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Review

Cross-cutting studies of per- and polyfluorinated alkyl substances (PFAS) in Arctic wildlife and humans

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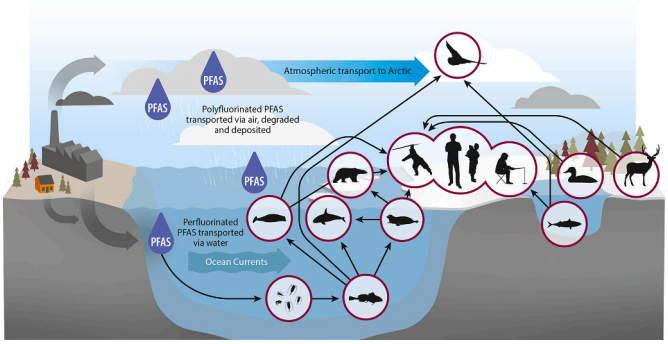
HIGHLIGHTS

- Long-range transport, reactions and novel PFAS affect profiles and levels in Arctic.
- Time-trends of PFAS across Arctic diverge among environment, wildlife and humans.
- Greatest PFAS concentrations present in liver of mammals and seabird eggs.
- PFAS persist, accumulate, and pose threats to Arctic biodiversity and humans.
- PFAS effects in humans and wildlife seem similar, but polar bears at greater risk.

GRAPHICAL ABSTRACT



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ABSTRACT

This cross-cutting review focuses on the presence and impacts of per- and polyfluoroalkyl substances (PFAS) in the Arctic. Several PFAS undergo long-range transport via atmospheric (volatile polyfluorinated compounds) and oceanic pathways (perfluorinated alkyl acids, PFAAs), causing widespread contamination of the Arctic. Beyond targeting a few well-known PFAS, applying sum parameters, suspect and non-targeted screening are promising approaches to elucidate predominant sources, transport, and pathways of PFAS in the Arctic environment, wildlife, and humans, and establish their time-trends. Across wildlife species, concentrations were dominated by perfluorooctane sulfonic acid (PFOS), followed by perfluorononanoic acid (PFNA); highest concentrations were present in mammalian livers and bird eggs. Time trends were similar for East Greenland ringed seals (*Pusa hispida*) and polar bears (*Ursus maritimus*). In polar bears, PFOS concentrations increased from the 1980s to 2006, with a secondary peak in 2014–2021, while PFNA increased regularly in the Canadian and Greenlandic ringed seals and polar bear livers. Human time trends vary regionally (though lacking for the Russian Arctic), and to the extent local Arctic human populations rely on traditional wildlife diets, such as marine mammals. Arctic human cohort studies implied that several PFAAs are immunotoxic, carcinogenic or contribute to carcinogenicity, and affect the reproductive, endocrine and cardiometabolic systems. Physiological, endocrine, and reproductive effects linked to PFAS exposure were largely similar among humans, polar bears, and Arctic seabirds. For most polar bear subpopulations across the Arctic, modeled serum concentrations exceeded PFOS levels in human populations, several of which already exceeded the established immunotoxic thresholds for the most severe risk category. Data is typically limited to the western Arctic region and populations. Monitoring of legacy and novel PFAS across the entire Arctic region, combined with proactive community engagement and international restrictions on PFAS production remain critical to mitigate PFAS exposure and its health impacts in the Arctic.

1. Introduction

In recent years, evidence from epidemiological and toxicological studies have raised attention to per- and polyfluoroalkyl substances (PFAS) as a potential hazard to human and environmental health. Effects include dyslipidemia, immune system functions, reproductive and developmental functions, as well as endocrine functions and metabolism (ATSDR, 2021). Bioaccumulative perfluoroalkyl acids (PFAAs) have been detected in large parts of the human population (Kato et al., 2011), making PFAS exposure and effects a global public health issue. Perfluorooctane sulfonic acid (PFOS), perfluorooctanoic acid (PFOA), and perfluorohexane sulfonic acid (PFHxS) were the first PFAS studied and have the greatest evidence of adverse health effects (ATSDR, 2021; EFSA, 2020). As several thousand individual PFAS exist (Glüge et al., 2020), many others than these initially reported PFAS are present in the environment and considered to have similar health effects (Ritscher et al., 2018; Lerner, 2018). PFAS concentrations and temporal trends in Arctic wildlife have been studied quite extensively, but biological effects have been considered to a lesser degree. Due to a lack of toxicological effect thresholds, no exhaustive risk assessment is currently possible for Arctic wildlife (Andrews et al., 2023).

PFAS are a complex group of compounds with high environmental persistence, owing to the stable C—F bond. However, precursors can undergo reactions to form more persistent PFAAs, including PFOS, PFOA and PFHxS, in the environment and in vivo (Glaser et al., 2021; Zhang et al., 2021). PFAS are emitted to the environment from various sources including manufacturing facilities, wastewater discharge, landfill leachates and the use in consumer products (De Silva et al., 2021). Numerous studies have reported the detection of PFAS in different abiotic and biotic environmental components such as surface and groundwater, rain, soil, sediments, in animals and in manufactured items (Dickman and Aga, 2022). PFAS' stability and mobility leads to pollution issues related to groundwater and drinking water (McMahon and Tokranov, 2022). It has also led to their global dispersion, including transport to and accumulation in the Arctic and Antarctic environments (Muir and Miaz, 2021; Bengtson Nash et al., 2010).

The Arctic is particularly vulnerable to PFAS given the proximity to industrialized regions, and transport via air and ocean currents. Transport patterns include the long-range atmospheric transport of neutral PFAA precursors, which can be oxidized to more stable compounds, and the ocean transport of ionic PFAS (e.g., PFOS), which is different from the typical transport pattern of well-known persistent organic pollutants (POPs) (Li et al., 2018; Wong et al., 2018; MacInnis et al., 2017). A particular role of sea spray aerosols in the global transport of PFAAs has been discussed, but is not fully understood (Johansson et al., 2019). Longer chain PFAAs (e.g. perfluorocarboxylic acids (PFCAs) of ≥C9 and

perfluorosulfonic acids (PFSAs), such as PFOS) are the compounds best known to biomagnify in food webs including those in the Arctic (Kelly et al., 2009; Muir et al., 2019).

PFOS and perfluorononanoic acid (PFNA) in particular are two major bioaccumulative PFAS currently measured in wildlife and humans as part of the Greenland monitoring program for persistent organic pollutants (POPs) (Rigét et al., 2013) and Canada's Northern Contaminants Program (Letcher et al., 2018a; Houde et al., 2020). PFOS is a regulated legacy PFAS listed in 2009 under Annex B of the Stockholm Convention on POPs (SC-POPs). Later, PFOA and PFHxS were listed under Annex A of the SC-POPs in 2019 and 2022, respectively. Long-chained PFCAs (C9-C21) (including PFNA) are a group of PFAS currently under review for regulation under the SC-POPs, based on bioaccumulation, toxicity, persistence, and ability to be transported over long distances (UNEP, 2023).

The first public report that suggested that the general population was exposed to fluorine-substituted organic compounds appeared in Nature in 1968 (Taves, 1968). A report from 1980 documented the presence of organic fluorine compounds in serum from American fluorochemical plant workers (Ubel et al., 1980). First reports on PFAS in the Arctic were published over 20 years ago (Giesy and Kannan, 2001; Bossi et al., 2005; Martin et al., 2004). Given their bioaccumulation in Arctic food webs, some PFAS have been found at high concentrations in wildlife species traditionally consumed by Indigenous populations living in the Arctic, especially in marine mammals, but also fish and caribou (Muir et al., 2019; Roos et al., 2022). As a consequence, besides occupationally exposed workers, Arctic human populations are among those experiencing the highest exposure to PFAS on the planet (Sonne et al., 2023; AMAP, 2022).

Although industrial production started >70 years ago, toxicology knowledge on PFAS lagged behind exposure data. Due to these slower developments (Grandjean et al., 2011), the broader scientific community is in the early stages of understanding the effects of PFAS on environmental and human health. For example, mammalian chronic toxicity studies have been published only based on rats, and insufficient attention has been paid to exposures during sensitive developmental stages. Few epidemiology studies have focused on exposures prenatally or during infancy, even though early development is a highly vulnerable period that must be taken into regard when determining exposure limits (Grandjean et al., 2015; Goeden et al., 2019). The International Agency for Research on Cancer (IARC) recently classified PFOA and PFOS as carcinogenic and possibly carcinogenic to humans, respectively. A recent review of PFAS exposures thoroughly assessed the health implications, but did not cover the Arctic concerns (NASEM, 2022).

Despite extensive monitoring data, effect information on wildlife is sparse, although awareness has recently grown on potential PFAS effects on wildlife (Andrews et al., 2023; Bangma et al., 2022). The recent assessment report of the Arctic Monitoring and Assessment Programme (AMAP) on biological effects on Arctic animals, documented for some PFAAs indications of neurotoxic effects in polar bears and effects on thyroid hormone balances in several species (AMAP, 2018; Dietz et al., 2019). The National Library of Medicine (PubMed) now lists a total of >20,000 publications when searching for titles using the words 'polyfluorinated' or 'perfluor*', but only 6000 for human studies. When Arctic is added as a keyword, only about 90 publications are listed. Before 1990, only 60 articles on PFAS had been published with these search terms. Accordingly, most of the articles on PFAS in the Arctic have been published in the last 20 years. As has been seen on numerous occasions on environmental pollutants (European Environment Agency, 2001), the evidence available today may well underestimate the true extent of PFAS toxicity.

This review is an outcome of the workshop "Contaminants in Wildlife and Humans" held in May 2023 in Sandbjerg, Denmark, organized by the Kingdom of Denmark to support AMAP. The workshop was part of an initiative by the Kingdom of Denmark and Canada to better integrate AMAP's work to monitor and assess contaminants, and to establish writing groups for wildlife health and human health in the Arctic. Four writing groups were established to prepare review articles, one of which (this paper) addresses cross-cutting knowledge regarding the presence and impacts of PFAS in Arctic wildlife and humans; other papers in preparation address biological effects in wildlife and humans, contaminants of emerging Arctic concern, and zoonosis.

The objective of this study was to address the fate of PFAS in the Arctic in a cross-cutting manner, combining information from different scientific disciplines to discuss processes relevant for the transport to and accumulation of PFAS in the Arctic, including exposure of wildlife and humans, time-trends and associated effects. Given the focus on an interdisciplinary approach, the study does not aim at an exhaustive presentation of the state of knowledge of PFAS in the Arctic but highlights an integrative approach to PFAS in the Arctic and associated gaps in methodology and scientific knowledge.

2. Analysis of PFAS

While initial work on PFAS used terms such as "fluorochemicals" or "perfluorochemical surfactants", the growing number of PFAS detected in the environment and their unique physical-chemical properties soon required an unambiguous definition of this group. Buck et al. defined PFAS as all aliphatic compounds with a -C_nF_{2n+1}- moiety (Buck et al., 2011). However, this definition excluded e.g. aromatic and cyclic molecules or molecules with functional groups on both ends of the carbon chain and was therefore revised by an expert group under the Organization for Economic Cooperation and Development (OECD) (OECD, 2021). According to their proposal, PFAS are fluorinated substances with at least one fully fluorinated methyl or methylene carbon atom (without any H or other halogen attached to it) (OECD, 2021). The experts highlight that the proposal should not be connected to decisions on how PFAS should be grouped in regulatory and voluntary actions, and it does not inform either whether or not a compound is harmful (OECD, 2021). Furthermore, they propose that depending on the purpose of a specific task, user-specific "working scopes" are created in a transparent manner that may be less comprehensive than the definition proposed in the report (OECD, 2021). The proposed definition excludes molecules such as tetrafluoroethylene, which do not have a saturated carbon atom, but includes certain polymeric PFAS. While some polymeric PFAS can be found across the world (same as other nano-, micro- and large plastic pieces) (Lohmann and Letcher, 2023), the focus here is on the non-polymeric, or small molecular PFAS. The PFAS scope of this review is essentially defined by the compounds measured in Arctic monitoring and research studies, primarily bioaccumulative PFAS in humans and wildlife and e.g. volatile fluorotelomer alcohols (FTOH) in air, with selection of these compounds and data for which cross-cutting discussions for Arctic wildlife and humans were possible.

Given the large number of PFAS in commerce, conventional target analyses only cover a relatively small part of possible PFAS. For example, the Drinking Water Directive of the European Union (EU) includes 20 PFAAs, and the EU recommends monitoring 22 (plus six emerging) PFAS in food and feed, of these 21 PFAAs and perfluorooctane sulfonamide (FOSA) (EU, 2020, 2022). A comprehensive list, also including PFAA precursors, has been proposed for human biomonitoring (Vorkamp et al., 2021). Similarly, the most recent version of the United States Environmental Protection Agency (US EPA) Method 1633 (US EPA, 2024), is wide in scope as pertaining to matrix (tissue, water, and solids) and targets 39 individual substances, of these 18 PFAAs (i.e. 11 PFCAs and 7 PFSAs), 3 fluorotelomer carboxylic acids (FTCAs), 3 fluorotelomer sulfonates (FTSs), 7 perfluorooctane sulfonamido-based (FASAs), 5 ether carboxylate, and 3 ether sulfonates. These target analyses are highly optimized regarding accuracy and precision and allow measurements of low levels in e.g. human matrices.

PFAS from blood plasma and serum are typically extracted following similar protocols in human (Halldorsson et al., 2012; Haug et al., 2018; Starling et al., 2014; Whitworth et al., 2012) terrestrial (Greaves and

Letcher, 2013; Tartu et al., 2018; Jouanneau et al., 2022; Choy et al., 2022) and aquatic species (Villanger et al., 2020). The distribution of some PFAS differs between human serum/plasma and red blood cells (Kärrman et al., 2006). While most studies measure PFAS in serum/plasma, levels of certain PFAS are higher in whole blood. For example, Swedish blood samples drawn in 2004 contained FOSA levels that were about five times higher in whole blood compared to plasma/serum, and levels in whole blood up to 19.7–22.9 ng mL^{-1} have been reported (Kärrman et al., 2006). Norwegian whole blood sampled in 2013/2014 was also enriched with FOSA, whereas other FASAs, i.e. *N*-methylperfluorooctanesulfonamide (Me-FOSA) and N-ethylperfluorooctanesulfonamide (Et-FOSA), were not detected, pointing at different exposure and/or distribution behavior despite the structural similarity (Poothong et al., 2017). Blood samples from China collected in 2020 contained Me-FOSA, Et-FOSA and FOSA in plasma (Liu et al., 2023), and like previous studies, FOSA was the only FASA elevated in whole blood (0.25 ng mL^{-1} vs. 0.042 ng mL^{-1} in whole blood and plasma, respectively). Therefore, both media should be measured to assess the real FOSA blood concentration in future studies.

Plasma or serum (0.1–1 g) is usually spiked with labeled internal standards, and proteins are precipitated using acetonitrile (Powley et al., 2005), methanol (Haug et al., 2009), or aqueous-organic solvent mixes (Greaves and Letcher, 2013). Extracts are subsequently cleaned using dispersive or cartridge solid phases, with graphitized carbon, C8, or weak anion exchange (WAX). These methods have been optimized with appropriate recoveries to measure several legacy and emerging PFAS, including short- and long-chain PFAAs, linear- and branched-PFOS (Greaves and Letcher, 2013; Jouanneau et al., 2022), PFAA precursors (e.g., FTCAs, FTSs, FOSAs, 4,8-dioxa-3H-perfluorononanoic acid (ADONA), perfluoro-2-methyl-3-oxahexanoic acid (HFPO-DA; "Gen-X"), and 9-chlorohexadecafluoro-3-oxanonane-1-sulfonate (F53-B)) (Tartu et al., 2018; Jouanneau et al., 2022; Villanger et al., 2020).

