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Review

State of knowledge on current exposure, fate and potential health effects of contaminants in polar bears from the circumpolar Arctic

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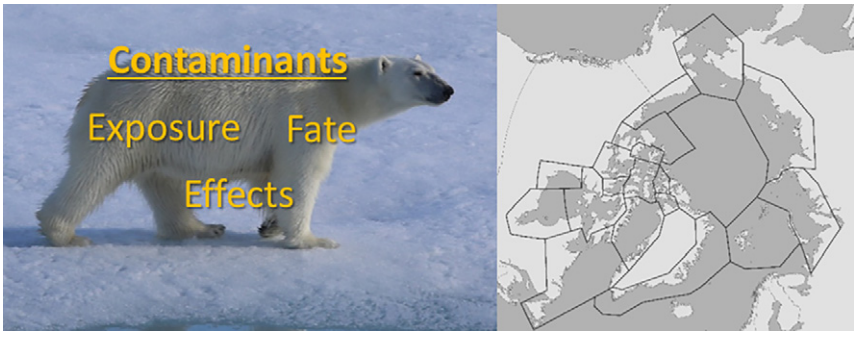
HIGHLIGHTS

- We critically review ~300 publications on polar bear ecotoxicology.
- We present current spatial trends of lipophilic POPs, PFASs and Hg.
- Legacy POPs are still the main compounds found in polar bears.
- Polar bear endocrine and immune system seems to be affected by contaminants.
- Understanding of population level risks and effects of contaminants is still limited.

GRAPHICAL ABSTRACT



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ABSTRACT

The polar bear (*Ursus maritimus*) is among the Arctic species exposed to the highest concentrations of long-range transported bioaccumulative contaminants, such as halogenated organic compounds and mercury. Contaminant exposure is considered to be one of the largest threats to polar bears after the loss of their Arctic sea ice habitat due to climate change. The aim of this review is to provide a comprehensive summary of current exposure, fate, and potential health effects of contaminants in polar bears from the circumpolar Arctic required by the Circumpolar Action Plan for polar bear conservation. Overall results suggest that legacy persistent organic pollutants (POPs) including polychlorinated biphenyls, chlordanes and perfluorooctane sulfonic acid (PFOS), followed by other perfluoroalkyl compounds (e.g. carboxylic acids, PFCAs) and brominated flame retardants, are still the main compounds in polar bears. Concentrations of several legacy POPs that have been banned for decades in most parts of the world have generally declined in polar bears. Current spatial trends of contaminants vary widely between compounds and recent studies suggest increased concentrations of both POPs and PFCAs in certain subpopulations. Correlative field studies, supported by in vitro studies, suggest that contaminant exposure disrupts

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Emerging compounds
Mercury

circulating levels of thyroid hormones and lipid metabolism, and alters neurochemistry in polar bears. Additionally, field and in vitro studies and risk assessments indicate the potential for adverse impacts to polar bear immune functions from exposure to certain contaminants.

Contents

1. Introduction

The polar bear (*Ursus maritimus*) is among the most chemically contaminated of Arctic species due to its position at the top of the food web and lipid-rich diet (Hobson et al., 2002; Letcher et al., 2010). Polar bears occur throughout the Arctic over continental shelf seas covered by sea ice for much of the year (Durner et al., 2009) and feed mostly on sea ice obligate seals, particularly ringed seals (*Pusa hispida*) and bearded seals (*Erignathus barbatus*) (Derocher et al., 2002; McKinney et al., 2017a; Thiemann et al., 2008). Due to the combination of this high trophic level and lipid-rich diet, polar bears are exposed to a wide range of bioaccumulative contaminants. Contaminants that have been documented at relatively high concentrations in polar bears include polychlorinated biphenyls (PCBs), organochlorine pesticides (OCPs), (brominated) flame retardants (FRs), perfluoroalkyl substances (PFASs; and mainly perfluoroalkyl acids and dominated by perfluorooctane sulfonic acids (PFOS)), and mercury (Hg). These compounds originate mainly from industrial and agricultural activities occurring at more southerly latitudes, and are transported by air and ocean currents as well as via river outflows to the Arctic. Although local pollution sources exist in the Arctic, their influence have been seen only in a limited geographical area and their contribution to larger scale contamination likely has been minor (Brown et al., 2014b; Kuzyk et al., 2005; Skaar et al., 2018). Recently, plastic litter including microplastics and nanoplastic have also been found in the Arctic ocean, sea ice, sediments and biota (Cózar et al., 2017; Peeken et al., 2018; Tekman et al., 2017; Trevail et al., 2015), and plastic particles may sorb organic contaminants and thus work as vector for contaminant transport (Mato et al., 2001).

