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Perfluoroalkyl Substances in the Circumpolar Arctic and Northern Populations

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Mini Review

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Abstract

Persistent organic pollutants including perfluoroalkyl substances (PFAS) are globally ubiquitous contaminants transported with sea currents and atmospheric movements, accumulating in the environment, food-chain, animals and humans and possess a potential health risk including the immune-, neurobehavioral-, and reproductive systems. The profile and concentrations found in humans elicit regional differences that might be related to the countries PFAS use, production, lifestyle, and diet. In the Arctic, the PFAS compounds were never produced or used, however, the Arctic Indigenous and northern populations consuming traditional diet including marine mammals at the top of the food-chain (e.g., whales, seals, polar bears) are particularly exposed to PFAS. This mini review gives a short overview on health effects in the circumpolar Arctic populations and aims to compare the PFAS levels in the Arctic with primary focus on the period 2010-20 and relate the levels with the general national country populations. As expected, regional concentration and profile differences were found over the circumpolar Arctic with the highest level found in Greenland. Moreover, in general the regulated PFAS (perfluorooctane sulfonate, perfluoro-octanoate, perfluorohexane sulfonate) tend to decrease and the unregulated PFAS (e.g., perfluorononanoic acid, perfluorodecanoic acid, perfluoroundecanoic acid) increases in concentration during this period. Generally, the PFAS levels were higher in men than women increasing with age. For most Arctic regions, the PFAS levels were higher compared to the general national country populations.

Keywords: Perfluoroalkyl Substances; Arctic Populations; Environment

Abbreviations: PFAS: Perfluorohexane Sulfonate; AMAP: Arctic Monitoring and Assessment Programme; POP: Persistent Organic Pollutants; OCP: Organochlorine Pesticides; PCB: Polychlorinated Biphenyls; PBB: Polybrominated Biphenyls; PBDE: Polybrominated Diphenyl Ethers; EFSA: European Food and Safety Authority; PFOA: Perfluorooctanoic Acid; PFNA: Perfluorononanoic Acid; PFHxS: Perfluorohexanesulfonic Acid; PFOS: Perfluorooctane-Sulfonic Acid; MMR: Mumps and Rubella; DNBC: Danish National Birth Cohort; PFOSA : Perfluor-Ooctanesulfonamide; MetS: Metabolic Syndrome; NWT: Northwest Territories.

Introduction

The Circumpolar Arctic include populations from the world's eight northernmost countries: Canada, The United States (USA, Alaska), Finland, Denmark (Greenland and the Faroe Islands), Iceland, Norway, Sweden, and The Russian Federation (Figure 1). The Arctic Monitoring and Assessment Programme (AMAP) is one of six Working Groups of the Arctic Council (Figure 1). The mandate of AMAP is

i. To monitor and assess the status of the Arctic region with respect to pollution and climate change;
ii. To document levels and trends, pathways, 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. Since AMAP was established in 1991, a series of reports on climate and pollution issues of the Arctic have been published in https://www.amap.no/.

Persistent organic pollutants (POP), originating from industrial processes, are transported along sea currents and atmospheric movement, and accumulating in the food chain, all over the globe, especially the arctic marine food chain [1-3]. POP are resistant to degradation and bio-accumulate ubiquitously in environment, animals, and humans [4-6]. Lipophilic POP, accumulating primarily in fatty tissues, include e.g. organochlorine pesticides (OCP), polychlorinated biphenyls (PCB), polybrominated biphenyls (PBB), and polybrominated diphenyl ethers (PBDE), whereas perfluoroalkyl substances (PFAS), including e.g. perfluorinated carboxylic acid (PFCA) and perfluorinated sulfonic acid (PFSA), are amphiphilic compounds binding to blood proteins and stored mainly in internal organs like liver, kidney, and fetal tissues [7-10]. Humans are exposed to POP mainly through food intake and industrial products e.g., cooling fluids, flame retardants, food packing, cook ware, and impregnated garments and furniture via dust inhalation or for fetuses via placenta transfer [5,11].

In general, the levels of most lipophilic POP are declining in the Arctic populations [12,13] due to a combination of global regulations, national bans, and the Stockholm Convention [14], reducing the level of the contaminants in the marine food web. For some Arctic populations, a reduction in consumption of traditional food including marine mammals such as polar bear, whales, walrus, and seals as well plays a role [15-18]. Even though the significant downwards trend of lipophilic POP elicit the results of international legislation, it must be kept in mind that PFAS and PBDE are still in use and only partly regulated [14]. The PFAS group, with half-lives in humans between 4 and 10 years, have been used since the 1950s and already at that time found in fish and humans [19, 20].