PFAS are extracted primarily from liver tissue in Arctic terrestrial and aquatic biota. However, other tissues, including kidney, egg and muscle or whole-body fish homogenate have also been analyzed to evaluate trophic magnification and/or human dietary exposure (Aas et al., 2014; Müller et al., 2011; Lescord et al., 2015). The extractions have followed similar protocols to those for liver extractions. Most extraction methods use between 0.25 and 2 g (wet weight) tissue and employ solvent extraction, typically methanol or acetonitrile with or without base addition (US EPA, 2024). After solvent extraction, further clean up using graphitized carbon or WAX materials can be applied. Analyte signals may be amplified by concentrating extracts via a steady stream of nitrogen gas. Recoveries are assessed by spike and recovery experiments. Depending on the purpose of the study, methods for biota predominately target long-chain PFAAs, while others also include short-chain PFAAs (Bossi et al., 2015; Letcher et al., 2018a; Aas et al., 2014; Müller et al., 2011; Lescord et al., 2015), FOSAs (Letcher et al., 2018a; Roos et al., 2022; Aas et al., 2014; Lescord et al., 2015) and other PFAA precursors, and branched-PFOS (Lescord et al., 2015). These PFAS are typically analyzed with high performance liquid chromatography mass spectrometry, in particular tandem mass spectrometry (LC-MS/MS) but also LC with high resolution mass spectrometry (HRMS). Biota extraction methods have been applied to sediment and soil with success (Ahrens et al., 2023; MacInnis et al., 2019a).

To study transport pathways of PFAS to the Arctic, other environmental media are also relevant for chemical analysis. Water samples are typically extracted with solid-phase extraction (SPE), for example using WAX cartridges (Benskin et al., 2012a). Neutral and volatile precursors are present in air (Bossi et al., 2016) and require analysis by gas chromatography (GC). Air monitoring for PFAS analysis is performed in several Arctic countries, for both neutral and ionized PFAS, usually based on high volume samplers (Wong et al., 2021). Bossi et al. (2016) sampled neutral PFAS using a quartz fiber filter and a polyurethane foam (PUF)/XAD-2/PUF cartridge. The filter and cartridge were spiked with labeled internal standards, extracted with methyl-*tert*-butyl ether: acetone (1:1) and analyzed by GC–MS (Bossi et al., 2016). Quality assurance measures across methods include method blanks and reference materials extracted alongside each batch of samples, instrument blanks, and repeated sample analysis to assess reproducibility and inter-day variation and field blanks for atmospheric samples.

To account for the high number of PFAS, complementary analytical methods are gaining importance, including determinations of "PFAS Total" and suspect/non-target screening (NTS) techniques. "PFAS Total" describes sum parameters that do not aim at identifying individual compounds, but quantify a total PFAS content, such as Total Fluorine (TF), Total Organic Fluorine (TOF), Extractable Organic Fluorine (EOF) and Total Oxidizable Precursors (TOP) (Kärrman and Yeung, 2021). Parameters like TF or TOF are not PFAS-specific but can also include other fluorinated compounds, including some non-readily extractable compounds (Lauria et al., 2022). EOF is measured on samples extracted using protocols optimized for isolating PFAS, and therefore includes targeted PFAS. However, the gap between targeted PFAS and EOF levels is often quite large, indicating the presence of unknown PFAS, PFAS precursors, or other fluorinated organic compounds (e.g., mono-fluorinated pesticides and pharmaceuticals) (Aro et al., 2022). NTS techniques aim at identifying unknown or suspected compounds, based on mass spectra obtained from HRMS and additional information, such as retention time indices (Hollender et al., 2023). A suspect screening approach is a promising technique to identify the presence of PFAS in Arctic samples other than those included in the target analysis. Ideally, NTS techniques can be used to identify compounds contributing to "PFAS Total", including TOP assays, towards a fluorine mass balance approach (Kärrman and Yeung, 2021). However, NTS approaches are typically very time-consuming and often constrained by higher detection limits than target analyses (Hollender et al., 2023; Chu and Letcher, 2024). Furthermore, the sampling and sample preparation carries risks of false positives and false negatives, through contamination and unintended removal of compounds, respectively (Hajeb et al., 2022). Including PFAS Total in routine monitoring has been suggested for the EU Drinking Water Directive, as a complementary method to the sum of 20 PFAAs (EU, 2020). Parametric values that ensure safe life-long consumption of the water, based on current scientific knowledge, have been defined for both parameters, i.e. 0.5 μg/L and 0.1 μg/L for PFAS Total and "sum of PFAS" (i.e. of the 20 PFAAs), respectively. Technical guidelines have recently been issued and specify the methods and their performance criteria (European Commission, 2024).

Recent studies have also applied sum parameters and/or NTS of PFAS in an Arctic context. In 2020, a comprehensive study including marine mammals from Greenland, Iceland, Sweden and the US Atlantic coast used a fluorine mass balance approach consisting of TF, EOF, suspect screening and target analysis (Spaan et al., 2020). Cioni and Plassmann (2023) analyzed PFAS via TF, EOF, TOP assay and target analysis in human serum from the general population of Tromsø. Chu and Letcher (2024) reported a targeted/NTS approach for PFAS with application to liver samples from polar bears from southern and western Hudson Bay. They reported a total of 32 PFAS identified by NTS of which 3 previously unknown PFAS were all (branched) isomers of perfluorodecanoic acid (PFDA), perfluorodecane sulfonate (PFDS) and perfluoroundecanoic acid (PFUnDA). Several PFAS, including short-chain PFCAs in air, were recently reported in an NTS study on Arctic biota, air and human serum (Zhu et al., 2024). Although still subject to method development and harmonization efforts (Dürig et al., 2023), these new analytical approaches hold a great potential for insights into the complex group of PFAS in a variety of Arctic samples.

3. Transport pathways of PFAS to the Arctic

Emissions of PFAS occur during production at fluorochemical industrial sites (D'Ambro and Pye, 2021), but also during the use phase of commercial products, and lastly during the disposal phase, with known emissions from wastewater treatment plants and landfills. Several studies estimated global PFAS emissions and identified different sources

as the most important ones, depending on the compound, also varying over time (Boucher et al., 2019; Wang et al., 2014). For example, the highest emissions of PFHxS were estimated to be caused by degradation of sulfonamide- and sulfonamidoethanol-based precursors, whereas highest emissions of PFDS were related to use and disposal (Wang and Boucher, 2017). The atmospheric long-range transport of PFAA precursors to polar regions and subsequent atmospheric transformation to persistent PFAAs will cause diffuse contamination of the environment and food webs, with PFAS being present and transported in air, rain, snow, and water. Bioaccumulation and biomagnification occur for some PFAAs through a series of enrichment steps in food webs, leading to indirect human exposure through diet. Thus, while near contaminated (source) regions, human exposure to PFAS from drinking water is of primary concern, in remote regions far from point sources such as airport operations and firefighting training sites, the consumption of local wildlife species that are central to Indigenous population culture, diet and nutrition has been identified as the main exposure pathway (detailed in Section 7 below).

Detailed atmospheric studies have shown the reaction pathways for polyfluorinated compounds and the transformation of e.g. 8:2 fluorotelomer alcohol (8:2 FTOH) into roughly equal amounts of PFOA and PFNA. 8:2 FTOH's atmospheric lifetime is about 20–40 days (Ellis et al., 2003; Wallington et al., 2006; Young and Mabury, 2010), sufficient for causing a global background of these chemicals. The yield of either PFNA or PFOA is about 3–6 % each, roughly sufficient to explain the presence of these and other PFCAs in remote regions. According to Wallington et al. (2006), smaller PFCAs (< C8) are likely to be formed in yields similar to that of PFOA. Global annual emissions of 8:2 FTOH were estimated at about 150 tons per year in 2004, with about 50 tons emitted from North America alone (Yarwood et al., 2007). Following 8:2 FTOH atmospheric transport to the Arctic, in situ transformation to PFNA is of particular concern to the Arctic region, as it bioaccumulates strongly in food webs (and stronger than PFOA) (Haukås et al., 2007). As a consequence, exposure to PFNA is elevated among many Arctic human populations. Indeed, in 2016–2017, when compared to the general Canadian population, exposure to PFNA was higher by a factor of 7 among Inuit pregnant women and adults living in Nunavik, Northern Quebec, Canada (Aker et al., 2023a).

Monitoring PFAS in abiotic environmental Arctic media in concert with wildlife improves the extent of our understanding in sources and mechanisms of transport. While PFOS and long-chain PFCAs (≥C9) are prevalent in Arctic wildlife, these are not the predominant PFAS in Arctic marine waters (Muir and Miaz, 2021). Garnett et al. (2021) measured PFAS in snow, sea ice and seawater in the Barents Sea, and reported short and long-chain PFAS in snow with a prevalence of perfluorobutanoic acid (PFBA, (2.6 ng L^{-1}), which comprised 83–89 % of the PFCA profile (∑C4-C12 PFCAs). Garnett et al. (2021) noted higher concentrations in seawater at 0.5 m depth compared to 5 m depth and proposed that the sea ice meltwater was a major contributor to the underlying seawater (Table SI-2). This is consistent with observations in Arctic lake ice and the water column (MacInnis et al., 2019b), where C4-C12 PFCAs were consistently detected in lake ice, with a prevalence of PFBA. During the melt period, depth sampling indicated higher concentrations at the surface of the water. These results emphasize the contribution of atmospheric deposition of PFAS to aquatic systems and underscore the importance of monitoring PFAS in atmospheric samples including snow, ice, aerosol, and air.

The oceanic transport of ionic PFAS occurs on slower time scales but also has the potential to transport the compounds away from production zones in industrial regions into the Arctic Ocean. Transport into the Arctic Ocean is dominated by Atlantic water masses entering via the Fram Strait (Gulf Stream from North America, and the Norwegian current), with some Pacific Water via the Bering Strait. However, transport from the Atlantic Ocean is limited by the formation of Arctic deep water, where the hitherto warm water of the Gulf Stream cools off sufficiently to cause sinking, thereby shielding the Arctic Ocean from water-borne contaminants. The presence of PFAS in ocean water was first reported by Yamashita et al. (2008). Concentrations of PFOA and PFOS reached hundreds of pg L^{-1} in the North Atlantic Ocean but were non-detectable in the Southern Ocean water samples. Importantly, there were no major vertical gradients of PFOA or PFOS in North Atlantic regions of deep-water formation, highlighting the movement of surface water to depth with the contained PFAS. In contrast, vertical profiles at other ocean sites displayed strong vertical gradients (Dunn et al., 2024). Beyond transport with water masses, PFAS can potentially also reach deeper waters through settling of particles (González-Gaya et al., 2019).

The impact of continental emissions and deep-water formation on the transport of PFAAs was examined in more detail for PFOS. Of the land-based emissions considered, about 20 % were transported northwards towards the Arctic, of which about 70 % were deflected again from the Arctic by the deep-water formation as part of the Atlantic meridional overturning circulation (Zhang et al., 2017). Even remote, sparsely populated waters of the Arctic Ocean are impacted by PFAS: In the Canadian Arctic waters in 2005, PFAS were detected everywhere, dominated by PFOA and PFOS at the 20 pg L^{-1} level (Benskin et al., 2012a). Isomer profiling suggested that PFOA in the eastern Arctic Ocean (2005–2009) was sourced mainly from slow oceanic transport of legacy electrochemical fluorination production, as used by its fomer producer 3 M, and described as historic sources (Benskin et al., 2012b). More southerly marine water samples demonstrated a contemporary mix of PFOA sources from fluorotelomerization and electrochemical fluorination processes (Benskin et al., 2012b). Yeung et al. (2017) combined measurements of PFAS in the Arctic Ocean in 2012 with ice core data to develop an Arctic Ocean model. For PFOS, ocean transport was estimated to account for almost all inputs to the Arctic Ocean, while for PFOA approximately 34–59 % of surface water concentrations were estimated to be from atmospheric inputs. The role of the cryosphere in the PFAS transport is not fully understood, but interactions between atmospheric deposition, accumulation in sea ice and releases to the surrounding water have been shown (Garnett et al., 2021). In addition, PFAS have been widely detected in ice cores and glaciers, making meltwater an important intra-Arctic transport pathway (Garnett et al., 2021; Young et al., 2007). Overall, the results implied that atmospheric sources are as important as ocean circulation for PFCAs, but ocean circulation dominates for PFOS. In addition, contributions are likely to change over time towards more recent fluorotelomer-based emission sources.

While results by Joerss et al. (2020) indicated the presence of HFPO-DA (also known as "Gen X"), a novel PFAS, in waters of the North Atlantic Ocean, the detection has not been replicated elsewhere (Dunn et al., 2024). HFPO-DA is a replacement compound for PFOA in the production of fluoropolymers. Although PFAS have been widely detected in rivers at lower latitudes (Pétré et al., 2022), the riverine transport of PFAS to the Arctic Ocean has not been well-studied. MacInnis et al. (2019b) applied a mass balance approach to Lake Hazen, Nunavut, Canada by analyzing PFAS in snowmelt, proglacial rivers, permafrost seep inputs and its outflow to the Arctic Ocean by the Ruggles River. This river alone amounted to 0.64 kg per year PFAS discharge (MacInnis et al., 2022).

In addition to the long-range environmental transport, local sources have been identified for PFAS in the Arctic, such as fire training sites, airports, landfills, and wastewater discharges (Ahrens et al., 2023). These have mainly been shown for Svalbard, but also for the Canadian Arctic (Lescord et al., 2015; Cabrerizo et al., 2018; Skaar et al., 2019) Overall, there is evidence that both atmospheric and oceanic transport of PFAS play a role in their transport into the Arctic region, along with local emissions from point sources within the Arctic, though quantifying these is inherently uncertain. In addition to long-range environmental transport, the import of and direct contact with PFAS-containing consumer goods and other manufactured products to the Arctic may also lead to exposure, but to a lesser extent (De Silva et al., 2021) (see Section 7).

4. PFAS source attribution to characterize exposures in Arctic wildlife and humans

Different sources release varying combinations of PFAS that can produce characteristic source signatures in the environment and exposed humans and wildlife (Zhang et al., 2016). Colloquially this is referred to as PFAS "fingerprinting." The composition of PFAS in different sources may not be unique because some common PFAS like PFOS and PFOA are found in most samples. However, much useful information on source contributions can be gleaned by examining the relative composition in different environmental, wildlife and human samples. As research on PFAS mixtures progresses, it will be important to examine whether exposures from different PFAS sources is associated with varying health outcomes.

Multivariate statistical analysis can help to identify predominant sources of PFAS exposure in Arctic/Subarctic populations. For example, Hu et al. (2018) compared the composition of PFAS in mothers, children and Faroese whaling men between 2004 and 2007. The PFAS profile in mothers/women was highly variable, likely due to enhanced elimination of PFAS during childbirth and breastfeeding (Mogensen et al., 2015; Timmermann et al., 2017) and can therefore not be used as a reliable indicator of external exposure sources in this context. Individual PFAS may also partition differently to tissues and have varying half-lives in organisms/humans. Thus, other than dietary habits, the original exposure profile can be affected by variability in partitioning and elimination rates between individuals such as adult males versus women of childbearing age. Prior work on long-finned pilot whales (*Globicephala melas*) in the North Atlantic has also shown that PFAS concentrations are lowest in females compared to adult and juvenile males due to enhanced elimination processes (Dassuncao et al., 2017).

Long-chain PFAAs typically bioaccumulate to higher concentrations than short-chain compounds in wildlife (Houde et al., 2011; Boisvert et al., 2019). Dassuncao et al. (2018) used hair total mercury concentrations in Faroese children as a tracer of seafood consumption and found a strong correlation with PFUnDA in the children's serum. In general, PFUnDA and PFNA can be useful tracers of seafood related PFAS exposures among Arctic populations (Hu et al., 2018). Even in the general U.S. population, consumption of seafood such as shellfish meals in the last 30 days is associated with higher concentrations of long-chain PFAAs in serum (PFNA and PFDA) (Hu et al., 2018). Similarly, Haug et al. (2010) showed that seafood accounted for 80–93 % of PFOS and PFUnDA in the serum of participants in the Norwegian Fish and Game Survey.