The PCBs and OCPs, as well as FR including hexabromocyclododecane (HBCDD) and congeners in penta-, octa- and deca-brominated diphenyl ether (BDE) formulation, and the highly bioaccumulative surfactant PFOS, which is one of many PFASs currently in use, are listed in Annex A or B of the Stockholm Convention on Persistent Organic Pollutants (POPs) (www.pops.int). The Stockholm Convention on POPs is a global treaty that regulates or bans the use and production of the listed compounds to protect human health and environment. The listed compounds share common properties; they are organic chemicals that remain intact in the environment for long periods, bioaccumulate, are subject to long-range transport, and possess toxic properties. Hg is a non-essential element, which may be of natural or anthropogenic origin, however, the anthropogenic contribution to Hg exposure in Arctic marine wildlife has been estimated to be above 90% (Dietz et al., 2009). Anthropogenic releases of Hg are globally regulated by Minamata Convention on Mercury that was ratified in 2017 (www.mercuryconvention.org/).

The health and viability of circumpolar polar bear subpopulations are not only challenged by contaminant exposure. The species was heavily harvested in the past, and due to international concern, the polar bear was protected by *The International Agreement on the Conservation of Polar Bears*. The agreement was signed in 1973 by the five Range States: Canada, Denmark (Greenland), Norway, the Soviet Union (Russian Federation), and the U.S, and entered into force three years later. The main aim of the agreement was to reduce hunting and protect polar bear habitat as well as to coordinate research related to conservation and management issues. As of 2019, the total population estimate for the 19 recognized subpopulations (Fig. 1A) is approximately 26,000 polar bears (95% confidence intervals 22,000–31,000) with roughly 66% of polar bears residing in the Canadian Arctic (Wiig et al., 2015). The threats facing polar bears have changed since the signing of the treaty, from over-hunting to other emerging issues, especially loss of sea ice habitat (Vongraven et al., 2012). The Arctic sea ice has been in rapid decline, with the number of ice-covered days having declined by 7–44 days per decade across polar bear subpopulations