The PFAS group include many substances with a wide range of structures and chemical properties [21]; 4000 [22] and 8000 [23] have been listed of which at least 600 PFAS are currently in use [24]. In 2020, the European Food and Safety Authority (EFSA) CONTAM Panel has set the tolerable weekly intake for sum of perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA), perfluorohexanesulfonic acid (PFHxS), and perfluorooctane-sulfonic acid (PFOS) to 4.4 ng/kg body weight per week [25].

The long-term effects of PFAS on the general health status are of concern and an overview of research of detrimental effects in overall [26,27], in the Greenlandic [7,28] and in Arctic populations are given in [29].

In overall, available data provide evidence with certainty that PFAS exposure can suppress the human immune response affecting reduced response to vaccines, delay mammary gland development and lower fetal growth, increase risk of thyroid disease and higher cholesterol levels, liver damage, kidney and testicular cancer and with lower certainty breast cancer [26,30].

Systematic reviews report the effect of POP on respiratory and *immune systems* [31-33]. Several studies in the circumpolar Arctic indicate that POP/PFAS exposure has a negative effect on the immune defense, in the Arctic and globally [34]. In a Faroese cohort, PFAS exposure associated with an increased risk of asthma among age 5 years children being un-vaccinated against measles, mumps and rubella (MMR) but not among 13 years old MMR vaccinated children. The authors suggest that the MMR vaccine might have the potential to negate the PFAS impairment of the immune system [35]. Furthermore, in the same cohort at ages 7 and 13 years, serum immunoglobulin E and prick tests showed that MMR vaccination associated with a reduced risk of developing asthma and allergy indicating a protective effect [36]. Furthermore, prenatal PFAS exposure showed inverse associations with antibody concentrations produced from tetanus and diphtheria vaccines 5 years later, and postnatal PFAS exposure associated with lower serum concentrations of antibodies against diphtheria and anti-tetanus concentrations [37,38]. A Greenlandic study reported a pro-inflammatory role of exposure to POP, demonstrated by the positive association with the markers of inflammation YKL-40 and hsCRP [39]. In Greenlandic pregnant women, it was observed significantly inverse association between several hematological markers (eosinophil, lymphocyte, neutrophil, and white blood cells) and POP including PFAS. The sumPFAS inversely associated with the monocyte, mean corpuscular hemoglobin concentration, plateletcrit, and

platelet count markers but positively with hematocrit and mean erythrocyte corpuscular volume. In overall, the study shows that PFAS influence several hematological markers suggesting immunosuppressive potential of POP/PFAS in Greenlandic Inuit, although further investigations are needed [40]. In contrast, environmental contaminants were not associated with atopy in Finish and Russian studies [41].

With respect to association between exposure to POP and *neurological effects,* there are evidence of adverse effects on child development, but the results are inconsistent, and few studies have studied associations with child behavior. Prenatal exposure to PFAS appear to have indications of negative effect on child behavior. In a Faroese cohort assessing prenatal and age 5 and 7 years PFAS exposure, hyperactivity and conduct problems were associated with higher PFAS levels at age 5-7 years [42]. In a Greenlandic cohort, INUENDO, prenatal PFAS exposure elicited negative effect on child behavioral development and increased hyperactivity [43,44]. In another Greenlandic mother-child cohort, ACCEPT, prenatal organochlorine pesticide exposure associated significantly with problematic child behavior including hyperactivity in 3–5-year-old children. However, at that age no associations were observed between PCB, PFAS, and heavy metals and problematic behavior [45]. In a Danish cohort, Danish National Birth Cohort (DNBC), prenatal PFAS (e.g. PFNA) exposure significantly associated with externalizing behavioral difficulties at age 7 and 11 years [46]. Exposure to POP / PFAS has the potential to interfere, and disrupt endocrine and hormonal related systems [7,9,29,47] including sex hormones and the thyroid hormones.

Studies indicate that *the reproductive system* [29,48-50] is sensitive to exposure to PFAS that can negatively affect fertility [51], and during pregnancy increase miscarriage [52-54], pre- eclampsia, and blood pressure [55]. PFAS can induce endocrine disrupted mediated effects on female reproduction parameters and through endocrine disruption being involved in related diseases e.g., in breast and thyroid [56]. Exposure to PFAS can have negative effects on fetal growth [50,57]. In the Greenlandic ACCEPT mother-child cohort, PFOA was significantly inversely associated with fetal growth indices, whereas positively associated with gestational age was at birth. In general, both lipophillic POP and PFAS showed a negative effect on fetal growth [58]. In the pregnant ACCEPT women's serum, the lipophilic mixture of POPs has a hormone-disrupting effect interfering with both the estrogenic and androgenic receptor activity, which can have a disruptive effect on fetal development and growth [59]. Similarly, it was observed an inversely association between the effect of the actual serum PFAS mixture in Danish pregnant women on estrogen receptor activity and the fetal growth [60]. In another Greenlandic cohort INUENDO, the study suggested that phthalates, PFAS, and organochlorine pesticides can be independently associate with impaired fetal growth [61].