Compared to adults, the serum of Faroese children contained higher proportions of shorter-chain PFCAs and precursors that are consistent with PFAS commonly found in consumer products such as carpets and textiles (Morales-McDevitt et al., 2021). Prior work noted the importance of North Atlantic pilot whales as a dietary source of PFAS exposure in the Faroe Islands (Weihe et al., 2008). However, Dassuncao et al. (2018) estimated using serum data and toxicokinetic modeling that seafood accounted for less than half of the PFAA exposures of Faroese children between the late 1980s and 2000s, but increased in the early 2010s. The relative importance of seafood as an exposure source increased even though marine mammal consumption rates and concentrations of PFOS and precursors in whale meat declined (Dassuncao et al., 2017). This likely reflects the phase out in production and use of some PFAAs in consumer products. However, declines in serum concentrations of legacy PFAS may also indicate replacement with alternate PFAS that have not been analyzed, rather than a true change in exposure sources over time.

When using PFAS composition to infer information on external exposure routes, it is important to compare samples collected at similar time periods because the composition of PFAS produced and accumulated in the environment has shifted over time (Wang and Boucher, 2017). Dassuncao et al. (2018) examined temporal shifts in the serum composition of PFAS in Faroese children over time and noted distinct differences in their composition before and after the phase out of production of PFOS and its precursors by 3 M using electrochemical fluorination around the year 2000. A clear temporal shift in the serum composition of PFAS away from PFOS precursors and C8 chemistry towards the shorter chain alternatives was apparent in serum PFAS profiles (Dassuncao et al., 2018). Similarly, large changes in the composition of PFAS in North Atlantic pilot whales were observed between 1986 and 2013 mainly due to declines in the PFOS precursor FOSA after the phase out of production of the parent chemical (POSF) by 3 M (Dassuncao et al., 2017); though trends in seals and polar bears differed (see Section 6.2). The rapid timescales over which these declines were achieved reinforce the success of global regulatory strategies at reducing environmental exposures of vulnerable Arctic and Subarctic populations to some legacy PFAS.

Like other POPs, several PFAS undergo bioaccumulation and enrichment in the food web, often dominated by PFOS and PFNA (while PFOA does not strongly concentrate in marine mammals and fish). However, strongest bioconcentration factors (BCFs) have been observed for C12-C14 PFCA, though measurements of these compounds are somewhat limited (De Silva et al., 2021). The greatest trophic magnification of PFAAs has been observed in avian and marine mammalian food webs. In the Arctic context, this singled out polar bears, toothed whales, and predatory birds as wildlife species with the greatest likelihood of accumulating high concentrations of PFAS (Bossi et al., 2005).

5. Concentration comparisons across wildlife

Since PFOS and PFNA often dominate the bioaccumulation and enrichment of known PFAS in Arctic food webs (Kelly et al., 2009; Bossi et al., 2005), we focused on PFOS and PFNA when comparing PFAS concentrations across Arctic wildlife. The geometric or arithmetic mean and median PFOS and PFNA concentrations for Arctic biota were compiled for an adult inter-species comparison. Data from samples collected directly from locations impacted by airports and/or wastewater discharge were excluded. Inter-species analysis was conducted for blood (i.e., plasma, serum, and whole blood), bird eggs, muscle, and liver tissue. Inter-species comparison of PFOS and PFNA concentrations were made with the assumption that serum and plasma concentrations were interchangeable and whole blood concentrations were half that of serum and plasma (Ehresman et al., 2007). Possible effects of time-trends of PFAS on body burdens were not considered. PFOS data were reported inconsistently in the literature, as such, the inter-species comparison of PFOS concentrations was based on mean or median concentrations of one of the following: branched PFOS, linear PFOS, or the sum of linear and branched PFOS. Data for lipid-rich tissues such as seal blubber are available for some species, but generally showing much lower concentrations of PFOS and PFNA than e.g. liver tissues (e.g. Boisvert et al., 2019) Therefore, these have not been included. In total, data for 102 animals and tissues were included in the comparison of PFNA and PFOS concentrations in Arctic biota between 2010 and 2023 (the complete dataset is in the Supplemental information Table SI-1).

Data are sparse for PFAS concentrations in muscle tissue from Arctic biota due to the focus of studies on PFAS in liver tissue; however, muscle from Arctic biota reflects an important food that is commonly consumed by subsistence harvesters and Indigenous communities, which should be considered in future monitoring programs. PFNA concentrations were reported for muscle tissue in Arctic biota (Fig. 1B), with the lowest concentrations reported in Arctic char (*Salvelinus alpinus*) (Lescord et al., 2015; Carlsson et al., 2016), wolves (*Canis lupus*) (Müller et al., 2011), and reindeer (*Rangifer tatrandus*) (Roos et al., 2022). A similar trend was observed for PFOS in muscle tissue, with the lowest mean and median concentrations observed in Arctic char (Lescord et al., 2015; Carlsson et al., 2016) and wolves (Müller et al., 2011).

PFNA and PFOS concentrations in plasma, serum, or whole blood (converted to plasma) were available for a small number of Arctic biota (Fig. 1D; Table SI-1) (Jouanneau et al., 2022; Choy et al., 2022; Villanger

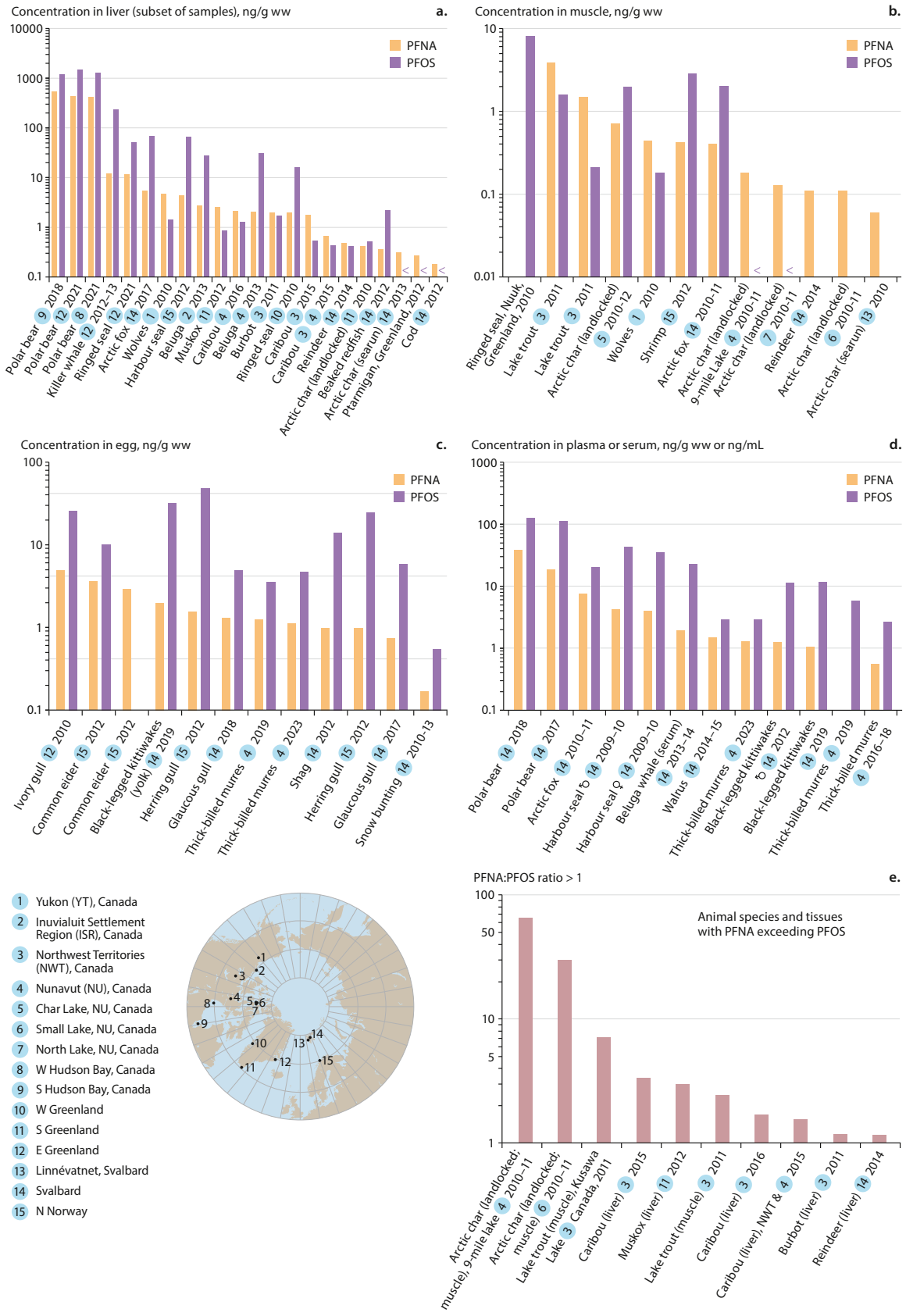

Fig. 1. Arctic wildlife concentrations of PFOS and PFNA in: a) liver tissue, b) muscle tissue, c) eggs, d) plasma or serum e) ratio of PFNA/PFOS of species for which higher PFNA concentrations compared to PFOS was observed. For details on concentrations and references please see Table SI-1.

et al., 2020; Aas et al., 2014; Elliott and Fernie, 2024; Tartu et al., 2014; Scotter et al., 2019; Herzke et al., 2023; Routti et al., 2014). Mean and median PFNA concentrations ranged from 0.55 ng g^{-1} ww in thick-billed murres (*Uria lomvia*) (Choy et al., 2022; Elliott and Fernie, 2024) to 38 ng g^{-1} in polar bear (Herzke et al., 2023) (more details on PFAS in Hudson Bay and East Greenland polar bears are in Section 6.2). PFOS concentrations were greater than PFNA concentrations in all plasma and serum samples analyzed. PFOS concentrations followed a similar trend to PFNA concentrations in plasma and serum, except for the Arctic fox (*Vulpes lagopus*) and walrus (*Odobenus rosmarus*). PFOS concentrations were lowest in thick-billed murres (2.6 ng g^{-1} ww (Choy et al., 2022; Elliott and Fernie, 2024); and highest in polar bear (111–125 ng g^{-1}) (Herzke et al., 2023).

Mean and median PFNA concentrations in liver ranged from 0.18 ng g^{-1} ww in Atlantic cod (*Gadus morhua*) (Kowalczyk et al., 2020) to 510 ng g^{-1} ww in polar bear; PFOS concentrations ranged from below detection limit in Arctic char (Carlsson et al., 2016) to 3100 ng g^{-1} ww in polar bear (Gebbink et al., 2016; Fig. 1A). The mean and median PFNA concentrations reported for polar bear were 3.8 to 21 times greater than the greatest concentration reported for ringed seal liver (Boisvert et al., 2019) and 32 to 176 times greater than the most elevated concentration reported for caribou liver (Roos et al., 2022). PFOS concentrations exceeded PFNA concentrations in liver in all samples except for caribou, reindeer, burbot *(Lota lota)* and searun Arctic char.

Mean and median PFNA concentrations ranged from 0.97 ng g^{-1} ww in herring gull (*Larus argentatus*) eggs (Huber et al., 2015) to 4.89 ng g^{-1} ww in ivory gull (*Pagophila eburnea*) eggs (Lucia et al., 2015), (Fig. 1C). PFOS concentrations in eggs ranged from 4.72 ng g^{-1} in thick billed murres (Elliott and Fernie, 2024), to 48.2 ng g^{-1} in herring gulls (Norwegian Environment Agency, 2013). The concentrations of PFNA and PFOS in bird eggs were higher than concentrations reported for muscle tissue from most species, except PFNA was more elevated in lake trout muscle, and PFOS was more elevated in ringed seal muscle. Representing a high trophic level terrestrial bird, peregrine falcon eggs (collected in Greenland between 1986 and 2014) had median concentrations of 3.0 and 55 ng g^{-1} ww for PFNA and PFOS, respectively (Vorkamp et al., 2019).

As shown in Fig. 1E, the concentration of PFNA only exceeded PFOS concentrations in terrestrial mammals (i.e., caribou and reindeer) and freshwater species of fish (i.e., burbot, landlocked char and lake trout), which has implications for consumers of locally harvested traditional foods. This pattern suggests that PFNA transport to the Arctic has stronger atmospheric pathways and therefore both accumulates in the terrestrial and aquatic food webs compared to PFOS, which was more elevated in marine species, reflecting ocean transport as more influential to the deposition of PFOS in the Arctic.

Overall, the review of PFNA and PFOS data from Arctic wildlife indicates that liver and bird eggs accumulate higher concentrations of PFAS than muscle. Marine mammals consistently had the highest concentrations of PFOS in tissues compared to terrestrial and aquatic species, while the contrary was observed for PFNA. There is an urgent need for future studies to focus on concentrations of contaminants in muscle tissue in addition to liver, to respond to questions surrounding food safety, since muscle and liver are both consumed as local traditional foods. In addition, non-lethal sampling of muscle, blood and bird eggs is possible and should be pursued when possible.

6. Time-trends of PFAS in environmental matrices, wildlife and humans

6.1. Time-trends of PFAS abiotic in environmental samples

Monitoring of PFAS in air via the Global Atmospheric Passive Sampling (GAPS) network has been ongoing since 2009 using sorbent impregnated PUF passive samplers and includes three polar sites: Alert, Canada (82.45°N 63.50°W), Barrow, Alaska (71.32°N 156.6°W, now known as Utqiagvik) and Ny-Ålesund, Svalbard (78.90°N 11.89°E). FTOHs were variable but highest concentrations were measured for 6:2 FTOH (<0.4 to 16 pg m^{-3}) compared to 4.4–10 pg m^{-3} 8:2 FTOH and <2–1.1 pg m^{-3}10:2 FTOH. Total FTOH concentrations were similar over the time of the monitoring campaign, i.e. 1.6 to 21.3 pg m^{-3} for ∑C6:2, 8:2, 10:2 FTOH between 2009 and 2015 (Rauert et al., 2018). New results were reported by Saini et al. (2023) for GAPS samples collected in 2017, which continued to show higher FTOH concentrations compared to FOSA and perfluorooctane sulfonamidoethanols. However, in the 2017 samples, 8:2 FTOH was the dominant FTOH, at 1.4–7.2 pg m^{-3} (Saini et al., 2023). In the same samples only Me-FOSA was detected (with up to 0.17 pg m^{-3}), whereas other sulfonyl-based polyfluorinated compounds were below detection limits. Using active air sampling at the same sites, Wong et al. (2018) measured increasing concentrations of 8:2 FTOH and 10:2 FTOH from 2006 to 2012, followed by annual decreases until their final year of sampling in 2017. Bossi et al. (2016) reported volatile neutral PFAS in samples collected with active air sampling at Villum Research Station, Station Nord (81°36′ N 16°40′ W) in Greenland. In this location, FTOHs were also higher than sulfonamides and sulfonamidoethanol-based PFAS. 8:2 FTOH was the dominant congener with concentrations as high as 9.7 pg m^{-3}. Bossi et al. (2016) reported monthly average concentrations for six years, but no temporal trends were noted during 2008–2013.

One challenge presented in annual monitoring is the propensity of changing parameters, such as changes in methodology, or shifts in blanks and detection limits (Wong et al., 2018; Saini et al., 2023). Dated environmental core samples offer benefits in preserving multi-decadal records in ice or sediment in one sampling effort. Ice cores from Lomonosovfonna, Svalbard, Devon Ice Cap, and the Mt. Oxford icefield have been sampled for PFAS in the last decade (Hartz et al., 2023; Pickard et al., 2018). These studies have reported continuous detection of trifluoroacetic acid (TFA) in addition to PFDA, PFOS, and other PFAS such as perfluorobutane sulfonamide (FBSA). All three sites had even – odd PFCA ratios (PFOA: PFNA; PFDA: PFUnDA) ranging from 0.5 to 2, which is consistent with product yields in fluorotelomer alcohol oxidation studies (Gebbink et al., 2016; Huber et al., 2015; Lucia et al., 2015). These findings support the possible transport and oxidation of 8:2 and 10:2 fluorotelomer based precursors to long-chain PFCAs, as discussed above. However, for short-chain PFCAs, the ratios suggested other sources, possibly, besides fluorotelomer oxidation (Hartz et al., 2023; Pickard et al., 2018) The depositional fluxes of PFDA and PFUnDA in 2007–08 were higher compared to 2017–18 in Svalbard ice core (Hartz et al., 2023). Pickard et al. (2018) noted increasing fluxes of PFOA and PFNA from 1985 to 2012 in the Devon Ice Cap. However, PFAS temporal trend monitoring in abiotic and biotic samples cannot solely be attributed to emissions and other factors are likely relevant such as climate impacts (Vorkamp et al., 2022). Nevertheless, ice cores present an innovative approach for temporal trend monitoring of PFAS.