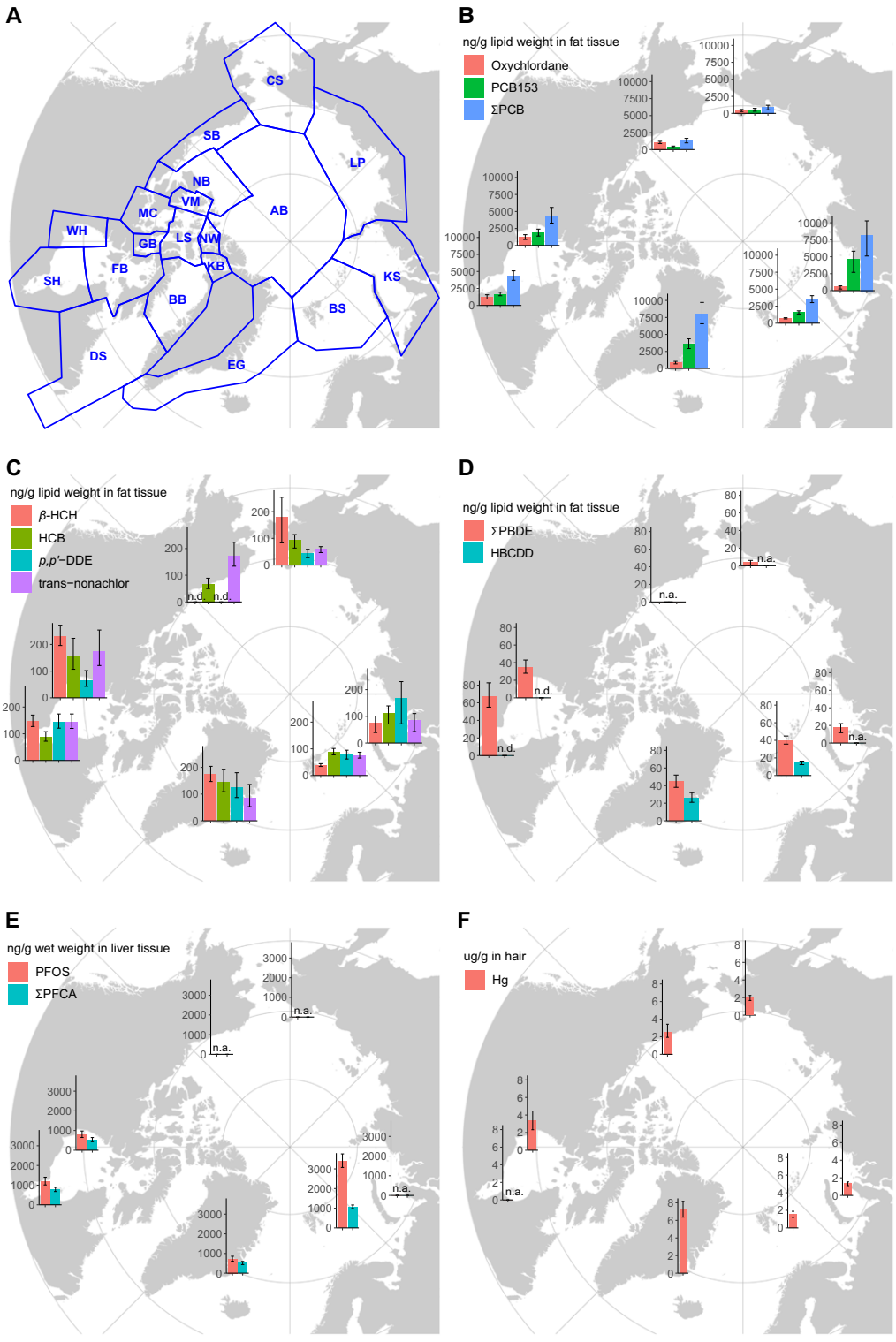

Fig. 1. Nineteen recognized polar bear subpopulations (A) and concentrations of persistent organic pollutants in adipose tissue (C–D), perfluoroalkyl substances in liver tissue (E) and total mercury (Hg) in hair (F) of polar bears sampled from southern Hudson Bay (SH), western Hudson Bay (WH), southern Beaufort Sea (SB), Chukchi Sea (CS), Kara Sea (KS), Barents Sea (BS) and East Greenland (EG) in 2012–2016 (Atwood et al., 2017; Bechshoft et al., 2016; Letcher et al., 2018; Tartu et al., 2017a, 2017b; Boltunov et al., unpublished; Riget et al., unpublished; Routti et al., unpublished). n.a. signifies not analysed. n.d. signifies not detected.