There are some indications that perfluor-ooctanesulfonamide (PFOSA), a PFOS precursor, might affect *female fecundability* [62,63], and especially for Greenlandic women, PFNA was associated with longer time-to-pregnancy [64]. Further research is needed to elucidate the effect of other PFAS to support the hypotheses.

An overview of the potential threat of exposure to PFAS to human spermatozoa was given in a mini review [65] and epidemiological studies link the increased exposure to PFAS with lowered testosterone and semen quality [66], including in Greenlandic men [67]. Although, current studies show some inconsistency across studies of effects on *female fertility and/or male reproduction parameters* weakening the overall conclusion [68]. There is evidence for mechanisms being involved, e.g. semen samples of high-exposure men to organochlorines at age 14 years and in adulthood were associated with sperm chromosomal disomy, suggesting impacts on testicular maturation and function [69]. In high exposed Faroese men, serum PCB disrupted the androgen/estrogen ratio and higher testosterone and sex-hormone-binding globulin [70]. Moreover, PFOS and PCB associated positively with luteinizing hormone and might suggest an interference with testosterone syntheses [71]. In addition, there is indication that PCB 153 can affect semen mobility and that organochlorine compounds and phthalates can adversely affect parameters of male reproductive health [70].

Although traditionally, metabolic syndrome (MetS) was related to unhealthy lifestyle and diet, studies suggest that environmental chemicals can, through endocrine disruption, be related to MetS such as increasing the risk of obesity, hypertension, and disruption of lipid and glucose metabolism [72]. Current knowledge associate PFAS exposure with MetS components such as lipid metabolism and obesity [72]. Studies in Greenlandic Inuit suggest an association between lifestyle and diet and POP/PFAS exposure and MetS components such as higher BMI and obesity [7,28,29,73-75] . Therefore, metabolic disruption is a topic of interest in the Arctic populations and the transition in diet from traditional marine food rich in healthy fatty acids to imported food with higher content of e.g. carbohydrate [17,76], might be involved in the simultaneous increase in diabetes in the original population [77,78]. In Greenlandic children aged 3,5 – 5,5 years old, the prevalence of overweight and obesity were higher than previously reported [79], supporting an earlier child study (age 5-9 years old, including Greenland) on prenatal PFOA and PFOS exposure and increase in waist-to- height ratio [80]. Maternal exposure to PFOS and PFOA associated with increased BMI z-scores and/or overweight/obesity in Faroese children [81].

In a review on epidemiologic evidence of the risk of PFAS induced cancer, the association with most evidence was testicular and kidney cancer. Some other studies suggested association between PFAS exposure and cancer e.g. prostate and breast cancer but require further long-term and large size studies [82]. PFOSA associated with breast cancer risk in a case-control follow-up 15 years after plasma sampling, a study nested in the DNBC [83], and in the Health Development Pregnancy Cohort, maternal PFOSA exposure associated with daughters' risk of breast cancer [84], but not for other analyzed PFAS. It has been observed a substantial increase in cancer among circumpolar Inuit during the last half of the 20th century especially for lifestyle and diet associated cancers such as breast, colon, and lung where environmental contaminant plays a role [85]. POP exposure can induce genetic alterations [86] e.g. DNA methylation [87], decrease defense against oxidative stress [88] and thereby increase the risk of cancer [29,89-92]. Significant, positive associations between breast cancer risk and PCB and PFAS exposure were observed in Greenlandic Inuit women [92]. Analyzing the combined mixture effect of serum lipophilic POP and PFAS on sex hormone receptor function, suggest sex hormone disruption as well as involvement of other pathways, respectively [93]. Studying the possible biological mechanism involved in exposure to POP and breast cancer suggest that PFAS might influence the risk by promotion of cell proliferation, accelerating the transition from G0/G1 phase to S phase of the cell cycle and stimulating migration and invasion of normal breast epithelial cells. Moreover, in vitro studies suggest a possible carcinogen mechanism of PFAS via inducement of oxidative stress, inhibiting the hepatocyte nuclear factor HNF4α, and stimulate expression of proto-oncogenes in liver cells [29]. It is well known that different chemicals can interact and result in additive, synergistic and non-additive outcomes. Focusing on single compounds might underestimate the negative health effects and more focus should be on chemical mixtures exposures and health effect. Moreover, negative confounding causing toxicity (e.g. heavy metals and smoking) and beneficial factors such as omega-3 PUFA in seafood should be a part of the future research models.