MacInnis et al. (2019a) reported PFAS congeners in dated sediment cores from freshwater Arctic lakes, namely Lake Hazen (Ellesmere Island, Canada) and Lake B35 (near western Hudson Bay, Canada). Both sediment cores showed increasing deposition of PFOA, PFNA, PFDA, PFUnDA and PFOS from 1980 to 2009/2011. However, the doubling times in Lake Hazen were shorter and attributed to accelerated glacier melt. Lin et al. (2020) measured PFAS in a marine sediment core in the Bering Sea at seawater depth 169 m. PFOS concentrations increased in sediment from 1952 (0.4 ng g^{-1}) until 2003 (0.9 ng g^{-1}), followed by decreasing concentrations, whereas PFNA increased from 1975 to 2015. One challenge in interpreting these sediment core data is that the depth profiles are expressed in concentration units and not normalized to sediment flux. Analysis of PFAS in sediment cores from Frobisher Bay, Nunavut highlighted the use of sediment cores to detect local sources of contaminants in the Arctic (Bartley et al., 2024). For example, Koojesse Inlet sediments showed high PFOS concentrations during 1980–2000 corresponding to the establishment of an air command base (Bartley et al., 2024). After 2000, fluorotelomer carboxylate concentrations

increased, which was attributed to a shift in the production of aqueous fire fighting foams (AFFFs) originally containing PFOS from electrochemical fluorination to the production of AFFFs containing fluorotelomer alcohols (Bartley et al., 2024).

6.2. Time-trends of PFAS in wildlife

Polar bears and ringed seals are key species for monitoring POPs under AMAP. Here, temporal trends of PFAS, with PFOS and PFNA selected as key bioaccumulative PFAS, are evaluated in liver tissue of polar bears and ringed seals from East Greenland and southern and western Hudson Bay in Canada. To our knowledge, no such time trend data exist for other Arctic regions. East Greenland polar bear and ringed seal data cover the period from 1984/1986 to 2021, and southern and western Hudson Bay polar bear and ringed seal data cover the periods 2007–2018 and 1992–2020, respectively. The study updates temporal trend conclusions reported in a series of previously published papers and reports for Greenland (Dietz et al., 2018; Rigét et al., 2019, 2013, 2016) and for Hudson Bay (Muir et al., 2019; Letcher et al., 2018a, 2018b; Houde et al., 2020; Butt et al., 2008).

In Greenland, polar bears are collected every year and ringed seals are usually collected every second year from Ittoqqortoormiit in Central East Greenland. In Canada, polar bears from southern and western Hudson Bay subpopulations and ringed seals around Arviat, Nunavut (western Hudson Bay) are harvested each year by Inuit hunters. Mostly reporting on PFAAs, namely PFSAs and PFCAs, but also including some neutral PFAS, concentrations have been determined in liver samples of both species. Details on sample preparation and analyses are described in Butt et al. (2008), Rigét et al. (2019), and Letcher et al. (2018a)

The statistical time-trend analysis in this case study was performed in R version 4.2.3 using the newly developed HARSAT (Harmonized Regional Seas Assessment Tool) package version 1.0.0 (https://harsat.amap.no). HARSAT is applied for data analysis by AMAP, the Baltic Marine Environment Protection Commission (HELCOM) and the Convention for the Protection of the Marine Environment of the North-East Atlantic (OSPAR) for the assessment of data concerning contaminants (hazardous substances) and their effects in the marine environment. A detailed description of the statistical methodology can be found in the AMAP Human Health Assessment (AMAP, 2022). In the analysis of trends, Greenland polar bears were grouped into subadults (males $\leq$5 years; females $\leq$4 years) and adults; no grouping was applied to the Canadian polar bears as these were mainly adult males. Ringed seals were grouped into subadults ($\leq$4 years) and adults. In examining non-linear patterns of change, HARSAT applies a procedure where log-transformed concentrations are assumed to vary smoothly over time; the fitted model is then used to assess evidence of patterns of temporal change; the amount of smoothing is effectively determined by the data in the time-series. Although not revealed in the HARSAT statistical analysis, visual examination of the patterns of change in PFOS in East Greenland ringed seals indicated a breakpoint with peak concentrations around 2006. Consequently, these were re-analyzed separately for trends in the periods 1986–2006 and 2006–2021. The adult Greenland ringed seal group contained too few data during the 1986–2006 period to allow for a similar analysis.

The temporal trends of PFOS and PFNA in East Greenland and southern and western Hudson Bay polar bears and ringed seals are shown in Figs. 2 and 3, respectively, and the summary statistics are shown in Table SI-3.

The results show that PFOS had the highest concentrations of all PFAS analyzed during the entire 1982–2021 period with concentrations up to 6160 ng g^{-1} ww measured in liver of individual East Greenland polar bears and up to 5290 and 1810 ng g^{-1} ww in southern and western Hudson Bay polar bears, respectively. Ringed seals had lower PFOS concentrations compared with polar bears, with concentrations in the liver of seals up to 1330 ng g^{-1} ww in East Greenland and up to 140 ng g^{-1} ww in western Hudson Bay. PFNA had the highest concentrations of any of the long-chain PFCAs analyzed with concentrations up to 742 ng g^{-1} ww in the liver of individual East Greenland polar bears and up to 1380 and 638 ng g^{-1} ww in southern and western Hudson Bay polar bears, respectively. Ringed seals had lower PFNA concentrations in the liver compared with the polar bears with concentrations in seals up to 39.2 ng g^{-1} ww in East Greenland and up to 23.1 ng g^{-1} ww in western Hudson Bay.

For PFOS in East Greenland polar bears and ringed seals, concentrations increased from the 1980s until the peak concentration in 2006 for both (Fig. 2A–D; Table SI-3). For the polar bears, PFOS concentrations declined from 2006 until 2013–2014, after which an increase was observed in both subadults and adults. The PFOS trends for both subadult and adult polar bears were significant ($p = 0.017$ and < 0.001, respectively) and followed a non-linear trend. For the ringed seals, the increase from 1986 to 2006 was also significant ($p = 0.011$ in subadults). After 2006, concentrations in the East Greenland ringed seals declined significantly with a tendency to a slight increase in the latest measurements from 2021 for both subadults and adults. The significant increase in PFOS in recent years for the polar bears (and to a lesser extent in the ringed seals) in East Greenland is surprising due to the regulation of PFOS and may be related to climate change effects such as increased mobilization, leaching, and uptake or changes in diet.

For PFOS in Hudson Bay (Fig. 2E–H; Table SI-3), concentrations in polar bears from southern Hudson Bay declined significantly from 2007 to 2018 ($p = 0.049$), whereas no significant trend was detected for western Hudson Bay ($p = 0.835$). PFOS in polar bears from western Hudson Bay appears to have been increasing up until 2012 after which a decline took place, but data are too few to conduct a meaningful statistical time trend analysis on these data for two periods. PFOS in ringed seals from Arviat in western Hudson Bay showed a significant trend for subadults ($p = 0.001$; Fig. 2G) indicating a non-linear trend with decreasing concentrations from 2002 to around 2008–2011, then increasing concentrations followed by a decrease again. The adult Arviat ringed seals showed no statistically significant trend during the 1992–2019 period ($p = 0.733$).

For PFNA in East Greenland, concentrations increased in both East Greenland polar bears and ringed seals during the 1984–2021 period (Fig. 3A–D; Table SI-3). Trends for subadult and adult polar bears and ringed seals were all significant ($p < 0.001$). The PFNA trends for subadult polar bears and subadult and adult ringed seals followed a log-linear trend, whereas the trend in adult polar bears was best described by a non-log-linear function. The estimated mean annual increase in PFNA during the last 20 years was between 6.2 and 8.2 % per year for the polar bears and ringed seals in East Greenland.

For PFNA in Hudson Bay, a highly significant increase was detected for the western Hudson Bay polar bears ($p = 0.009$; Fig. 3F) and Arviat adult ringed seals ($p = 0.002$; Fig. 3H), whereas a near-significant trend was seen for the Arviat subadult ringed seals ($p = 0.081$, Fig. 3G). Polar bears from southern Hudson Bay showed no significant trend ($p = 0.554$; Fig. 3E). The estimated mean annual increase in PFNA during the last 20 years was between 4.0 and 8.0 % per year for the polar bears and ringed seals in western Hudson Bay (here excluding southern Hudson Bay polar bears that showed no significant trend).

In conclusion, for East Greenland polar bears, PFOS concentrations increased from the 1980s until a peak concentration in 2006 followed by a decrease until 2013–2014. From 2014 to 2021, concentrations increased again, approaching concentrations from the peak in the mid-2000s. A similar overall trend was observed for ringed seals from East Greenland. The increase in PFOS in East Greenland in recent years is surprising due to the phaseout of PFOS by the main manufacturer in 2002 and the listing under the SC-POPs in 2009. However, reasons for the temporal trends may be, in part, related to climate change effects. Finally, PFNA increasing trends in these marine mammal species support the need for national and international actions to regulate long-chain PFCAs and their precursors. Long-chain PFCAs are currently reviewed under SC-POPs following their nomination by the Canadian

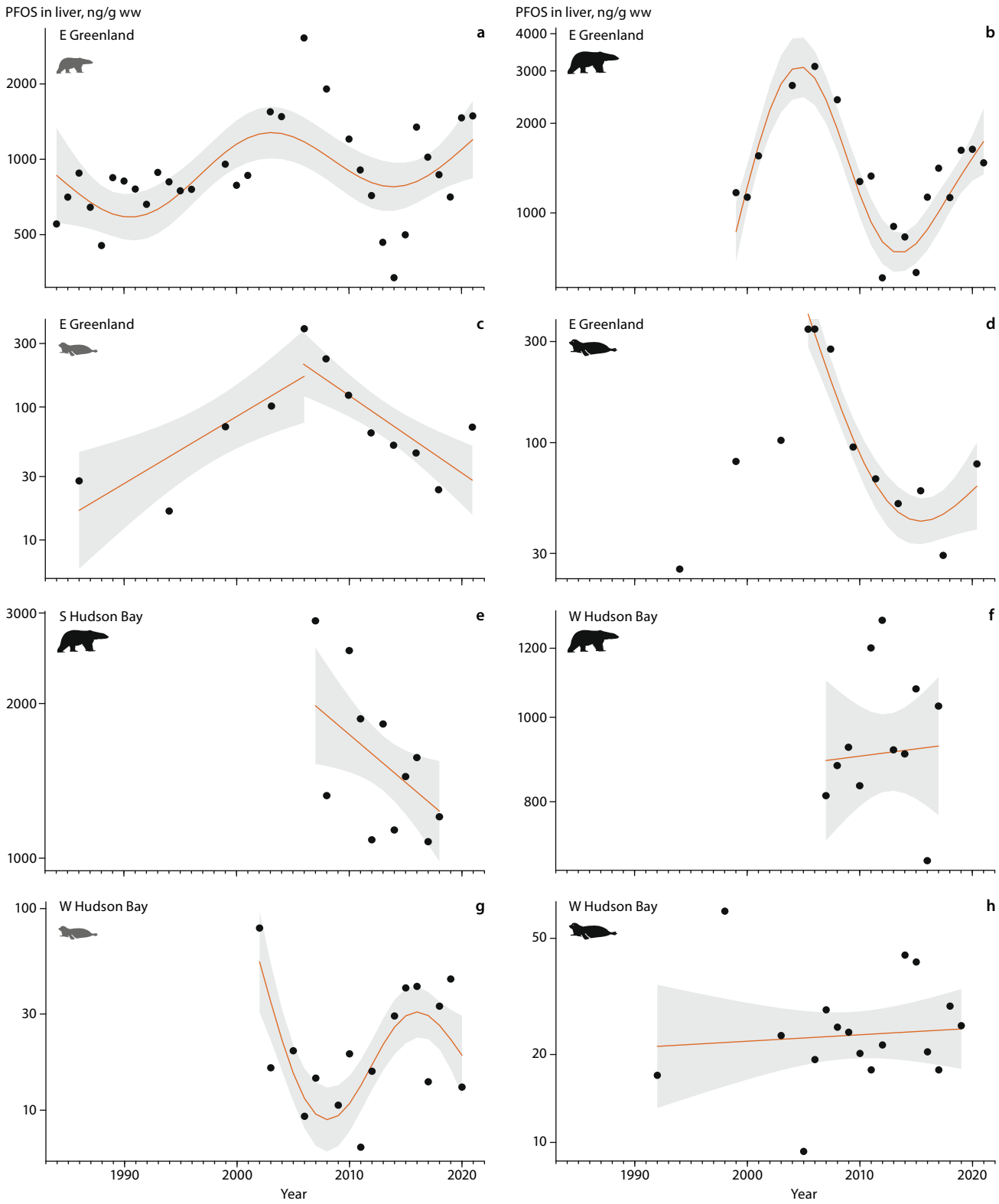

Fig. 2. Annual median concentration temporal trends of PFOS concentrations in livers of a) subadult polar bears from Ittoqqortoormiit, East Greenland, b) adult polar bears from Ittoqqortoormiit, East Greenland, c) subadult ringed seals from Ittoqqortoormiit, East Greenland, d) adult ringed seals from Ittoqqortoormiit, East Greenland, e) polar bears (mainly adult males) from southern Hudson Bay, Canada (Letcher et al., 2018b), f) polar bears (mainly adult males) from western Hudson Bay, Canada (Letcher et al., 2018b), g) subadult ringed seals from Arviat, western Hudson Bay, Canada (Houde et al., 2017), and h) adult ringed seals from Arviat, western Hudson Bay, Canada (Houde et al., 2017). For the Greenland ringed seals (c and d), trends were analyzed separately for the 1986–2006 and 2006–2021 periods. All shown trend lines were significant ($p < 0.05$), except for the western Hudson Bay polar bears (f) and the Arviat adult ringed seals (h) ($p = 0.835$ and 0.733, respectively).

