. The genetic variants found to be under selection for cold environments can also predispose for cancer [3]. Greenlandic Inuit seems to have developed genetic adaptions with diet and climate [98].

Prenatal exposure to contaminants such as POP can cause changes in sex-specific DNA methylation of genes associated with networks of reproductive, cardiovascular and neural/behavioural disruption [99]. Genetic polymorphisms in the key genes involved in metabolism of xenobiotic chemicals could influence the levels of POP and heavy metals and modify the association between exposure and contaminant levels in the Arctic population. This can in turn influence the human health effects of these contaminants [3,100].

In an ex vivo perfusion system it was shown that the organic anion transporter 4 (OAT4) expressed in human placenta can modify the transfer of PFAS through placenta and thereby, OAT4 May protect the foetus by decreasing foetal exposure to PFAS [101].

Dietary and lifestyle transition and the genetic variants selected for adaptation at extreme cold conditions might increase cancer risk in later life [102]. The genetic variants of genes involved in the synthesis and metabolism of oestrogens, especially *CYP17A1*, can modify the effects of POP exposure on breast cancer risk [95].

Adverse effects of POP exposure on male reproductive function, such as semen quality, are related to polymorphisms in the genes involved in aryl hydrocarbon receptor (AhR) signalling [103]. For the Arctic population, POP exposure is associated with global DNA methylation in the sperm [3]. Dioxin exposure in Russian young peripubertal adults was shown to associate with sperm DNA methylation [104]. In Greenlanders PFAS exposure inversely associated with sperm DNA methylation suggesting interference with the sperm epigenetic processes [105], a topic which warrants further research.

The Inuit have genetic and physiological adaptions to a diet rich in PUFAs. Mutation in genes regulating

mitochondrial long-chained fatty acid oxidation was strongly associated with a range of metabolic phenotypes in Greenlanders and may influence attained height in Greenlanders [106].

Previously, exposure to DDE was found associated with Parkinson disease in Arctic Inuit [107]. The xenobiotic efflux membrane p-glycoprotein gene (ABCB1) modified the associations of exposure to lipophilic POP and Parkinson's disease. People with variants of membrane transporter ABCB1 may be more susceptible to Parkinson's disease [108,109].

Genetic association studies traditionally being performed in large homogeneous populations; however, several studies have shown that it can be valuable to use founder populations and use small and historically isolated populations. Moltke et al 2014 [80] aimed to identify genetic variants associated with glucose homoeostasis in the Greenlandic population by mapping association of four T2D-related traits: plasma glucose and serum insulin levels at fasting and 2 h after an oral glucose load. They found a novel association of a common TBC1D4 nonsense variant with T2D and elevated circulating glucose and insulin levels after an oral glucose load. Thus, a genetic variant in the gene *TBC1D4* involved in glucose homoeostasis is associated with glucose homoeostasis and Type 2 diabetes in the Greenlandic population [80]. Chemical substances can interact and induce similar effects additively, synergistically or non-additively. Mostly, studies focus on single chemical exposures and not mixture exposures and might thereby underscore the effect outcome(s). Negative confounding can underestimate chemicals causing toxicity (e.g. MeHg, PCB) and compounds having benefits (e.g. omega-3 PUFA in seafood) [5].

Maternal smoking and ethnicity modify the association of prenatal exposure to PCB and birth weight [110]. Moreover, it was shown that nutrition status can influence metabolic syndrome risk and Zn may modify the association of incident metabolic syndrome with omega-6 PUFAs and PUFA metabolism enzymes [111].

Summary on key finding of environmental exposures and health effects

In birth cohort studies, prenatal exposure to MeHg can explain most of the neurodevelopmental deficits. However, postnatal MeHg exposure also appears to contribute, especially in relation to visuospatial processing and memory. Marine fatty acids appear to diminish the MeHg effect on the central nervous system. Prenatal exposure to PFAS and organochlorines have negative effect on child behaviour, whereas parent-reported prenatal exposure to PCB153 and DDE compounds seems not to have a negative effect on child behaviour at preschool age.