PFAS Concentrations in Circumpolar and Northern Populations

A study aiming to compare the PFAS concentrations in serum from pregnant women in birth cohorts from four countries (Denmark, China, Norway, and Greenland) observed similar concentration and composition of serum PFAS for the Danish and the Norwegian women but otherwise different across the cohorts [5]. Generally, higher sum PFAS levels were seen in Greenlandic and Chinese women, and the PFSA were highest in Greenland although comparable levels for PFOS for the four countries, and the PFCA were highest in China but perfluoroundecanoic acid (PFUnA / PFUnDA) being higher in Greenlandic women; the lowest PFOA levels among the four cohorts was observed in Greenland [5]. These differences in PFAS profile might relate to country use and production of PFAS, population lifestyle and diet, and the health risks might also differ between the countries.

Across the circumpolar Arctic populations, there are relatively strong time trends for some POP going back to 1990s. Time trends for PFAS among pregnant women and women in childbearing age are covered for several time-periods (1990-1999, 2000-2007, 2007-2013, 2013-2018) [12]. In general, the contaminant levels differ by regions and mostly higher in males than females, and long- chain PFAS (≥ 6 carbons) such as PFOS and PFOA are more frequently measured in serum at higher concentration than short-chain PFAS e.g., perfluorobutane sulfonic acid (C4, PFBS) and perfluorobutanoic acid (C4, PFBA). Predominately, PFOS and PFOA are measured across the Arctic with the highest concentrations observed in Greenland, especially at the east coast [8,34,76] (Table 1).

Table 1A & Table 1B shows the PFAS levels of six compounds often measured in serum of Arctic original populations and northern populations primarily of Caucasian origin, respectively.

In the Kuskokwim region of *Alaska,* the levels of PFOS and PFOA elicit a slightly increase since 2009-2012, although comparable with the levels in the USA population NHANES study and many non-Arctic regions [12]. Notable exceptions are that PFNA and PFUnDA are elevated among St. Lawrence Island residents compared to men and women participating in NHANES (USA). The elevated concentrations of long chain PFAS in serum are likely due to exposure from traditional foods [12,94].

In the *Canadian Arctic*, the largest difference between eastern and western Canadian Arctic were for PFOS and the smallest difference were for PFOA and PFHxS. PFNA, perfluorodecanoic acid (PFDA) and PFUnDA tend to be higher in the Nunavik population (Table 1A) [12]. In the western region Old Crow, Yukon, the serum PFAS were similar or lower compared to the general national Canadian population (2016-2017), whereas PFNA levels were higher and increasing by age [95]. The regions of the Northwest Territories (NWT) elicited similar PFAS data with Yukon, although a bit higher PFOS level, and showed detectable serum data for PFOS, PFOA, PFNA and PFHxS, but most samples were in non-detectable levels for PFBA, perfluorohexane acid (PFHxA), PFUnDA and PFBS [95]. The highest concentration of all was in the eastern Nunavik region of Canada, particularly PFOS and PFNA, being up to 2-10-fold higher for some contaminants. The time trends of PFAS

during 2004, 2007, 2012, 2017 in pregnant Inuit women from Nunavik elicited significant declines for PFOS, PFOA and PFHxS ($p<0.0001$). In contrast, PFCA such as PFNA, PFDA, and PFUnDA were increasing during 2012 - 2017 [96]. In adults from Nunavik, the PFAS concentration was in general twice the level in the general national Canadian population, PFNA and PFUnDA 7-fold higher and PFDA 4-fold higher. PFOS, PFNA, PFDA, PFUnDA and PFHxS increased with age, but not PFBA. Notably, the PFNA in adolescents (age 16-19 years) were higher than PFOS and PFOA [97].

In *Greenland*, the geographical mother-child ACCEPT cohort established during 2010-2015 [76,98,99] observed a general regional difference in PFAS levels with the highest level in the order east > north > Disko Bay > west > south of Greenland (Table 1A). The study observed notably higher levels of the PFCA, PFNA and PFUnDA than PFOA [38]. A declining trend for PFOS and PFOA appeared, when comparing Greenlandic women since 1997/2006 to 2015 [13,58,92,99,100]. A recent time trend study reported, for both women and men across Greenland, between 1994 and 2015, a significant 5.82–11.7% annually decrease for the regulated PFOS, PFOA and PFHxS, whereas an increasing trend for women across Greenland of the un-regulated PFNA, PFDA and PFUdA [13]. The time trend tendency was supported by the ACCEPT follow-up study 3-5 years since pregnancy (2019-2020) on intra-individual levels (Table 1A) [18]. Moreover, the ACCEPT follow-up study median concentrations of most PFAS (but not PFDA and PFUnA) were significantly higher in fathers than in mothers, being 1.4–4.6 times higher, and for the residential town a generally higher level was seen in Ilulissat compared to Sisimiut and Nuuk [18] (Table 1A). In addition, the ACCEPT follow-up study included 3-5 years old children, and the PFAS levels were measured in blood spots showing the following order of mean concentrations PFOS > PFOA > PFNA > PFOSA > PFUnA > PFHxS > PFDA and similar levels for the remaining compounds; interestingly, the PFOSA was not measured in serum above the detection level (1.19 µg/L) of the mother and fathers indicating the importance to measure the PFAS in the different blood matrices [101,102].