(Stern and Laidre, 2016). As a response to the changing pressures, the Range States recently developed the *Circumpolar Action Plan: Conservation Strategy for Polar Bear* (Range States, 2015). The Circumpolar Action Plan recognizes the loss of Arctic sea ice due to climate change as the largest single threat to polar bears, while contaminants, diseases and parasites, human-caused mortality, mineral and energy resource exploration and development, shipping, and tourism-related activities represent additional threats (Range States, 2015). These threats are also recognized by the International Union for Conservation of Nature (IUCN) Red List of Threatened Species, which has classified the polar

bear as *vulnerable* in most years since 1982 (Wiig et al., 2015). A species classified as *vulnerable* is considered to be facing a high risk of extinction in the wild.

Coordination of research on contaminants at the circumpolar level has been required by the Circumpolar Action Plan due to the transboundary nature of contaminants and their various adverse health effects (Range States, 2015). One of the specific actions in the plan is to *Compile a state of knowledge on contaminants (both global and local source) that affect polar bears and their prey*. Recent reports have summarized data on the temporal trends of POPs in the Arctic, contaminants of emerging Artic concern as well as biological effects of contaminants on Arctic marine mammals and other wildlife (AMAP, 2016, 2017, 2018; Routti et al., 2018). However, new information has been published since the data cut-off points of these reports, and a comprehensive review summarizing the information of contaminant levels and effects in polar bears is lacking. The aim of this review was to provide a comprehensive summary of current exposure, fate and effects of contaminants in polar bears from the circumpolar Arctic.

2. Exposure and fate of contaminants in polar bears

2.1. PCBs and organochlorine pesticides

Although PCBs and OCPs, including DDTs, chlordanes (CHLs), hexachlorocyclohexanes (HCHs), and hexachlorobenzene (HCB) used for industrial and agricultural purposes have been regulated in some countries at national level since the 1970s, and globally by Stockholm Convention on POPs since 2004 (Stockholm Convention, 2001), they are still present at high concentrations in the Arctic marine environment. The main pathway of PCBs into the Arctic Ocean is river discharge followed by ocean currents and atmospheric deposition (Sobek and Gustafsson, 2014), whereas river discharge is less important for DDT transport (Carrizo et al., 2017). Atmospheric currents represent dominant pathways to deliver chlorinated pesticides to the Arctic, except for β-HCH, which enters the Arctic mainly through ocean currents (Barber et al., 2005; Li and Macdonald, 2005). Local pollution may also act as a source of contaminants in certain Arctic marine regions. For example, PCB pollution in the Saglek area of Labrador, Canada, has resulted from poor waste handling at a local military station (Kuzyk et al., 2005). Concentrations of PCBs were elevated in marine sediments and the coastal food web within a 10 km distance from the contaminated site (Kuzyk et al., 2005). Further studies have reported 2 to 4 times higher PCB concentrations in ringed seals exposed to the local pollution at restricted areas compared to ringed seals feeding outside of Saglek Bay (Brown et al., 2014a, 2014b). Studies from the Svalbard archipelago, Norway, have also identified local PCB sources from coal-mining settlements (Cranberg et al., 2017; Jartun et al., 2009). Consequently, contaminant concentrations were higher in benthic species in close proximity to these sources compared to pelagic species and to species from sites lacking such point sources (Evenset and Christensen, 2009).

Due to the large quantities emitted and their high potential for long-range transport and biomagnification in polar bear food webs (Kelly et al., 2007), PCBs and CHLs comprise a major portion of the lipophilic contaminant burden currently found in polar bears (Letcher et al., 2018; Tartu et al., 2017b). More specifically, it is oxychlordane and, to a lesser extent, heptachlor epoxide metabolites of chlordanes and nonachlors, respectively, that constitute most of the sum (Σ) CHL concentrations in tissues. PCBs and ΣCHLs were by far quantitatively the most abundant contaminants in adipose tissue as has been reported for several subpopulations (Gebbink et al., 2008; Greaves et al., 2012; Letcher et al., 2018; Tartu et al., 2017b). Concentrations of ΣPCBs were approximately 8 to 12 times higher in polar bear fat than in ringed seal blubber, whereas the difference was smaller for ΣCHLs and other OCPs (Kleivane et al., 2000; Kucklick et al., 2002; Letcher et al., 2009, 2010).