Vitamin D deficiency might be increasing the risk of autism spectrum upon exposure to environmental toxins. Moreover, low habitual iodine intake in pregnant women is associated with mothers reporting poorer child language, poorer school performance, and increased likelihood of special educational needs at the age of 8 years.

Dietary exposure to environmental contaminants in the circumpolar area indicates a negative impact on the immune system, such as demonstrated by inhibition of antibody formation to child vaccines. Inflammation markers in Inuit were associated with traditional Greenlandic diet with high POP content. Limited evidence suggests a link between POP exposure and childhood asthma and eczema. Early life MMR vaccination might be an effect-modifier being protective against allergy and asthma. Further studies are needed on pre- and postnatal windows of vulnerability and identification of the most immunotoxic substances.

Transition from a traditional marine diet to imported western food is evident in Greenlandic pregnant women. Currently, traditional marine foods represent 12% of the diet with imported western foods responsible for the remaining 88%. However, despite a decrease in the intake of traditional foods, POP and metal levels in pregnant Inuit women are still higher than in Caucasian women (e.g. Danish women) and occur at a level shown to affect foetal growth (e.g. PFOA, Cd, Cu) and development in Greenlandic Inuit. Although lower than in the past, smoking frequency for pregnant women in Greenland is still high (36%) and affects foetal growth. The high rate of tobacco smoking during pregnancy and impacts on foetal growth are of concern and require action.

Reproductive health is affected by POP exposure. PFAS exposure may impair female fertility and high exposure to some environmental organochlorines/metals/phthalates may affect the male reproductive system. POP interfere with the male reproductive system such as inverse association with semen quality/motility (e.g. dioxins, PCB153), positive associations with reproductive hormones (e.g. HCB and Cd vs testosterone), inverse associations between testosterone and DEHP metabolites, positive associations between POP and reproductive parameters (Hg vs inhibin B, HCB vs sex hormone-binding globulin), and sperm aneuploidy/disomy in adulthood suggesting impacts on testicular maturation and function. However, further studies are needed to confirm these findings.

The protective effect of EPA and DHA in Inuit diets on myocardial infarctions is diminished by the adverse effect of exposure to MeHg in the diet. Therefore, promoting the increased consumption of fish species with high EPA+DHA levels and low MeHg levels may help to prevent myocardial infarctions among Inuit.

No significant associations were observed between PCB, organochlorine pesticides and blood pressure among Greenlanders. Most remarkable is a recent prospective study of Inuit in Greenland showing no association between blood Hg and risk of developing cardiovascular diseases.

POP are endocrine-disrupting chemicals that mimic the function of endogenous hormones, such as by eliciting xeno-oestrogenic and xeno-androgenic activities. The combined xeno-oestrogenic activity of lipophilic POP and combined PFAS serum mixtures in pregnant women is inversely associated with foetal growth indices.

POP (PCB, OC, PFAS and PBDEs) can interfere with thyroid hormone homoeostasis. Early-life exposure to POP affects newborn thyroid hormone levels, and may increase risk of neurological disorders (e.g. ADHD).

Some studies suggest that maternal exposure to endocrine-disrupting chemicals can increase risk of childhood obesity. Exposure to POP affects diabetic parameters, such as beta cell function and may be a risk factor for developing Type 2 diabetes.

The identification of genetic risk in TBC1D4 gene variants with loss-of-gene-function give new insights into the genetics of Type 2 diabetes and support the existence of high-effect genetic risk factors in isolated populations such as Greenlanders.

As endocrine-disrupting chemicals POP elicit xeno-oestrogenic activity and can downregulate placental ABCG2 protein expression (efflux transporters in the placenta) increasing the risk of foetal POP exposure.

Cancer among certain Indigenous Arctic Peoples is of increasing concern. The circumpolar Inuit have rates for several cancer sites that exceed all other regions in the world. From 1989 to 2008, a marked increase in lung, colorectal and female breast cancers linked to a western lifestyle has been shown, while cervical cancer has declined. Endocrine-disrupting chemicals such as some POP (e.g. PCB, PFAS), heavy metals (e.g. Cd), and phthalates are potential carcinogens and may play a role in the increased incidence of breast, prostate and lung cancers. These contaminants might interact with microorganisms to influence the development of liver cancer.