Another mother-child cohort, INUENDO, including *Greenlanders* was established 2002-2004 [61,70,103]. Data on PFAS for the mothers and male partners 2002-2004 showed very much higher levels of PFOS being up to ten-fold (20.6 and 47.4 ug/L, pregnant women, and men, respectively) compared to the other PFAS measured (e.g., PFHxS, PFNA, PFDA, PFUnDA). Moreover, higher level was found in men up to 2-fold or more especially for PFOS, PFOA, PFNA, PFDA [69,104]. An OCEANS study including the INUENDO and the IVAAQ cohort study involved recruitment of *Greenlandic children* during 2012-2015 aged 7 – 12 years (Table 1A) [104]. Five Greenlandic communities were included: four from the west coast (Disko Bay area, Nuuk, Sisimiut, Manitsoq) and one from the east coast (Tasiilaq). Most PFAS were detected in almost all children with PFOS being predominant, while the levels of PFHxA and perfluoroheptanoic acid (PFHpA) were below detection limit in 94% and approximately 22% of the children, respectively. As observed in the ACCEPT cohort study, the region of residence associate with the contaminant level being highest at the east coast being e.g., up to 9.1-fold higher than the PFOS level in Nuuk eliciting the lowest level, and the highest concentration of PFOA was seen in Ilulissat. Generally similar levels were observed in girls and boys except for PFHpA being highest in boys. Moreover, consumption of traditional Greenlandic food was associated with increased concentration of environmental chemicals [104].

Comparing the PFAS levels of Greenlandic pregnant women cross-sectional year 2010-15 (Table 1A) with Danish pregnant women during 2008-13 [5,105], all PFAS (PFOS, PFOA, PFNA, PFDA, PFUnDA) but PFHxS, elicited the highest level in Greenlandic pregnant women.

In *Icelandic pregnant women* PFOS and PFOA were measured in Reykjavik 2009 and the reported levels were similarly compared to most other circumpolar data although slightly lower PFOS (6.2 µg/L plasma) and higher PFOA (4.8 µg/L plasma) [12].

Table 1B gives the PFAS levels of the six compounds most often measured in serum of northern populations of primarily Caucasian origin.

The *Faroe Islands* have initiated several mother-child cohorts since the 1980s (Table 1B). The cohort 1, sampled 1986-1987, measured the PFAS levels since birth, age 7-, 14-, 22- and 28-years old children in 2013-2016. The time trend of PFAS from age year 7 to year 28 was clearly a decrease over the time of 21 year for the regulated PFOS, PFOA, PFHxS (partly) and an increase of unregulated PFNA and PFDA [106]. The *Faroe Island* cohort 3 were sampled 1998-2000, including mother-child pairs, reported similar PFAS at ages 5 and 7.5 years, but a large decline in PFOS and PFOA levels in the children at age 13 years, whereas the levels for PFHxS, PFNA and PFDA elicited no clear shift among the children [12]. The *Faroe Island* cohort 5 was initiated 2007- 2009 and the levels of PFAS were measured in the mother and for the child at age 1.5, 5 and 9 years old. The time trend of PFAS elicited a decline in PFOS and PFOA levels between 1.5 and 5 years of age, whereas the other PFAS (PFNA, PFDA, PFHxS) appeared higher at 5 years of age [107]. A general decrease in PFAS levels was reported for children between 5 and 9 years of age [12]. In summary, the PFAS exposure data for the *Faroe Island* cohort 1, 3 and 5 were reported to peak in 2000 and decreased by 14.4% per year since with the majority decrease attributed to regulation and therefore rapid decrease of PFOS and PFOA [108].