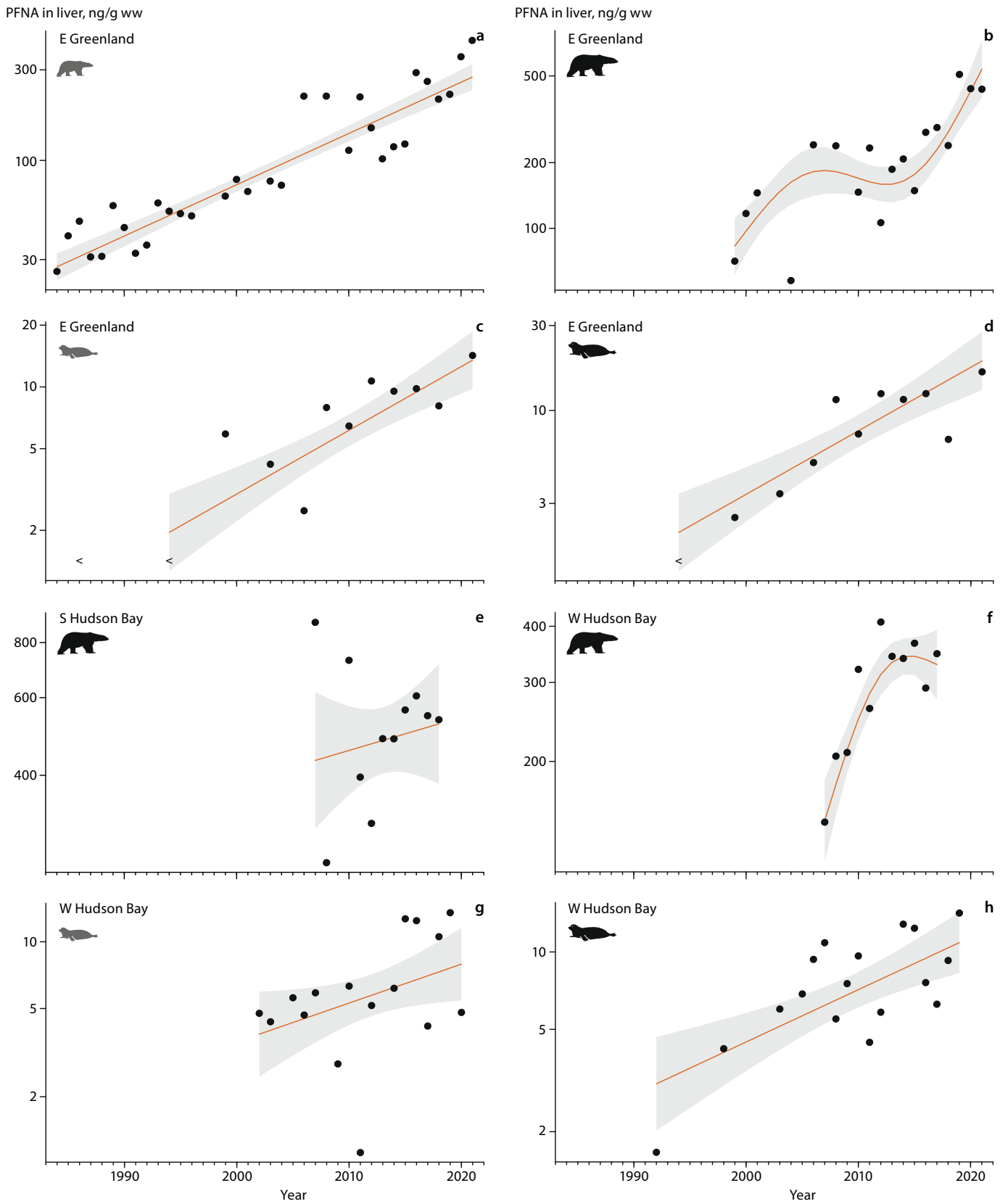

Fig. 3. Annual median concentration temporal trends of PFNA concentrations in livers of a) subadult polar bears from Ittoqqortoormiit, East Greenland, b) adult polar bears from Ittoqqortoormiit, East Greenland, c) subadult ringed seals from Ittoqqortoormiit, East Greenland, d) adult ringed seals from Ittoqqortoormiit, East Greenland, e) polar bears (mainly adult males) from southern Hudson Bay, Canada (Letcher et al., 2018b), f) polar bears (mainly adult males) from western Hudson Bay, Canada (Letcher et al., 2018b), g) subadult ringed seals from Arviat, western Hudson Bay, Canada (Houde et al., 2017), and h) adult ringed seals from Arviat, western Hudson Bay, Canada (Houde et al., 2017). All shown trend lines were significant ($p < 0.05$), except for the southern Hudson Bay polar bears (e) ($p = 0.554$) and the Arviat subadult ringed seals (g) ($p = 0.081$). The < symbol shows that the annual median was below the limit of detection (LOD) and marks the LOD value.

Government in 2021 (UNEP, 2023).

6.3. Time-trends of PFAS in circumpolar Arctic human populations

There are also relatively strong contaminant time trends for human populations across the circumpolar Arctic, with a focus on pregnant women due to vulnerability of prenatal exposure of the fetus. Time trends cover the years 1990–2018 (AMAP, 2022; Adlard et al., 2021). The time trends vary by contaminants and regions in general, possibly related to the extent local Arctic populations rely on a traditional diet, for example, including marine mammals. Moreover, PFAS concentrations were in general higher in males than females and increased with age. The long-chain PFAAs, such as PFOS and PFOA, were frequently found in serum at higher concentration than short-chain compounds, e.g., perfluorobutane sulfonic acid (C4, PFBS) and C4-PFBA. The predominant PFAS measured across the Arctic was PFOS followed by PFNA,

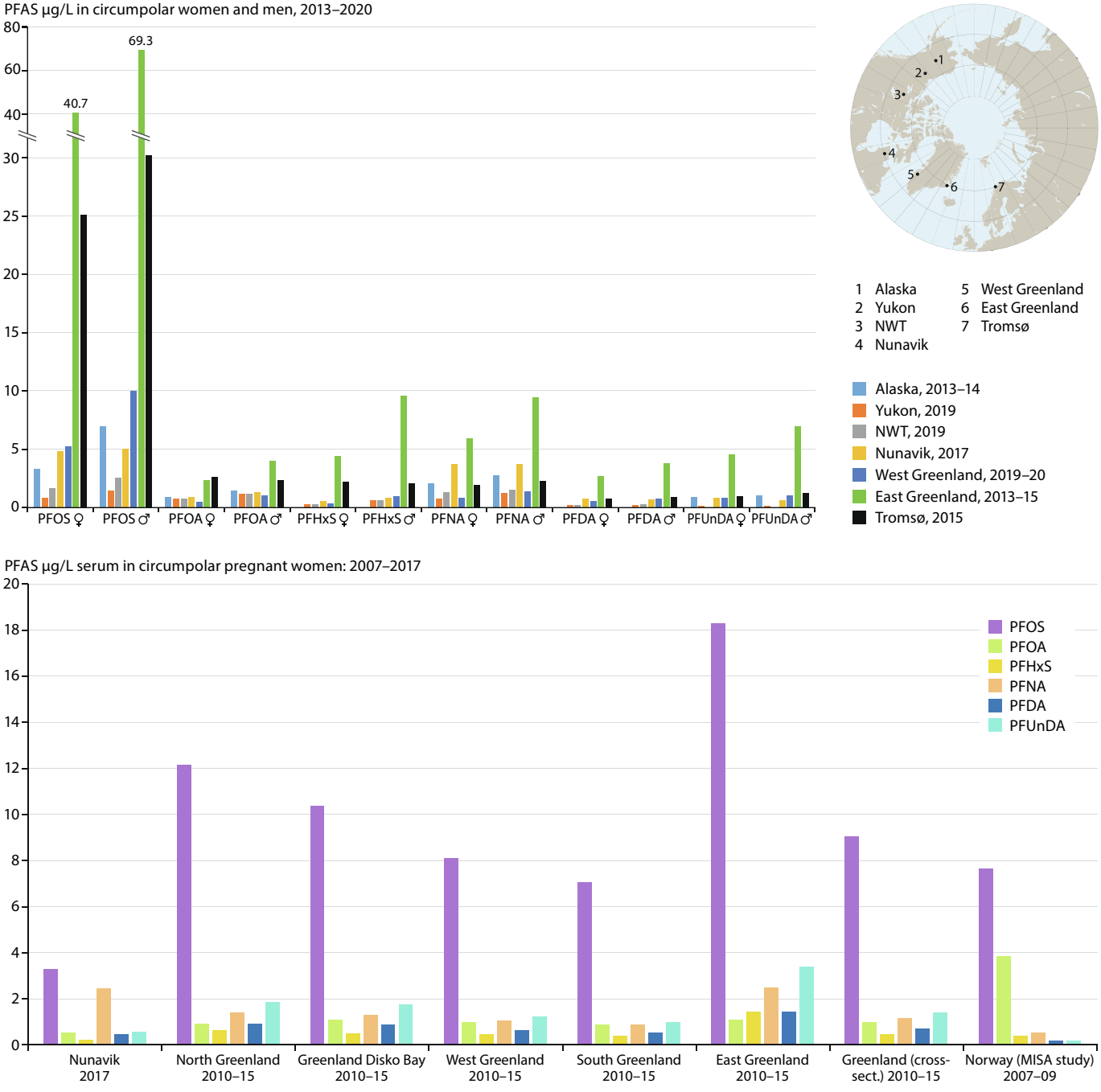

Fig. 4. Top: PFAS concentration in circumpolar adults 2013–2020, age range 28–48 years: serum data in µg L^{-1} serum, geometric means; M: men; W: women; Alaska USA, mean age M/W 29/28; Old Crow, Yukon, Canada: mean age M/W 43/39; NWT: Northwest Territories, Canada, mean age M/W 48/45; Nunavik, Canada, mean age M/W 39/37 years; West GRL: ACCEPT follow-up at the west coast Greenland, mean age M/W 37/34 years; East GRL: mean age M/W 41/36. Bottom: PFAS concentration in circumpolar pregnant women 2007–2017: data in µg L^{-1} serum, geometric means; pw: pregnant women; Nunavik, Canada, means age 24 years; GRL: Greenland, the Greenlandic geographical ACCEPT birth cohort established 2010–2015 including pw from 16 towns: North (Qaanaaq, Upernavik, Uummannaq, mean age 28 years), Disko Bay (Ilulissat, Aasiaat, Qeqertarsuaq, Qasigiannguit, mean age 27), West (Sisimiut, Maniitsoq, Nuuk, Paamiut, mean age 27), South (Qaqortoq, Nanortalik, Narsaq, mean age 29), East (Tasiilaq, Ittoqqortoormiit, mean age 27); GRLcross: Greenlandic ACCEPT pw cross sectional, mean age 28 years; MISAN: The northern Norway Mother-Child Contaminant Cohort including pw from Finnmark, Tromsø and Nordland in northern Norway, mean age 31 years.

PFHxS and PFUnDA, generally with the highest concentrations measured in East Greenland (Fig. 4, top panel) (Bonefeld-Jørgensen et al., 2023). Among pregnant women, the PFAS concentrations were also particularly high in the eastern and northern part of Greenland (Fig. 4, lower panel) (Bonefeld-Jørgensen et al., 2023).

Higher levels of PFNA were in general also observed in the Canadian Arctic; among pregnant women and adults in Nunavik (Aker et al., 2023a; Caron-Beaudoin et al., 2020), the Northwest Territories and Yukon (Garcia-Barrios et al., 2021), and the St. Lawrence Island, Alaska (USA) (Byrne et al., 2017), as well as in Greenlandic pregnant women but not in the northern Norway pregnant women (MISA) (Fig. 4, top and lower panel).

A time trend study (1994–2015) including both women and men across Greenland showed a significant 5.82–11.7 % annual decrease for the regulated PFOS, PFOA and PFHxS, but an increasing trend for the unregulated PFNA, PFDA and PFUnDA (Long et al., 2021). This time trend was supported by the Greenlandic birth cohort ACCEPT follow-up 3–5 years since pregnancy 2019–2020 on an intra-individual level. (GRLwest, Fig. 4) (Wielsøe et al., 2022).

The Finnish LUKAS2 children cohort study is based in Kuopio and thus outside the typical AMAP area, but it has been included in AMAP human health assessments. In the years 2005–15 (Fig. 5A), the PFAS concentration in the same individual at ages 1, 6 and 10.5 years old, clearly decreased by age for PFOS, PFOA, PFHxS and PFNA (Koponen et al., 2018). Both growth dilution and PFAS regulations might play a role in this trend. The Faroe Islands have initiated several mother-child cohorts since the 1980s (Adlard et al., 2021). Cohort 1, started in 1986–1987, measured the PFAS levels since birth and at age 7-, 14-, 22- and 28-years through to 2013–2015. On the Faroe Islands, the time trend of PFAS from ages 7 to 28 clearly showed a decrease over the time for the regulated PFOS, PFOA, PFHxS (partly) and an increase for unregulated PFNA and PFDA in children (Shih and Blomberg, 2021) (Fig. 5B). In general, male, and older age showed higher concentrations (Cohort 1), thus in Cohort 5 at age 9 years the PFAS levels were lowest (Fig. 5).

A comparison of Northern Norway adolescents (mean age: 16 years) and Oslo adults (mean age: 41 years) revealed similar concentrations for PFOS, PFOA, and PFHxS, but lower levels for the Northern Norway adolescents for PFNA, PFDA and PFUnDA (Fig. SI-1A). A Swedish PFAS time trend during 1996–2017/19 of first-time mothers in Uppsala showed a clear decrease of PFOS and PFOA, but increasing levels of PFNA, PFDA and PFUnDA (Gyllenhammar et al., 2020). When comparing Swedish northern adults (Donat-Vargas et al., 2019), first-time mothers from Uppsala, and Swedish cross-sectional adolescents (Fig. SI-1B), the northern adults (aged 56 years) clearly had the highest concentrations of PFOS, PFOA and PFNA, whereas the first-time mothers (aged 30 years) had the highest PFHxS levels. PFOS and PFOA concentrations were similar in first-time mothers and cross-sectional adolescents (aged 15 years, see Fig. SI-1B).

For Swedish first-time mothers, a consistent reduction in the concentrations of PFOS and PFOA ($p < 0.001$) was observed, contrary to the increasing trends observed for PFHxS, PFNA, PFDA and notably PFUnDA, which exhibit a steady linear increase ($p = 0.019$). In Nunavik pregnant women in 2016–2017 (Caron-Beaudoin et al., 2020), a decreasing trend was observed for PFOS ($p = 0.068$) and PFOA ($p = 0.005$); however, distinct from the Swedish trends (Gyllenhammar et al., 2020), concentrations of PFHxS in Nunavik showed a declining trend ($p = 0.048$), while presenting a similar increasing trend for PFNA ($p = 0.036$) and a non-significant increasing trend for PFDA and PFuDA (PFUnDA) (Donat-Vargas et al., 2019). The longitudinal analysis of PFAS concentrations in the maternal blood in Sweden and Nunavik reveals discernible patterns of fluctuation in the levels of various PFAS chemicals over time, which might reflect the differences in exposure profiles via e.g. traditional versus market diets and/or consumer products. This illustrates the need for continuous monitoring and research to understand the underlying factors and implications of these variations in different locations in the Arctic (AMAP, 2022).