The genetic polymorphisms of key genes involving metabolism of xenobiotic chemicals could influence the levels of POP and heavy metals in humans and modify the level of environmental contaminant exposure in the Arctic population. This in turn can influence the association with the health effects of these contaminants. Genetic variants emerging as an adaptation to extreme environmental conditions can increase cancer risk as an interaction with transition to Western lifestyle and diet. A genetic variant in a gene (*TBC1D4)* involved in glucose homoeostasis is associated with glucose homoeostasis and Type 2 diabetes in the Greenlandic population. Exposure to POP increases risk of Parkinson's disease for humans carrying variants of membrane transporter ABCB1 gene.

DNA methylation is a genetic modification that can influence gene expression. Prenatal exposure to POP can cause changes in sex-specific DNA methylation of genes associated with reproductive, cardiovascular and neural/behavioural disruption. DNA methylation can increase and/or decrease gene expression and DNA methylation relates to the risk of breast cancer. Genetic variants involved in the synthesis and metabolism of oestrogens can increase risk of breast cancer. Exposure to POP such as PCB, dioxin, and PFAS can affect sperm DNA methylation and polymorphisms and thus might adversely influence male reproductive function.

Effect modifiers are other factors that can affect the association between a specific exposure and its outcome. Maternal smoking and ethnicity modify prenatal POP exposure and lower birth weight, and non-Caucasian women that had smoked during pregnancy had a higher risk having offspring with low birth weight. Zinc may modify the association between incident metabolic syndrome and omega-6 PUFAs and PUFA metabolism enzymes. The protective effect of omega-6 PUFAs such as linoleic acid on metabolic syndrome and the positive association between serum delta-6-desaturase and risk of metabolic syndrome were stronger for the middle-aged and older men from eastern Finland with higher serum Zn concentrations.

Conclusion

This summary on health effects associated with measured contaminants in the Arctic document the absolute need for a continued biomonitoring of environmental exposures, lifestyle, diet and the parameters related to health outcomes. Future investigation must focus more on genetically and effect modifiers and mixture of environmental contaminant exposures in contrast to single compounds since chemical compounds can interact and result in additive and/or synergistically effect outcomes.

Abbreviation list

ADHD	Attention-deficit hyperactivity disorder
Ag	Silver
AhR	Aryl hydrocarbon receptor

BMI	Body mass index
Br	Bromine
Cd	Cadmium
Cr	Chromium
Cu	Cupper
DEHP	Di(2- ethylhexyl) phthalate
DHA	Docosahexaenoic acid
DINP	Diisononyl phthalate
EPA	Eicosapentaenoic acid
ER	Estrogen receptor
Fe	Iron
FGI	Fetal growth indices
HBV	Hepatitis B virus
HCB	Hexachlorobenzene
Hg	Mercury
HNF4α	Hepatocyte nuclear factor 4 alpha
HQ	Hazard quotient
MeHg	Methylmercury
Ni	Nickel
OAT4	Organic anion transporter 4
OCP	Organochlorine pesticide
PBDE	Polybrominated diphenyl ether
PCB	Polychlorinated biphenyl
PCDD	Polychlorinated dibenzodioxin
PFOA	Perfluorooctanoic acid
PFAS	Per- and polyfluoroalkyl substance
PFOS	Perfluorooctane sulphonic acid
POP	Persistent organic pollutant
PUFA	Polyunsaturated fatty acid
QA/QC	Quality assurance/quality control
TCDD	2,3,7,8-tetrachlorodibenzodioxin
TEQ	Toxic equivalent
TH	Thyroid hormones
T4	Thyroxine
T3	Triiodothyronine
TPO-Ab	Thyroid-peroxidase-antibody
TSH	Stimulating hormone
Zn	Zinc

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Disclosure statement

No potential conflict of interest was reported by the author(s).

Author contributions

Conceptualization, Eva Cecilie Bonefeld-Jørgensen (E.B-J); writing – original draft preparation, E.B-J; writing – review and editing, E.B-J, Manhai Long (ML); all authors have read and agreed to the published version of the manuscript.

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