1A. Country	Alaska		Arctic Canada							Greenland (ACCEPT)								Greenland (OCEAN)
Region/ Cohort	St Lawrence Island		Old Crow, Yukon		Northwest Territories		Nunavik			Cross-sectional	North	Disko Bay area	West	South	East	West** followup		West & East***
Sample Year	2013-2014		2019		2019		2017			2010-2015						2019-2020		2012-2015
Sex	M	W	M	W	M	W	M	W	pW	pW	pW	pW	pW	pW	pW	M#	W	Children (M+F)
Mean age	29	28	43	39	48	45	35	35	24	27.5	28.4	27.1	27.3	28.6	27.4	37.2	33.8	10[c]
Sample N	38	47	26	28	57	55	3	3	91	499	32	122	283	43	19	76	101	338
PFAS*																		
PFOS	6.96	3.29	1.4	0.78	2.5	1.6	7.7	5.3	3.3	9.06	12.2	10.4	8.17	7.12	18.3	7.71	4.36	8.68[c]
PFOA	1.45	0.85	1.1	0.76	1.1	0.72	1.4	0.74	0.55	1.04	0.97	1.10	1.04	0.91	1.12	0.96	0.38	2.28[c]
PFHxS	<DL	<DL	0.56	0.26	0.58	0.23	0.98	0.47	0.26	0.52	0.67	0.49	0.49	0.42	1.49	0.76	0.27	na
PFNA	2.75	2.07	1.2	0.77	1.5	1.3	4.3	3.6	2.5	1.19	1.42	1.3	1.1	0.94	2.52	1.12	0.67	1.40[c]
PFDA	<DL	<DL	0.16	0.16	0.22	0.20	0.90	0.84	0.52	0.74	0.98	0.88	0.67	0.55	1.51	0.52	0.44	0.49[c]
PFUnDA	1.04	0.88	0.11	0.10	<0.10	<0.10	0.87	0.91	0.60	1.42	1.91	1.77	1.25	1.01	3.4	0.60	0.63	na

1B. Country	Faroe Island[§]				Norway				Sweden			Finland		
Region/ cohort	Cohort 1		Cohort 3	Cohort 5	MISA[a]	Northern adolescent		Oslo adult's	Northern adults	Cross-sectional adolescent	First time mothers Uppsala	Eastern LUKAS2 cohort Children [e]		
Sample Year(s)	2013-16		2011-12	2016-18	2007-09	2010-11		2013-14	2001-13	2016-17	2017-19	2005-06	2010-11	2014-15
Sex	M	W	M + F	M + F	pW	M	F	M + W	W	M + F	W (3W, AD)[d]	M + F	M + F	M + F
Mean age	28	28	13.2	9	31	16.5	16.3	41	56 ± 6	14.7 (10-21)	30.4 (21.9-45.3)	1	6	10.5
Sample N	220	179	526	381	391	445	495	61	187	1096/1098	110	54	54	54
PFAS*														
PFOS	9.14	4.59	6.6	3.27	7.7	5.71	6.52	6.95[b]	15[c]	4.6[c]	3.2[c]	5.5 [c]	2.1 [c]	1.5[c]
PFOA	1.16	1.06	2.0	1.44	3.9	2.14	1.86	2.39[b]	2.7[c]	1.40[c]	1.0[c]	6.6 [c]	2.7 [c]	1.5[c]
PFHxS	0.54	0.25	0.4	0.27	0.43	0.80	0.95	0.95[b]	1.2[c]	1.80[c]	1.8[c]	0.47 [c]	0.42 [c]	0.21[c]
PFNA	1.14	0.78	0.7	0.65	0.58	0.61	0.48	1.06[b]	0.83[c]	0.4[c]	0.4[c]	0.8 [c]	0.54 [c]	0.36[c]
PFDA	0.40	0.29	0.3	0.24	0.23	0.27	0.19	0.40[b]	0.33[c]	0.2[c]	0.2[c]	na	na	na
PFUnDA	na	na	na	0.17	0.24	0.17	0.14	0.43[b]	0.22[c]	<LOQ	0.2[c]	na	na	na

Table 1: PFAS concentrations in circumpolar Arctic regions with primary focus on the period 2010-2020: A. original populations / Inuit; B. populations primarily of Caucasian origin.

N: number; *: µg/L serum, PFAS concentrations are given in geometric mean if nothing else is given; M: men; W: women; pW: pregnant women; Greenland (ACCEPT): the recruitment of pW was performed in 16 towns: North (Qaanaaq, Upernavik, Uummannaq), Disko Bay (Ilulissat, Aasiaat, Qeqertarsuaq, Qasigiannguit), West (Sisimiut, Maniitsoq, Nuuk, Paamiut), South (Qaqortoq, Nanortalik, Narsaq), East (Tasiilaq, Ittoqqortoormiit); **: The ACCEPT follow-up: Ilulissat (Disko Bay: M/W: 8%/11%), Sisimiut (M/W: 17%/21%, Nuuk (M/W: 66%/68%); #: the father; na: not available; ***: the OCEAN study including five communities fours from the west coast (Disko Bay area, Nuuk, Sisimiut, Manitsoq) and one from the east coast (Tasiilaq).