Although overall levels have been high, concentrations of PCBs and most OCPs showed wide variation between individual polar bears, which may be related to age, sex, breeding status, changes in body fatness and energetic requirements, food web length and diet composition, and finally individual differences in biotransformation capacity (Letcher et al., 2010; Routti et al., 2018 and references therein). PCBs and several OCPs, such as CHLs, accumulated with age in males, but not in females (Bernhoft et al., 1997). However, accumulation of POPs as a function of age and consequently differences between males and females have not been reported recently (Atwood et al., 2017; Ciesielski et al., 2018; Letcher et al., 2018; McKinney et al., 2011b). This was likely related to the importance of birth cohort rather than age on lifetime exposure as contaminant emissions have changed over time (Binnington and Wania, 2014; Dietz et al., 2018; Quinn and Wania, 2012). Polar bear females transfer lipophilic pollutants to their offspring through lipid-rich milk (Bernhoft et al., 1997; Bytingsvik et al., 2012a; Polischuk et al., 2002). This leads to high levels of pollutants in their offspring with, for example, 2.7 times as high circulating PCB concentrations in polar bear cubs compared to their mothers (Bytingsvik et al., 2012a; Polischuk et al., 2002). Due to partitioning of PCBs and OCPs to lipid-rich tissues (Gebbink et al., 2008), seasonal changes in fat depots related to food availability, reproduction and habitat use have a strong influence on tissue concentrations of these compounds. A study on female polar bears from the Barents Sea subpopulation has shown that concentrations of PCBs, CHLs, and β-HCH were mainly determined by variation in body condition (Tartu et al., 2017b). Concentrations of these compounds in polar bear plasma and fat were 4 to 9 times higher in the thinnest compared to the fattest polar bears, whereas they were only 1.5 to 1.8 times higher in the individuals feeding at highest versus lowest trophic levels (Tartu et al., 2017b). Thus, in general, levels of lipophilic POPs are highest when polar bears are at their thinnest from approximately November to April–May, depending on local sea ice conditions and food availability (Cattet, 2000; Derocher and Stirling, 1992, 1996; Polischuk et al., 2002; Tartu et al., 2017b). Reduced spatial extent of sea ice at the subpopulation scale is related to higher tissue concentrations of lipophilic POPs in polar bears from Svalbard (Tartu et al., 2017b). For the southern Beaufort Sea, polar bears that came shore during the increasingly lengthy ice-free period, had lower concentrations of CHLs, but not other OCPs or PCBs, than those that remained on the sea ice year-round (Atwood et al., 2017). This was likely mediated by a diet shift from ringed seals to bowhead whale carcasses (McKinney et al., 2017a; Rogers et al., 2015).

Choice of prey is also one of the factors affecting contaminant exposure in polar bears. Polar bears preferably feed on ice-obligate seals (Derocher et al., 2002; Thiemann et al., 2008). Nonetheless, under reduced ice conditions, they may feed on alternative prey, if available, including sub-Arctic marine mammals (Aars et al., 2015; McKinney et al., 2013) and land-based food resources, such as whale carcasses, seabirds, geese, eggs and reindeer (Gormezano and Rockwell, 2013a, 2013b; Iles et al., 2013; Iversen et al., 2013, 2014; McKinney et al., 2013, 2017a; Prop et al., 2015; Rogers et al., 2015; Schliebe et al., 2008; Stempniewicz et al., 2014; Tartu et al., 2016). Contaminant concentrations can vary widely among prey species with concentrations generally higher in marine relative to terrestrial prey (Letcher et al., 2010). Among the potential marine mammal prey, the highest PCB and OCP concentrations have been found in toothed whales, and the levels of OCPs relative to PCBs were much higher in whales than in seals (reviewed by Routti et al., 2018). Contaminant concentrations also can vary among seal species and according to feeding habitat and prey of the seals (Kleivane et al., 2000). Furthermore, the presence of transient and sub-Arctic species, which have higher contaminant levels than comparable Arctic species, in Arctic marine food webs is likely to enforce increases in exposure to contaminants for predators feeding on them (McKinney et al., 2012; Morris et al., 2016).