7. Exposure assessment for humans in the Arctic

In Nunavik, northern Quebec, exposure to long-chain PFCAs was up to seven-fold higher compared to the general Canadian population (Aker et al., 2023a; Caron-Beaudoin et al., 2020). The results indicate a unique exposure pathway to PFAAs in Arctic populations. Indeed, when

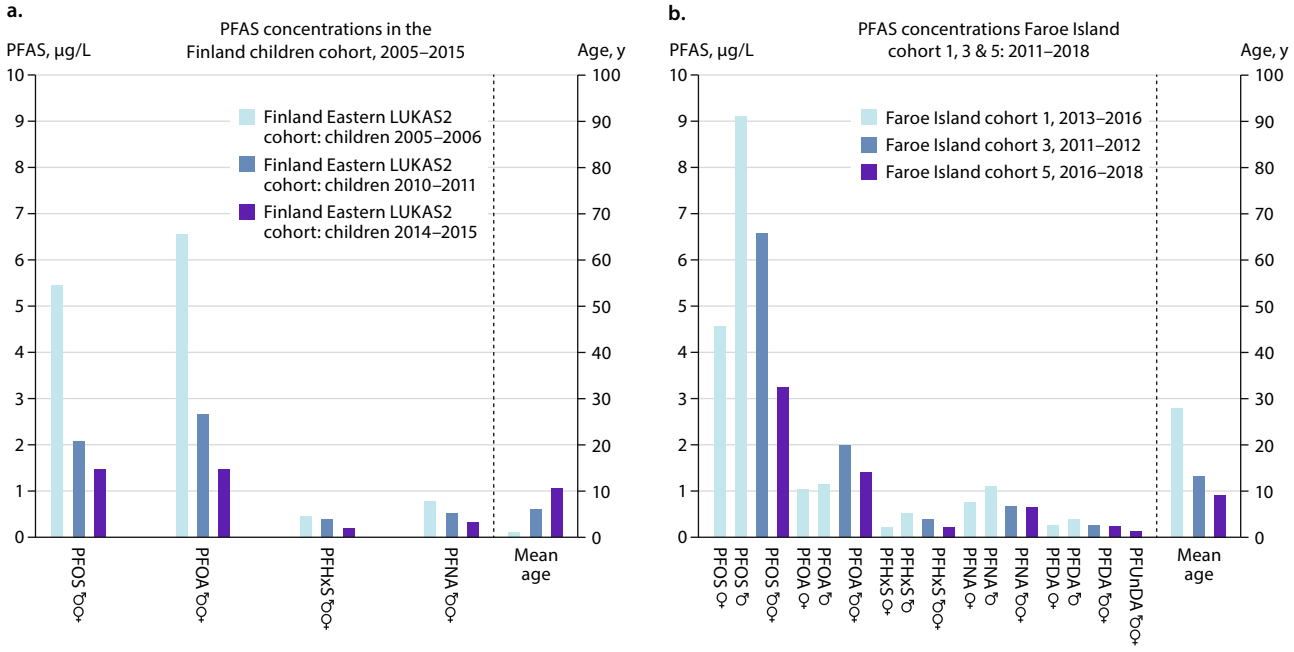

Fig. 5. PFAS levels in consecutive Finish children and Faroe Island cohorts over time. a) PFAS concentration in the Finnish LUKAS2 children cohort 2005–15: the data represent the same individual at the three time points; data in µg L^{-1} serum (median); girls (♀) and boys (♂) included (Koponen et al., 2018). b) PFAS concentrations in Faroe Island cohorts 2011–2018: data in µg L^{-1} serum (median); girls (♀) and boys (♂) included; the data are for the oldest children in the three specific cohorts 1 and 3 and 5 (Shih and Blomberg, 2021).

comparing food consumption profiles, Nunavik Inuit consuming more frequently traditional foods, and particularly marine mammals, had significantly higher PFAAs when compared to those predominantly consuming market foods (Aker et al., 2023a). There are consequently geographical differences in exposure with respect to the different wildlife species, and even different marine mammal species preferred by Indigenous populations, in different regions and sub-regions of the Arctic. This is reflected in Fig. 4 showing a higher exposure to PFAAs among Greenlandic pregnant women in eastern and northern regions compared to the western and southern regions, which includes the city of Nuuk and where the consumption of traditional foods and marine mammals is less frequent (Long et al., 2021; Wielsøe et al., 2022). However, the cross sectional PFAS levels among pregnant women in Greenland are comparable to the other Northern population data (Bonefeld-Jørgensen et al., 2023), such as Northern Norway pregnant women (Fig. 4), Northern Norway adolescent and Oslo adults (Fig. SI-1A), Faroe Island cohorts (Fig. 5B) and adults in Sweden (Fig. SI-1B). These data demonstrate that PFAS exposure extends beyond traditional food intake, and likely includes PFAS from consumer products imported to the Arctic (Poothong et al., 2020; Sunderland et al., 2019). This may include locally harvested or grown foods accumulating PFAS from locally contaminated grounds (ex. landfill leaching or local industries), but also imported foods and the use of food packaging materials. Exposure at home or in the office may also contribute to the direct exposure to PFAAs, and their precursors, from PFAS treated furniture and carpets, indoor air, and dust (Morales-McDevitt et al., 2021). Cosmetics and personal care products also pose a possible source to dermal exposure to PFAS (De Silva et al., 2021; Kotthoff et al., 2015). Until today, in the US and southern Canada, drinking water contamination is widespread and has been the prime regulatory focus (Hu et al., 2016). In the Arctic, the drinking water source is in general not groundwater but meltwater and surface water. New random samples of drinking water in Qaanaaq and Nuuk in Greenland as well as Kuujjuaq in Nunavik showed that the drinking water was free of detectable PFAS (De Silva, pers. comm.).

8. PFAS-related changes in health of humans and wildlife

Studies have identified and reported that sufficient exposure to some PFAS has been associated with changes in health parameters measured in humans and wildlife. The following section examines current knowledge of associations with measured PFAS tissue concentrations and related changes in the health of Indigenous and Arctic communities and wildlife species and populations inhabiting the Arctic.

8.1. PFAS-related changes in health relative to human exposure

Some PFAS pass the placenta and result in prenatal exposure (Fig. 6) (Appel and Forsthuber, 2022). For example, 33 % of the maternal PFAS (sum of PFOS, PFOA, PFNA, PFDA, PFUnDA, PFHxS) was found in the placenta and 36 %–15 % were found in fetal liver (36 %), lung (36 %), lipid/fat (27 %), heart 23 %, and brain (15 %) (Björvang et al., 2021). A systematic meta-analysis review (sampling 1999–2018) on broad global populations found U-shaped trans-placental transfer efficiencies (TTE) for PFCAs of different chain length (C6-C14) and a downward trend for the transfer of PFSAs (C6 to C8) (Appel and Forsthuber, 2022). Comparing same chain lengths shows that PFSAs are transferred less efficiently than PFCAs (e.g. perfluorohexanoic acid, PFHxA, mean TTE = 2.71 vs PFHxS mean TTE = 0.62. see (Appel and Forsthuber, 2022)); the TTE were lower when maternal blood samples were drawn during pregnancy than at delivery (Appel and Forsthuber, 2022).

Breast-feeding is a dominant exposure route for infants, and a highly relevant exposure pathway in the Arctic (ATSDR, 2021; EFSA, 2020; LaKind et al., 2023). While many studies have documented PFAS levels in breastmilk, the most common biomarker for assessing exposure to PFAS across population groups, including pregnant women and infants,

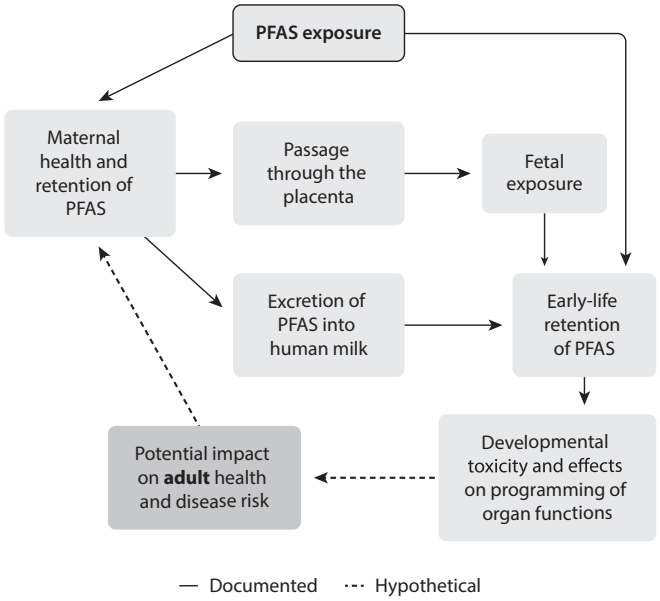

Fig. 6. Pathways and impacts of PFAS on maternal and developing human health.

is blood (usually serum or plasma) since it reflects exposures that have occurred during the past several years. When exposure stops, then the slow elimination means that a small, but constant fraction is being excreted each month, each year (Liu et al., 2018). This means that first-order toxicokinetics can be assumed (Egeghy and Lorber, 2011; Lorber and Egeghy, 2011). The time it takes for half the compound to be eliminated is called the (biological or elimination) half-life ($t_{½}$). The most recent estimates of half-lives show <2.5 years for PFNA, slightly above 3 years for PFOA, somewhat more for PFOS, and >8 years for PFHxS (Chiu et al., 2022; Rosato et al., 2024). Still, reliance on serum concentrations may be problematic, as the accumulation of very high PFAS concentrations in various organs shows that "deep" compartments, e.g., in the liver, may potentially have much longer retention times (Perez et al., 2013). Thus, PFAS concentrations in blood are not representing the total body burden, and standard (one-compartment) models may not reflect the (slow) elimination of the PFAS from the body. While there are analytical difficulties analyzing PFAS in tissues, early evidence of PFAS storage in several organs was published (Maestri et al., 2006). Some PFAS may also accumulate in red blood cells rather than serum or plasma (see Section 2), thus relying only on these biomarkers to assess exposure may underestimate it for some congeners such as FOSA being at higher level in red blood cells (Kärrman et al., 2006). In addition, at normal kidney function, urinary elimination of PFAS is barely measurable, and urine samples may therefore not be useful for monitoring of individual exposures. However, a recent study in East Greenlandic Inuit suggests that women might excrete PFAS more easily through the kidney than males. The estimated PFAS renal clearance and ratio of urine to serum were significantly higher for females, suggesting a sex difference in excretion via the kidney, maybe partly because men had higher serum PFAS levels (Long et al., 2023; Kudo et al., 2002).

The U.S. National Toxicology Program (NTP) recognized both PFOS and PFOA as "presumed" human immunotoxicants, i.e., the level of evidence just below "known" (National Toxicology Program, 2016). The first studies in this area were conducted in the Faroe Islands (Grandjean, 2018). Additional evidence from these studies shows that PFHxS and PFNA are also associated with weakened immune resistance to infectious disease in children (Budtz-Jørgensen and Grandjean, 2018). Immunotoxicity has been the subject of recent reviews (von Holst et al., 2021; Zhang et al., 2022) and has been recognized as the critical effect by major authorities (US EPA, 2022; NASEM, 2022). While most

evidence has focused on PFOS, PFOA, PFHxS, and PFNA (Budtz-Jørgensen and Grandjean, 2018), it does not mean that immunotoxicity is limited to these PFAS. In a study of Norwegian children, researchers found that increased concentrations of PFOA, PFNA, and PFHxS were linked to statistically significant increases in the frequency of infections such as the common cold and gastroenteritis (Granum et al., 2013; Impinen et al., 2019). Similar findings have been recorded from other countries (Dalsager et al., 2021, 2016; Timmermann et al., 2020). In Greenlandic pregnant women, studying associations between serum POP levels and hematological markers showed a significantly inverse association between several hematological markers (eosinophil, lymphocyte, neutrophil and white blood cells) and POPs including PFAS (Knudsen et al., 2018).

Because the immune system is also crucial in detecting and eliminating cancer cells, immunotoxicity may play a role for carcinogenicity (IARC, 2017). However, PFAS possesses several additional key characteristics linked to carcinogenicity (Temkin et al., 2020), and experimental support for the carcinogenicity of PFOA has been published by the U.S. NTP (National Toxicology Program, 2020). The IARC concluded in December 2023 that PFOA is carcinogenic to humans (Group 1), based on sufficient evidence for cancer in experimental animals and strong mechanistic evidence (for epigenetic alterations and immunosuppression) in exposed humans. There is also limited evidence for cancer in humans (renal cell carcinoma and testicular cancer) and strong mechanistic evidence in human primary cells and experimental systems (for epigenetic alterations and immunosuppression, as well as several other key characteristics of carcinogens) (IARC, 2017).

A recent systematic review and meta-analysis on the relation between exposure to PFAS and breast cancer risk found that epidemiological research on the potential association is contradictory (Cong et al., 2023). The risk of breast cancer in Arctic populations may be increasing and an array of suspected factors include a significant short-time transition in life-, health- and diet, and, due to intake of marine mammals, high exposure to POPs/PFAS, possibly in conjunction with certain genetic polymorphisms involving carcinogen activation (Wielsøe et al., 2018; Fredslund and Bonefeld-Jorgensen, 2012; Ghisari et al., 2014) For Greenlandic Inuit, the Cong et al. (2023) review revealed an association between PFAS and breast cancer (Wielsøe et al., 2018; Fredslund and Bonefeld-Jorgensen, 2012; Ghisari et al., 2014). Moreover, the review found that all included Asian studies reported a correlation between PFAS and breast cancer and since Inuit are of Asian descent it was speculated whether genetic susceptibility might play a role (Cong et al., 2023).

Concerning human reproductive system functions, PFAS exposure is associated with a broad range of adverse effects on reproduction documented in adult women and men. For women, PFAS exposure can lead to higher rates of infertility, miscarriage, pre-eclampsia, and higher blood pressure during pregnancy (Yang et al., 2022). Recent studies have also found associations with risk of malformation (Ou et al., 2021), miscarriage (Yang et al., 2022; Ou et al., 2021; Wikström et al., 2021) and preterm birth (Huo et al., 2020); a reduced chance of becoming pregnant was found in southern Canada at elevated serum concentrations of both PFOA and PFHxS (Vélez et al., 2015). In a Norwegian mother-child cohort study (2003–2004) self-reported time-to-pregnancy suggested an association between plasma FOSA and decreased fecundability odds (Whitworth et al., 2016). In Greenlandic Inuit couples, higher PFNA levels were associated with a longer time-to-pregnancy (Jørgensen et al., 2014). In men, PFAS exposure can result in lower sperm counts and fertility rates (Joensen et al., 2009; Toft et al., 2012; Vested et al., 2013) and may possibly be related to early-life exposures (Hærvig et al., 2022). A joint analysis of data from three countries (Greenland, Poland and Ukraine) suggested a substantially lower proportion of morphologically normal sperm cells at increased serum concentrations of PFOA and PFHxS (Toft et al., 2012). In vitro fertilization appears to be less successful at higher PFAS exposures of the parents (Ma et al., 2021).

Prenatal exposure to PFAS can result in preterm birth, low birth weight, and delayed fetal growth (Apelberg et al., 2007; Johnson et al., 2014; Waterfield et al., 2020) as also noted by regulatory agencies (ATSDR, 2021; EFSA, 2020). These outcomes may well be mediated by endocrine disruption, perhaps also during early development. Thus, increased PFAS exposure in early life was associated with changes in sex hormone concentrations both in boys and in girls during or after puberty (Maisonet et al., 2015; Lopez-Espinosa et al., 2016). Hormonal disruptions at elevated PFAS exposures have been detected already in early infancy (Jensen et al., 2020). In fertile Faroese men PFOS exposure was associated positively with sex hormone-binding globulin and luteinizing hormones, and might interfere with Leydig cells testosterone synthesis (Petersen et al., 2018).

These endocrine abnormalities likely also include an increased risk of developing metabolic syndrome (Zare Jeddi et al., 2022). Because a wide range of hormones play a crucial role in sustaining and operating physiological functions, disruptions to the endocrine system represent a confluence of deleterious impacts on the body as a whole. The thyroid gland appears to be a target organ for PFAS exposure, as supported by the C8 panel's study recognizing the association between PFOA and PFOS exposure and thyroid disruption (Winquist and Steenland, 2014). These associations have also been reported at background exposures (Melzer et al., 2010), as also recognized by ATSDR (2021). Recent studies on thyroid effects including pregnant women and newborns (Huo et al., 2020; Reardon et al., 2019; Preston et al., 2020; Derakhshan et al., 2022) suggest that thyroid toxicity may occur prenatally. Because the thyroid gland is the target for a substantial number of other environmentally toxic chemicals, PFAS exposure may contribute to adverse health effects to the thyroid gland from complex exposures, possibly exacerbated by borderline or frank iodine deficiency (Webster Glenys et al., 2016). Due to the strong link between hormones and early neurological development, disruptions of the thyroid gland also adversely impact development of neurological functions (Zoeller and Rovet, 2004), although it is not yet clear to which extent early-life exposure to PFASs affect brain development.

For Alaska Native people, exposure to PFAS associates with altered circulating thyroid hormones (TH) (TSH, T4, T3) concentrations, which seem to differ between the sexes (Byrne et al., 2018). In a Norwegian study, a relationship between PFAS, TH and thyroid-binding proteins was observed suggesting that PFAS exposure during pregnancy can modify the TH homeostasis (Berg et al., 2015). A Danish review included 15 scientific publications on pregnant women and/or infants on correlations between exposure to PFAS and thyroid hormones. Taken together, most studies supported the evidence of an increase in maternal TSH and a decrease in T4 and T3. The studies in this review reported some correlation between PFAS level and TSH levels in infants, but these data are less conclusive (Boesen et al., 2020).

A study of 1130 new mothers in the Faroe Islands (Timmermann et al., 2017) showed that a doubling of maternal serum PFAS concentrations was associated with a reduction in duration of both total and exclusive breastfeeding, most pronounced for PFOS and PFOA, where a doubling was associated with a reduction in total breastfeeding of about six weeks.