F: female; DL: detection limit; LOQ: limit of quantification; §: the oldest children in the three specific cohorts (1 or 3 or 5); a: The northern Norway Mother-Child Contaminant Cohort including pregnant women from Finnmark, Troms, and Nordland in northern Norway; b: the PFAS concentrations are given in arithmetic mean; c: median (IQR); d: AD: weeks after delivery; e: sample data in same individual at the three time points.

The level of PFAS in pregnant women (MISA) of the *Northern Arctic Norway* sampled 2007-2009 [109] (Table 1B) elicited similar levels as Danish pregnant women for samples taken in the same period for both PFOS, PFOA, PFNA, PFDA, PFHxS and PFUnDA [5]. However, comparing the MISA pregnant women with Greenlandic ACCEPT pregnant women cross-sectional (Table 1A), the Inuit women had higher PFOS, lower PFOA and similar PFHxS levels, but approximately 2-fold higher levels of PFNA, PFDA, whereas the PFUnDA level was almost 6-7-fold higher in the Greenlandic women (Table 1A & B) [5,12]. In *Northern Arctic Norway* adolescents 2010-2011 at mean age 16-17 years, the PFAS elicited the highest level of PFOS and PFOA, inversely associated with age, and being slightly lower compared to the MISA pregnant women (Table 1B). Higher PFHxS levels compared to the MISA data were found, whereas the level of PFNA, PFDA and PFUnDA were like the MISA data. Pooled adult men and women PFAS data from Oslo, Norway sampled during 2013-14 at mean age 41 (range 20-66) measured in serum, plasma, and whole blood. A strong correlation among the three matrices was observed, however of the measured PFAS, PFOSA was found at the highest concentrations in whole blood, and PFHxA was only detected in whole blood, indicating the importance of measuring PFAS in both serum/plasma and whole blood [101]. Again, PFOS and PFOA elicited the highest serum levels, and compared to the MISA pregnant women lower PFOA, higher PFHxS, PFNA, PFDA and PFUnDA (Table 1B) [101].

In *Wästerbotten,* the *Northern region of Sweden,* PFAS were measured in 187 women 1990 – 2003 (age 46 ± 6) and again 2001-2013 (56 ± 6) (Table 1B). The study found relatively high PFOS levels compared to other Arctic data. The concentration of six PFAS with concentration above detection limit showed in this 10 years period a 15% and 29% decrease for PFOS and PFOA, respectively. In contrast, PFNA and PFHxS elicited an increase of 53% and 13%, respectively [110]. A cross-sectional national survey of adolescents conducted in 2016-2017 (mean age 14.7 (range 10-21) showed higher PFAS (PFNA, PFHxS, PFOS) levels in boys than girls (Table 1B). Compared to the Northern adolescents in Norway, the Swedish showed lower PFOS, PFOA but higher PFHxS [12,111]. Swedish PFAS time trend during 1996 – 2017/19 of first-time mothers in Uppsala showed in this period a clear decrease of PFOS and PFOA but increasing levels of PFNA, PFDA and PFUnDA (Table 1B) [112].

In *eastern Finland* the PFAS levels in cord blood from a birth cohort at the Turku University Hospital 1997-2002, were as follows (median µg/L; n=156): PFOS 5.2, PFOA 2.1, PFNA 0.01, PFHxS 0.01, and PFDA 0.01; these Finish data showed significant lower levels of PFOS, PFOA and PFNA compared to Danish cord blood from the joint birth cohorts at Rigshospitalet and Hvidovre Hospital 1997-2001 [(median µg/L; n=59) PFOS (9.1), PFOA (2.6), PFHxS (0.01), PFNA (0.06), PFDA (0,01)] recruited in the same period [91]. Moreover, a time trend study of children from the Finnish birth cohort study (LUKAS2) in Eastern Finland (recruited at Kuopio University Hospital) was conducted during 2005 – 2015 for children at 1, 6 and 10.5 years of age with sample data in same individual at the three time points (Table 1B) [113]. The data elicited a clear significant decreasing trend over time for PFOS, PFOA, PFNA and PFHxS (not significant) with no obvious difference between boys and girls. PFOS and PFOA accounted for 73-80% of the median concentrations, where the PFOA level was higher than PFOS at 1 and 6 years of age [113].

Although, the observed age decreasing time trend in the children must take into consideration the influence on serum concentration by e.g., parallel growth dilution, variation in elimination rates with ages and temporal changes in external exposures.