In polar bears biotransformation plays an important role in exposure and accumulation, which includes the formation of persistent and

bioaccumulative metabolites (Letcher et al., 2000; AMAP, 2017). The pregnane X receptor, which along with the aryl hydrocarbon receptor and the constitutive androstane receptor induces xenobiotic-metabolizing phase I (cytochrome P450, i.e. CYP) and conjugating phase II enzymes (Kohle and Bock, 2009), is activated by a wide range of contaminants in polar bears (Lille-Langøy et al., 2015). Polar bears are capable of efficient metabolism of numerous POPs, e.g. PCBs are biotransformed to hydroxylated (OH) and methylsulfonyl ($MeSO_2$) PCBs, while DDT is biotransformed to DDE and further to $MeSO_2$-DDE, and CHL and nonachlor pesticides are biotransformed to oxychlordane and heptachlor epoxide, respectively (Letcher et al., 1998, 2009). Additionally, five different classes of PCB metabolites, including OH-$MeSO_2$-, OH_2-$MeSO_2$-, SO_3-, SO_4- and OH-SO_4-PCBs, have been recently found in polar bear serum (Liu et al., 2018). The biotransformation efficiency i.e. ΣOH-PCBs/ΣPCBs is higher in fatter versus thinner bears, which may be related to induction of CYP enzymes regulated by nutritional status (Tartu et al., 2017b). As polar bears can have highly biomagnified levels of some POPs, and OH-PCBs show a strong affinity towards circulating proteins, circulating concentrations of OH-PCBs in polar bears were several times higher than those of PCBs (Bytingsvik et al., 2012a; Sandala et al., 2004; Sandau et al., 2000). Conversely, PCB concentrations in fat and liver dominate over PCB metabolites, in this case $MeSO_2$-PCBs, which partition towards lipid-rich tissues like their parent compounds (Gebbink et al., 2008). In contrast to the lipophilic parent compounds, OH-PCBs are transferred to a lesser extent from mothers to cubs; with OH-PCB concentrations in cubs about one-half of the concentrations found in mothers (Bytingsvik et al., 2012a).

Contaminant concentrations vary substantially among polar bear subpopulations. For this review, we collected information on spatial trends of PCBs and OCPs between polar bear subpopulations sampled in 2012–2016 (Table S.1). PCB and OCP concentrations as measured in polar bear adipose tissue were available for the following subpopulations: southern and western Hudson Bay, East Greenland, Barents Sea, Kara Sea and Chukchi Sea subpopulations (Letcher et al., 2018; Tartu et al., 2017b; Riget et al., unpublished; Boltunov et al., unpublished). For southern Beaufort Sea polar bears, only plasma concentrations of PCBs and OCPs have been measured (Atwood et al., 2017). The plasma concentrations (ng/g wet weight) were converted to adipose tissue concentrations (ng/g lipid weight) based on average ratios of individual compounds in plasma and adipose tissue of Barents Sea polar bears ($n = 85$; data from Tartu et al., 2017b). It should be noted that subpopulation comparisons were not corrected for variation as a function of any biological factors, such as body condition, reproductive status, age, or sex (Bernhoft et al., 1997; Tartu et al., 2017b). Most of the individuals included in the comparison were adults, but the proportion of each sex as well as sampling period varied between subpopulations (Table S.1). However, as discussed above, age and sex were not likely to have major effects on these trends.