In a prospective study of American overweight adults, elevated PFAS exposure was linked to an increased loss of bone mineral, thus suggesting a risk of osteoporosis (Hu et al., 2019). Associations have also been found between prenatal or childhood PFAS exposures and indicators of childhood and adolescence bone health (Jeddy et al., 2018; Cluett et al., 2019). Faroese children at age 9 years showed that bone density was negatively associated with PFAS exposures in childhood, i.e., PFDA and PFNA at 18 months and 5 years and PFOA at ages 5 and 9 years, while associations with PFOS were weaker (Blomberg et al., 2022). These findings agree with experimental toxicology studies (Koskela et al., 2016, 2017) that were considered crucial for risk assessment by ATSDR (2021).

Overweight, obesity and dislipidemia have also been linked to increased exposure to PFAS. Several prospective studies related to child

cohorts from Denmark (Domazet et al., 2016), Norway (Lauritzen et al., 2018), and the Faroe Islands (Karlsen et al., 2017) are in support of a causative association of weight gain as a result of elevated developmental PFAS exposure. In 5–9 year old Greenlandic children, prenatal PFOA and PFOS exposure were associated with child weight-to-height ratio > 0.5, and high PFOA prenatal exposure in Greenlandic girls weakly associated with being overweight (Høyer et al., 2015). In Nunavik, while no association with body size was found, increasing circulating lipids was associated to increased exposure to all PFAAs (PFOA, PFNA, PFDA, PFUnDA, PFHxS, and PFOS) among Inuit adults, without evidence of interaction between congeners (Aker et al., 2023b).

8.2. PFAS-related changes in health relative to wildlife exposure

Wildlife species involving fish, birds, and mammals have been the subject of assessments of PFAS exposure and accumulation, but only a limited number of investigations have delved into the actual biological implications of these substances. The current research predominantly focuses on seabirds, ringed seals, and polar bears as recently summarized in an Arctic biological effects assessment (Dietz et al., 2019). To date, there is little information identifying effects of PFAS, including PFOS and other PFAAs, on Arctic wildlife and wildlife in general, and most findings are correlative. Effect-thresholds for PFAS concentrations do not exist for (Arctic) wildlife relative to PFAS, as recently assessed for, e.g., humans by the European Food Safety Authority concerning weekly oral exposure and blood concentrations (EFSA, 2020). The following studies represent the current state of knowledge about possible PFAS-related changes (or lack of) in the health of Arctic wildlife.

Investigations with Arctic seabirds like black-legged kittiwakes (*Rissa tridactyla*) reveal that PFAS exposure may influence reproductive behaviors (e.g., egg-turning frequency) and concentrations of reproductive hormones including prolactin, testosterone, corticosterone, and thyroid hormones. Although the direct effects on reproductive success and survival rates remain uncertain, these potential biological effects could adversely affect population dynamics, possibly through extended egg nurturing periods which might alter the balance between adequate nest care and nutritional foraging (Blévin et al., 2020). Tartu et al. (2014) identified negative relationships between baseline plasma corticosterone and certain PFAS during the chick-rearing phase of black-legged kittiwakes, suggesting possible hormone displacement due to the high affinity of PFAS for proteins (Tartu et al., 2014). Parallel findings with kittiwakes in Kongsfjorden, Svalbard, indicate that testosterone levels in egg yolks were positively correlated with maternal levels of PFNA, PFUnDA and PFDA in first-laid eggs, suggesting possible disruption of steroidogenesis and potentially affecting embryonic development (Jouanneau et al., 2023). Another Svalbard study highlighted greater protein oxidative damage in kittiwakes with elevated PFAS levels, noting diminished non-enzymatic antioxidant capacities in specimens with higher linear PFOS plasma concentrations, which could disrupt hormonal balance and cause DNA damage (Costantini et al., 2019).

Several investigations have linked PFAS levels with thyroid hormone concentrations across seabird species. In adult male (but not femals) thick-billed murres (*Uria lomvia*) in Hudson Bay, a rise in circulating free T3 was observed with increased levels of PFOS, PFNA, and other PFAS, and with T4 and PFOA, but total T3 declined with PFOS and two other PFAS compounds (Choy et al., 2022). This dysregulation of T3 and T4 was also correlated with alterations in body weight and hatch dates among murres, possibly influencing incubation behavior and subsequently hatching dates (Choy et al., 2022), suggesting that population dynamics may be altered in conjunction with other environmental stressors. Comparable associations between PFAS and thyroid hormones have been observed in other seabird species, with both positive and inverse correlations reported, indicating varying effects on metabolic energy and thyroid function (Melnes et al., 2017; Nøst et al., 2012; Blévin et al., 2017). Collectively, the associations of various PFAS with corticosterone, testosterone, and thyroid hormones in multiple seabirds, suggest that PFAS can disrupt hormone homeostasis likely through interactions with transport proteins and receptors.

Some PFAS may also influence telomere length and telomere dynamics (the rate of change in telomere length over time) that studies have reported as associated with longevity and survival of birds and other vertebrates. For glaucous gulls (*Larus hyperboreus*) in Svalbard (2010–2019), higher concentrations of PFNA and perfluorotetradecanoate (PFTeDA) were correlated with slower rates of telomere shortening, and high blood concentrations of PFOA and PFHxS were positively associated with higher re-sighting probabilities and apparent survival of males but not females (Sebastiano et al., 2020), indicating a sex-specific response to PFAS in adult glaucous gulls as well as murres (Choy et al., 2022).

With Arctic mammals, more recent PFAS research has included whales and seals, but predominantly addressed polar bears. Common minke whales (*Balaenoptera acutorostrata*) in the Barents Sea had Σ_{14}PFAS concentrations in muscle that were 3.2× higher in fetuses (23 ± 8.7 ng g^{-1} ww) than adult males (7.2 ± 2.0 ng g^{-1} ww), and 5.1× higher than adult females (4.5 ± 1.1 ng g^{-1} ww). The pattern of PFAS levels among age and sex groups suggests that there is substantial placental transfer of PFAS from mother to fetus minke whales (Andvik et al., 2023). Nevertheless, these measured PFAS concentrations were below estimated thresholds for the risk of health effects to this population of minke whales (Andvik et al., 2023).

Research into the effects of PFAS on the health of ringed seals has been sparse compared to polar bears, likely due to their significantly lower PFAS exposure levels. An in vitro study assessing T-lymphocyte proliferation in response to PFOS and PFOA exposure in leukocytes from ringed seals in East Greenland indicated no modulation of lymphocyte proliferation at up to 1000 ng g^{-1} wet weight. Consequently, it was concluded that the ringed seal population in East Greenland currently faces no significant risk of altered lymphocyte proliferation due to PFAS or POPs exposure (Levin et al., 2016).

Investigations into the consequences of PFAS exposure on polar bears have focused on potential links to liver abnormalities. Although no direct correlations have been established, the observed chronic exposure levels and types of liver lesions in polar bears show similarities to outcomes in laboratory settings, suggesting a potential contributory role of PFAS to these lesions in polar bears. Research by Bytingsvik et al. (2012) evaluated exposure effects of PFAS by analyzing PFAS plasma levels in maternal polar bears and their nursing cubs. While maternal transmission is a significant exposure pathway, the ratio of cub to mother concentrations suggests that PFAS transfer is relatively minor compared to that of lipophilic contaminants such as polychlorinatred biphenlys (PCBs). However, the detection of PFAS levels in polar bear mothers and their cubs exceed levels linked to adverse health effects in humans, highlighting concern for potential health impacts on polar bears in Svalbard. This underscores the need for further investigation into PFAS-related health implications in this species.

Further assessments by Dietz et al. (2015) utilized a physiologically based pharmacokinetic (PBPK) model to estimate the risk of reproductive and genotoxic effects across eleven polar bear subpopulations from Alaska to Svalbard, covering 1999–2008. These analyses revealed PFOS as a significant genotoxic agent, second only to PCBs, contributing to 3–19 % of the genotoxicity risk. A subsequent study by Dietz et al. (2018) extended this analysis to polar bears in central Eastern Greenland from 1983 to 2013, confirming the role of PFOS as a critical contributor to genotoxicity across different age and sex groups of bears, especially in 2006. Thyroid hormone dynamics have also been scrutinized in relation to PFAS exposure. Bourgeon et al. (2017) observed a decline in FT3 concentrations with increasing PFAS levels in Svalbard polar bears during the spring, indicating possible disruptions in hormonal homeostasis, potentially mediated by interference with transport proteins and receptors and reflecting similar PFAS-hormonal findings with Arctic

seabirds (discussed above).

Research into the neurochemical impacts of PFAS on polar bears by Greaves and Letcher (2013) reported PFAAs across eight brain regions in polar bears from East Greenland. This study shows that PFAAs cross the blood-brain barrier, with inner brain regions showing higher PFAA concentrations, suggesting differential exposure and potential vulnerability of various brain areas to PFAS-related effects. Further investigations into the neurochemical and steroid hormone alterations in polar bear brains from East Greenland, highlighted significant associations between PFAS levels, in particular PFOS, and changes in neurochemical biomarkers and steroid hormone concentrations across all examined brain regions. These findings suggest that PFAS may induce early neurobehavioral and health changes, potentially through disruptions in steroid synthesis or peripheral steroidogenic feedback mechanisms. Metabolic and immunological impacts of PFAS exposure have also been explored, revealing that PFAS levels inversely correlate with key metabolic biomarkers in the liver, impacting crucial pathways such as arachidonic acid, glycerophospholipid, and amino acid metabolism. This interaction suggests potential adverse effects on both metabolism and immune function in polar bears, highlighting the complex multi-stressor environment they face due to PFAS exposure combined with other ecological pressures (Tartu et al., 2017; Morris et al., 2019).

In summary, information on PFAS-related changes in health measures of Arctic wildlife is correlative and mainly available for seabirds, ringed seals, and polar bears. Studies on black-legged kittiwakes and/or thick-billed murres show that exposure to PFAS may affect reproductive hormones, nesting behaviors, and indirectly alter hatching dates, but the resulting biological effects on reproduction and survival are unknown. Likewise, some studies have shown correlations with PFAS concentrations and thyroid hormones in several seabird species like kittiwakes, fulmars and thick-billed murres, and polar bears. The health of polar bears is likely at elevated risk from the high PFAS concentrations they accumulate. The high chronic exposure to PFAS and various types of liver lesions in polar bears from East Greenland are similar to those found in other species in controlled laboratory studies indicating the potential that PFAS could contribute to the development of liver lesions in polar bears from regions with similarly high exposures.

Given the limited understanding of PFAS in relation to (Arctic) wildlife health, we recommend that future research address PFAS-related changes in health measures of Arctic wildlife species and populations, especially marine mammals and those in terrestrial food webs (e.g., foxes, caribou, other sentinel species), focusing on PFAAs that accumulate with higher concentrations and/or those that repeatedly show correlations with health endpoints across multiple species. An understanding of the impacts of PFAS on the behaviors and reproductive success of Arctic wildlife, as suggested in some seabirds (Tartu et al., 2018; Karlsen et al., 2017), is required to inform on PFAS-related population dynamics and the varying adaptability among wildlife species to multiple stressors (Choy et al., 2022; Tartu et al., 2017; Morris et al., 2019) including climate change, climate-PFAS interactions (Borgå et al., 2022), and in the context of PFAS within multiple contaminant mixtures (Dietz et al., 2019). Additional research is also required to accurately determine whether PFAS exposure has increased threats to wildlife health compared to legacy POPs and other pollutants, and in combination with those. Several studies suggest some PFAS and PCBs may be similarly toxic to the health of apex predators (Dietz et al., 2018, 2015). Dietz et al. (2019) concluded that since 2000, some Arctic seabirds, killer whales and pilot whales in Svalbard and Greenland, and polar bears from East Greenland to Alaska, have been exposed to various organohalogen compounds that exceed putative estimated risk thresholds reported for the immune system, endocrine systems, and/or reproductive success of non-Arctic species. Historically, temporal trends in risk quotients for carcinogenic, immune, and reproductive effects for polar bears (71–99 %) followed decadal trends in PCBs (1983–2013), but currently, risk factors to polar bear health have expanded because of climate change and now involve the polar bears' age, birth year and lifetime exposure to PCBs and PFOS, plus historical contaminant-emission patterns (Dietz et al., 2018). Similar physiological and endocrine changes are reported in wild birds and polar bears either specific to PFAS or PCBs, but to date, comparative toxicity studies are limited in number and largely focus on polar bears. Future research is necessary to better understand the comparative toxicity of PFAS, legacy POPs and other contaminants, including in the context of environmental chemical mixtures, for multiple (Arctic) wildlife species and populations.

8.3. Comparing human and wildlife health responses to PFAS

A comparison of the reported PFAS-related changes in health measures of human and wildlife suggests that PFAS concentrations seem to influence similar physiological, endocrine, and reproductive systems, and are likely carcinogenic in humans, polar bears, and seabirds inhabiting the Arctic (in this review, other health endpoints may be affected across species but were not commonly assessed in wildlife and humans). The similarity of responses across vertebrate classes is (perhaps) not surprising since circulating PFAS concentrations in blood have been similar in humans and even higher in polar bears. In East Greenland polar bears, PFAAs, especially PFOS, were measured in all brain regions and correlated with neurochemical biomarkers. PFOS was determined to be a carcinogenic agent second only to PCBs in polar bears, while PFOA is an identified carcinogen for humans, and some PFAS were reportedly associated with breast cancer in Greenlandic Inuit. Thus, overall, PFAS represent a hazard in the Arctic, with increasingly documented risks of adverse changes in health of humans and wildlife.

9. PFAS tissue distributions and risk quotients: humans and wildlife

9.1. Tissue distributions (PK modeling)

Physiologically based pharmacokinetic modeling (PBPK) is a powerful tool to improve our understanding on the relative contribution of different exposure pathways, such as diet, air, dermal contact to the internal (measured) concentration in blood, and other body fluids or tissues. Several PBPK models for PFOA and PFOS have been reported. For PFOA, most of them are a further development from the model published by Loccisano et al. (2011). This model contained compartments for blood, gut, liver, kidney, filtrate, fat, skin, and a lumped compartment for remaining body tissues. The model included oral and intravenous exposure. In this model, the plasma and liver were the primary target tissues for PFOA with possible involvement of enterohepatic circulation. This model was modified and applied by EFSA (2020), but only the oral exposure route was included. Husøy et al. (2023) recently published an updated version of the EFSA model, including additional uptake- and excretion routes as dermal external exposure and fecal excretion. The aggregated internal exposure showed that the major contributor to the internal exposure is diet for both males and females while still underestimating the measured blood concentrations, indicating the need to further evaluate exposure routes and our understanding of the PFAS circulation in the human body. Further, for seven women, the internal exposure of PFOA was found to be higher from personal care products than from diet, indicating the importance of including a broad spectra of exposure routes into the models.

Regarding PFOS, Deepika et al. (2021) developed an age-dependent PBPK model to predict and compare the PFOS tissue distribution and plasma concentration across different age groups. Chou et al. applied PBPK models to conduct dose-response analysis of toxicity studies for PFOS exposure (Chou and Lin, 2020). The same authors refined existing PFOS PBPK models to also include renal reabsorption/excretion during pregnancy and lactation in PFOS. To evaluate the performance of existing PBPK models for PFOS and PFOA, Fabrega et al. carried out a sensitivity analysis for PBPK models developed before 2016 (Fàbrega

et al., 2016). The elimination constants as well as the free fraction and the intake, were the most influential parameters, being up to 83 % for PFOS and 99.9 % for PFOA, indicating the need to further improve existing PBPK models.

For PFHxS, Sweeney (2022) developed a PBPK model describing PFHxS disposition in humans that can be applied to retrospective, current, and future human health risk assessment of PFHxS recapitulating observed trends across sex, age, and calendar years. Confidence in the model was greatest for application to adults in the 2000–2018-time frame and for shorter-term future projections. PBPK models of other PFAS, PFNA and PFDA, were extrapolated from male and female rats to a human PBPK model based on human physiological parameters by Kim et al. (2019) emphasizing the need to improve our understanding of the uncertainty in the predictability using extrapolation. Even with PBPK models either not existing or still in different stages of development for most PFAS, prediction through models is a valuable tool for human risk assessment and should be further improved upon.