Summary

The profile and concentrations of PFAS found in the circumpolar Arctic populations elicit regional differences that might be related to PFAS exposure via lifestyle and diet. This PFAS differences might affects the health risk. The Arctic indigenous and northern populations consuming traditional diet including marine mammals at the top of the food-chain (e.g., whales, seals, polar bears) are particularly exposed to POP/PFAS. Regional concentration and profile differences were found cross sectional over the circumpolar Arctic with the highest level found in Greenland. In general, during the 2010-20 period, the regulated PFAS (PFOS, PFOA, PFHxS) tend to decrease and the unregulated PFAS (e.g., PFNA, PFDA, PFUnDA) increased in concentration. Higher PFAS levels were found in men than women, and higher levels in older humans than adolescent and young children. For most Arctic regions, the PFAS levels were higher compared to the general national country populations.

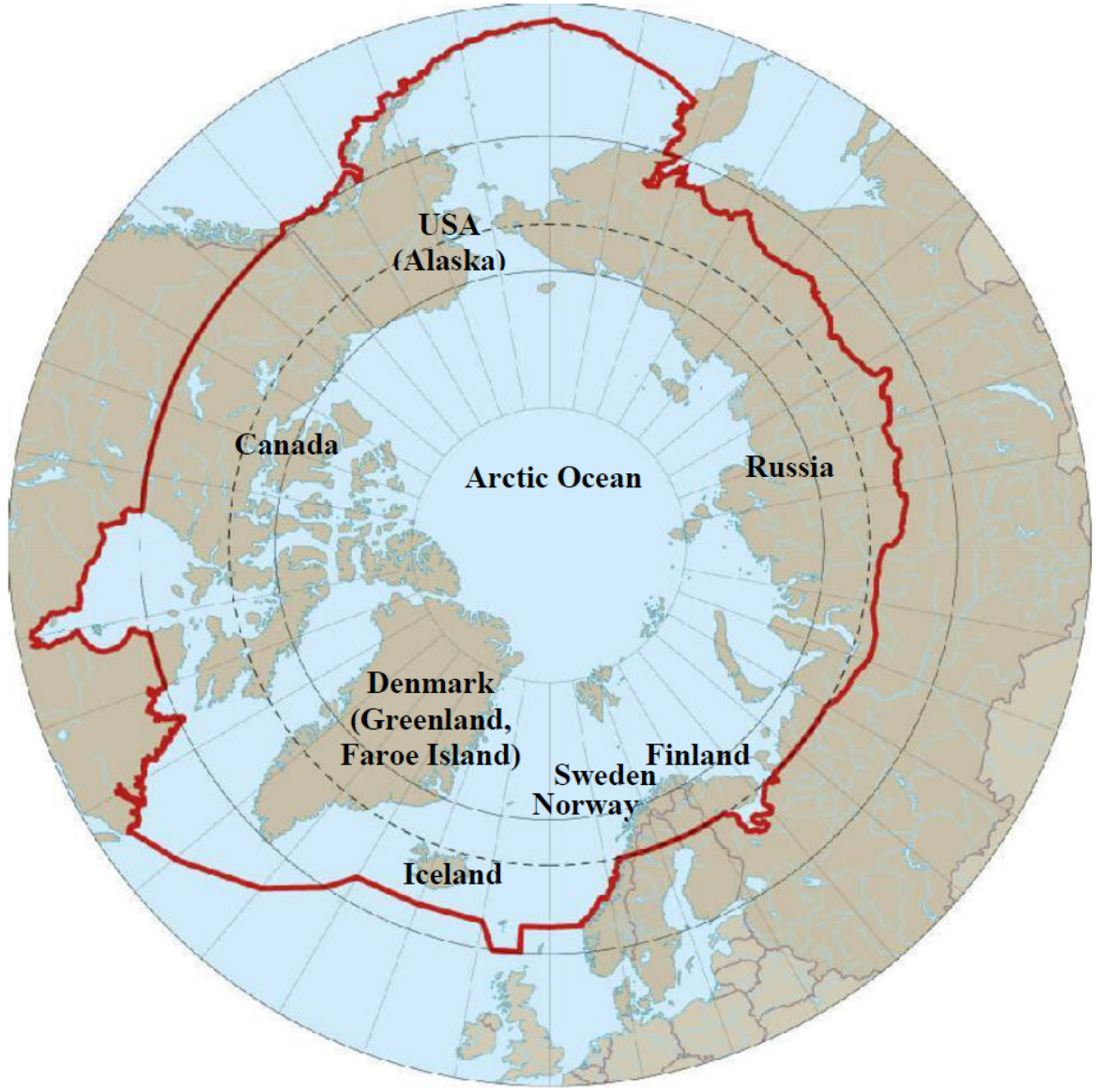

Figure 1: Map of the eight countries surrounding the Arctic Ocean in the Arctic region. Red line gives the area border of the AMAP assessment programme (Modified from AMAP (1998) and [114]).

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