Concentrations of PCBs in the Kara Sea and East Greenland subpopulations were approximately twice those in the Hudson Bay and Barents Sea subpopulations, whereas considerably lower concentrations were found in the Chukchi Sea and southern Beaufort Sea (Fig. 1B). The higher levels of PCBs in the Kara Sea subpopulation may have been related to discharge of PCBs by rivers in the Russian Arctic (Sobek and Gustafsson, 2014), whereas spatial variation in diet likely explained the high concentrations in East Greenland (McKinney et al., 2011b) as discussed in the next paragraph. Concentrations of trans-nonachlor were higher in polar bears from Hudson Bay and the southern Beaufort Sea compared to the subpopulations from other areas (Fig. 1C). A similar tendency was found for oxychlordane that had concentrations increasing westwards from the Chukchi Sea and Kara Sea towards the Barents Sea and East Greenland, and highest concentrations in the Hudson Bay and southern Beaufort Sea subpopulations (Fig. 1B). This is in agreement with the higher usage of chlordanes in the U.S. compared to other parts of the world (www.inchem.org). Concentrations of β-HCH were higher for the East Greenland, Hudson Bay and Chukchi Sea subpopulations than in other areas, whereas HCB concentrations tended to be more uniform with slightly higher concentrations in East Greenland compared to other areas (Fig. 1C). Concentrations of *p,p′*-DDE tended to be higher in the Kara Sea, southern Beaufort Sea and East Greenland subpopulations.

A more detailed spatial subpopulation assessment on PCBs and OCPs was conducted on 11 polar bear subpopulations from Alaska, Canada, East Greenland and Svalbard sampled in 2005–2008. The assessment concluded that PCB and *p,p′*-DDE levels increased from Alaska to Svalbard, whereas ΣHCH and β-HCH levels showed an opposite trend, and ΣCHLs did not show a longitudinal pattern (McKinney et al., 2011b). These trends were consistent with earlier studies based on samples collected in 1989–1993 and 1996–2002 (Norstrom et al., 1998; Verreault et al., 2005). Spatial differences were also found in chemical tracers of diet measured as stable isotope values and fatty acid ratios, which partly explained the high PCB concentrations in the East Greenland and Barents Sea subpopulations (McKinney et al., 2011c). However, the diet-adjusted PCB concentrations for the Hudson Bay subpopulations were higher than the non-adjusted concentrations, suggesting that PCB exposure in the polar bear food web from Hudson Bay was higher compared to other areas spanning from Alaska to Svalbard (McKinney et al., 2011c). Studies based on samples collected in the early 1990s have suggested that polar bears from the western and central Russian Arctic had even higher PCB, CHL and DDE concentrations than those from the eastern Russian Arctic or Svalbard (Andersen et al., 2001; Lie et al., 2003).

Contaminant exposure also varies between individuals within subpopulations according to their habitat use. For example, in a study published 15 years ago, PCB concentrations were higher in female polar bear that used large pelagic areas of the Barents Sea than in those that stayed in close proximity to the Svalbard archipelago (Olsen et al., 2003). This difference was suggested to be related to larger energy needs and thus larger intake of prey and contaminants by the pelagic bears, or possibly to their reliance on the marginal ice zone food web (Olsen et al., 2003). A follow up study reported higher OH-PCB concentrations with larger home ranges, and also a more selective diet in the offshore versus coastal female polar bears (Tartu et al., 2018). However, concentrations of lipophilic PCBs or OCPs were not related to space use strategy in this study, which may have been related to the offshore bears being fatter than the coastal ones (Tartu et al., 2018).