9.2. Derived risk quotients (humans/wildlife) to estimate effects

Human data normally originates from analyzed blood plasma or serum samples. Arctic human data were extracted from published reports (AMAP, 2022; Aker et al., 2023a; Byrne et al., 2017; Wielsøe et al., 2022; Long et al., 2023) and focused on recent exposure data (i.e. in the years following the inclusion of PFOS in the SC-POPs in 2009) among communities or sub-regions of the Arctic heavily relying on marine mammal diet and for adult populations specifically since these are the most highly exposed to PFAS when compared to children or pregnant women.

As very few data were available for PFOS in wildlife plasma concentrations, most of the data were converted from liver to plasma concentrations. The conversion factor for PFOS was estimated and the median ratio between liver and plasma concentrations from 58 polar bears from East Greenland collected between 2011 and 2021 was used, according to these equations:

$$\text{PFOS plasma concentration } (\mu g L^{-1}) = 0.2769 \times \text{Liver concentration } (ngg^{-1}\ ww) \quad (1)$$

$$\text{PFNA plasma concentration } (\mu g L^{-1}) = 0.4216 \times \text{Liver concentration } (ngg^{-1}\ ww) \quad (2)$$

PBPK models were developed for adult male and female rats (*Rattus rattus*) to describe the pharmacokinetics of PFOA and PFOS (Loccisano

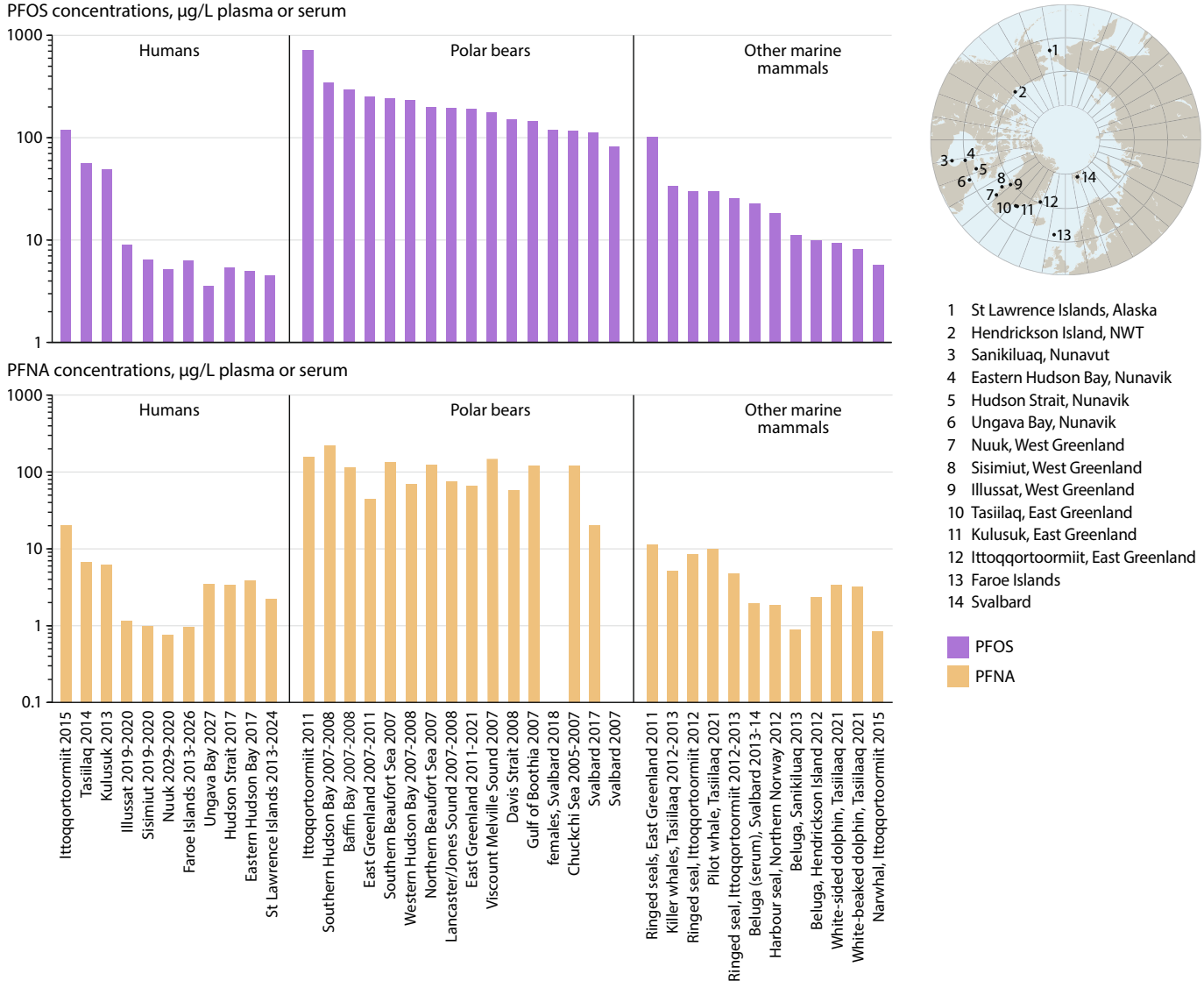

Fig. 7. Ranked histograms over human, polar bear and other marine mammal blood average plasma concentrations of PFOS and PFNA (µg L^{-1}) across the Arctic from 2007 and later (see Table SI-4 for details).

et al., 2012). The models contain a description of saturable renal resorption, free fraction of chemical in plasma, and saturable binding in liver. Both male and female rat models for each chemical were consistent with available data resulting from oral and dietary dosing regimens on male and female rats. The predicted plasma concentration curves followed trends observed in experimental data, and model predictions were within a factor of two of experimental values. The PBPK models predicted a conversion factor between liver and plasma of ~0.2. The observed ratios for experimental data on average was 0.18, ranging between 0.11 and 0.25, depending on the magnitude of the daily dose (Loccisano et al., 2012). Both the predicted PBPK model (0.2) as well as our estimate (0.14) of the ratio between the liver and plasma were within the range found by Loccisano et al. (2012).

The highest PFOS average concentrations in plasma or serum of circumpolar Indigenous populations - relying on marine mammal diet for subsistence - was observed among Inuit from Ittoqqortoormiit (Scoresby Sound), East Greenland, in 2015 (median 120.0 μg L^{-1} for both men and women) (Long et al., 2023) (Fig. 7, Table SI-4). For polar bears, 14 of 18 polar bear subpopulations across the Arctic had estimated plasma mean levels ranging between 146 and 715 μg L^{-1}, exceeding this highest average PFOS levels in human populations, dependent on region and sampling year (Fig. 7, Table SI-4). As reported in Sonne et al. (2023), the Ittoqqortoormiit study participants in 2015 exceeded the established immunotoxic thresholds set by EFSA's for the most severe risk category (>31.9 μg L^{-1}), based on blood serum concentrations for Σ4PFASs (i.e. PFOS, PFOA, PFHxS and PFNA). Thus, these 14 polar bear subpopulations were exposed to elevated PFOS, when compared to the Ittoqqortoormiit human population, considered to be at an even higher risk of effects on the immune system. Indeed, the highest mean concentration in polar bear, at 715 μg L^{-1}, is 6-fold higher than the average of the Ittoqqortoormiit human population and 22-fold higher than the EFSA guideline (31.9 μg L^{-1}) of severe risks even without the contribution from PFOA, PFNA and PFHxS.

When qualitatively comparing PFOS serum levels between human populations in Fig. 7 (Table SI-4), Inuit men and women living in communities of the Greenland East coast (Ittoqqortoormiit, Tasiilaq and Kulusuk) who tended to consume marine mammals at higher trophic levels, e.g. polar bears (*Ursus maritimus*) and killer whales (*Orcinus orca*), presented a much higher exposure to PFOS than Inuit living in communities on the West coast of Greenland (Ilulissat > Sissimiut > Nuuk). In western Greenland communities, PFOS serum levels were also positively associated to marine mammal consumption although the animal species more frequently consumed were likely at lower position in the trophic food chain (e.g., seals and beluga, *Delphinapterus leucas*) than polar bears and killer whales (Wielsøe et al., 2022). Moreover, serum PFOS levels decreased the further south the communities were located, in line with increased consumption of imported foods such as in Nuuk (Wielsøe et al., 2022). Regional differences in exposure to PFOS were likewise observed in Nunavik, where Hudson Strait communities who presented higher plasma PFOS levels more often rely on beluga whales for subsistence than the Ungava and Eastern Hudson Bay communities. In Nunavik, beluga whales are central to Inuit culture and diet, whereas polar bears are only sporadically consumed (but slightly more often consumed in the Eastern Hudson Bay communities) and killer whales are historically not hunted and consumed as they are rarely observed on Nunavik coastlines, although an increasing number of killer whales have been observed by Nunavik hunters in this region (Allaire et al., 2021). Beluga are toothed whales that are lower in the trophic food chain than killer whales and polar bears and found to present lower PFOS levels (Fig. 3), which may partly explain the lower exposure to PFOS in Nunavik Inuit adults when compared to Eastern Greenland.

The ringed seals represent the dominant prey item of polar bear and an important food item for many Inuit populations, and their estimated PFOS plasma concentration in the Ittoqqortoormiit region was on average 2.3-fold lower (Mean = 52 μg L^{-1}; range: 26–101 μg L^{-1} of the three studies) than the highest concentrations found in the human population from this region (Median = 120 μg L^{-1}). The ringed seal average PFOS concentrations (Mean = 52 μg L^{-1}; of the three studies) on the other hand was 7.4-fold lower than the East Greenland polar bear average (Mean = 386 μg L^{-1}; of the three studies). This difference was lower than previously reported liver tissue difference between these two species by Boisvert et al. (2019), where the ringed seals (Mean = 108 ng g^{-1} ww) had PFOS concentrations reported to be 24 times lower than the polar bear (Mean = 2583 ng g^{-1} ww) from the same area in 2011–2012. The average PFOS plasma concentrations of the toothed whales (17.4 μg L^{-1}; range: 5.7–34 μg L^{-1}; five species) from East Greenland were on average 3-fold lower than the ringed seals (Fig. 7). Of the three post 2007 toothed beluga whale populations compiled in the present study, the average estimated plasma PFOS levels were of 14.7 μg/L (ranging from 10 to 23 μg L^{-1}) and 3.6-fold lower than the ringed seals. For other contaminants like the conventional POPs and mercury, the beluga concentrations normally lie well above the carnivore species like polar bears and Arctic seals, which is clearly not the case for PFOS (Galatius et al., 2013).

The PFNA serum or plasma concentrations in humans were on average 5.2-fold lower than PFOS concentrations (range: 1.1–8.6-fold). The highest serum PFNA concentration was found in Inuit from Ittoqqortoormiit in 2015 (19.8 μg L^{-1}) (Fig. 7 and Table SI-4) (Long et al., 2023). As for the PFOS, the polar bear estimated plasma PFNA concentrations (Mean = 107 μg L^{-1}; range 20–215 μg L^{-1}; 14 populations) were the only wildlife species exceeding the highest serum PFNA concentrations reported in Inuit population from Ittoqqortoormiit, Eastern Greenland (Fig. 7, Table SI-4). The limited data on PFNA from other species were all below the Ittoqqortoormiit Inuit serum concentrations, with ringed seals being highest (Mean = 8.1 μg L^{-1}), whereas the toothed whales were even lower (Mean = 3.4 μg L^{-1}) ranging from long-finned pilot whale (9.8 μg L^{-1}), beluga (1.8 μg L^{-1}) and lowest in narwhals, *Monodon monoceros* (0.82 μg L^{-1}) all from East Greenland (Fig. 7 and Table SI-4). Contrary to PFOS, considering that lower concentrations of PFNA were present in beluga whales, this suggests that wildlife species consumed other than beluga contribute to elevated exposure to PFNA in Nunavik, possibly terrestrial species as suggested in Section 5 and more importantly in the Eastern Hudson Bay where plasma PFNA levels were significantly higher when compared to the Hudson Strait and the Ungava Bay region (Aker et al., 2023a).

10. Recommendations/outcomes

Increasing trends of certain long-chain PFCAs (C9-C20), including PFNA, are observed in the Arctic, highlighting the persistence and ongoing threat of these contaminants. The dramatic increase of PFNA in wildlife and human should be considered in the current review for regulation under the Stockholm Convention of POPs, as it is evident that the impact of PFAS extends beyond abiotic environmental contamination, posing health risks to both wildlife and human populations, particularly in the Arctic. The declining trend for PFOS both in wildlife and human populations highlights the effectiveness of international efforts and regulations. However, the recent increasing trend for PFOS found in polar bears in East Greenland might indicate initial effects of climate change, already impairing species' feeding behaviors and most likely their exposure to PFAS. Furthermore, the distribution and availability of species in the Arctic is changing rapidly, which will likely cause changing dietary patterns among Inuit; the combined outcome of climate change impacts and PFAS exposure is complex but concerning and should be a research priority in the years to come.

While quantifying the relative importance of oceanic versus atmospheric pathways of PFAS to the Arctic remains challenging, both are important, but operate on different timescales. Oceanic transport will continue to deliver legacy PFAS, particularly PFOS to the Arctic, while PFCAs seem more atmospherically transported, likely resulting from the atmospheric transport and transformation of volatile PFAAs precursors such as FOTH in the Arctic. Indeed, marine mammals consistently had

the highest concentrations of PFOS in tissues compared to terrestrial and freshwater species, while the contrary was observed for PFNA, suggesting that PFNA transport to the Arctic has stronger atmospheric pathways while ocean transport is more influential for PFOS. Similar conclusions of the importance of ocean transport for PFOS were also reached by ocean model results. The presence of local sources also needs to be better constrained, while the import of PFAS-containing products and consumer goods will result in additional exposure to humans and the environment.

Communities that rely on traditional diets face significantly higher PFAS concentrations than those relying more on market foods. Several PFAS, in particular long-chain PFCAs, can be useful tracers of seafood related PFAS exposures among Arctic populations. In fact, similar results can even be found in industrialized countries, showing that Arctic Indigenous communities involuntarily serve as sentinels of contamination concerns. Data for PFAS in wildlife and humans is currently restricted to the western Arctic communities and lacking for the Russian Arctic. PFAS contamination poses challenges to food security and sovereignty as well as to multiples species' health across the Arctic. A precise biomonitoring of multiple PFAS over time in traditional foods and among vulnerable human groups including in the Russian Arctic is therefore crucial.

Developing standardized testing protocols is also necessary, considering PFAS variability across species and regions, and in different biological matrices when possible (e.g. liver, plasma/serum, blood, and other parts of traditional foods consumed by Indigenous populations). Currently, knowledge on Arctic PFAS is often limited to the standard measurement of the few well-known PFAS. Additional approaches, including suspect and non-target screening, and total organofluorine measurements are promising approaches to better understand the totality of PFAS exposure, and help in exposure source assessment.

Ensuring the safety of traditional foods is paramount, requiring knowledge empowerment and national and international advocacy to further ban PFAS. When local sources of exposure are well identified, support for alternative food systems lower in PFAS and aligning with cultural and nutritional needs has been an approach adopted by some local health authorities. Moreover, transparent communication about PFAS levels in the human body and wildlife is vital, particularly in Arctic communities with higher exposure due to traditional lifestyles. Thus, healthcare providers must navigate PFAS data complexities to inform individuals about potential risks, emphasizing the right to know and informed decision-making.

Effective PFAS contamination management demands robust national and international regulatory frameworks, including production limits and emission controls for problematic substances, waste management regulations, and proper cleanup of contaminated sites. International cooperation is crucial due to PFAS's transboundary nature; an ambitious approach under discussion by the European Commission is to phase-out production and use of PFAS unless deemed essential for society and well-being (Cousins et al., 2019). Overall, there is sufficient evidence that PFAS is a global pollution problem with adverse impacts on the environment and human health of the Arctic towards accelerating the phase-out production and use of PFAS worldwide.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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