Temporal trends of PCBs and OCPs have varied among the Barents Sea, East Greenland and Hudson Bay subpopulations. Concentrations of ΣPCBs and OCPs in polar bears from the Barents Sea (adult females 1997–2017) and East Greenland (subadults 1983–2013) generally declined 5 to 10% per year prior 2005–2010 (Dietz et al., 2013b, 2018; Lippold et al., 2019). However, *p,p′*-DDE and HCB concentrations in Barents Sea polar bears and ΣPCBs, ΣDDTs, ΣCHLs, HCB, β-HCH, dieldrin and Σchlorobenzene (ClBz) in East Greenland polar bears have increased recently (≥8%/year), (Dietz et al., 2018; Lippold et al., 2019). β-HCH concentrations remained stable in the Barents Sea polar bears (Lippold et al., 2019). In western Hudson Bay polar bears, and at intervals over the period of 1991 to 2007, ΣDDT (and *p,p′*-DDE, *p,p′*-DDD, *p,p′*-DDT) and α-HCH decreased 8.4% and −11%/year, and β-HCH increased 8.3%/year (McKinney et al., 2010). Some of the less persistent PCB congeners decreased significantly 1.6%/year to 6.3%/year, whereas PCB153 levels tended to increase 3.3%/year. CHLs declined, whereas non-monotonic trends were detected for metabolites (heptachlor epoxide, oxychlordane). ΣChlorobenzenes, octachlorostyrene, Σmirex, Σ$MeSO_2$-PCB and dieldrin concentrations did not significantly change. Comparison of samples collected in 2013–2014 relative to those collected in 2007–2008 suggested that PCB and OCP concentrations have declined in the southern Hudson Bay polar bears, whereas concentrations of most OCPs from the Western Hudson Bay subpopulation increased (Letcher et al., 2018; McKinney et al., 2011b). The inconsistent trends of PCBs and OCPs for subpopulations were likely related to geographical differences in primary and secondary emissions as well as climate-related changes in polar bear ecology.

2.2. Flame retardants

Halogenated compounds have been widely used as FRs. Brominated FRs are a large group of chemically diverse compounds, which are additive or reactive substances that are part of synthetic polymers. As has been recently reported (AMAP, 2017 and references therein), the majority of brominated FRs that are contaminants of emerging Arctic concern are additive FRs and are subject to long-range transport by air currents (Macdonald et al., 2005; Wania and Dugani, 2003; Wania and Mackay, 1993).

Several brominated FRs that were previously produced in high volumes, such as polybrominated biphenyls (PBBs), polybrominated diphenyl ethers (PBDEs; including deca-BDE (BDE209)), HBCDD and tetrabromobisphenol A (TBBPA), are increasingly regulated and in the case of PBDEs and HBCDD are globally regulated as they are listed under Annex A of the Stockholm Convention on POPs. This ban on penta-, octa- and deca-BDE mixtures has resulted in the production and use of an array of replacement FR compounds, which include e.g. decabromodiphenyl ethane (DBDPE), 1,2-bis(2,4,6-tribromophenoxy) ethane (BTBPE), hexabromobenzene (HBBz), pentabromoethylbenzene (PBEB), pentabromotoluene (PBT), the β-isomer of 1,2-dibromo-4-(1,2-dibromoethyl)cyclohexane β-tetrabromocyclohexane, β-TBECH (or β-DBEDBCH), 2,4,6-tribromophenyl-2,3-dibromopropyl ether (TBP-DBPE), 2-ethylhexyl-2,3,4,5-tetrabromobenzoate (EH-TBB), bis(2-ethylhexyl)tetrabromophthalate (BEH-TEBP), 2,3,5,6-tetrabromo-p-xylene (TBX), and pentabromobenzene (PBBz) and related compounds. There are also chlorinated compounds used as FRs, or chlorinated flame retardants, e.g. syn- and anti-isomers of Dechlorane Plus (DDC-CO) and related compounds, chlorinated organophosphate esters (OPE) and short-chain chlorinated paraffins (SCCPs) (AMAP, 2017 and references therein). (Chlorinated) Organophosphate esters (OPEs) have been used for a long time as FRs and plasticizer chemicals, and increasingly as replacement alternatives for phased out FRs such as PBDEs and HBCDD (van der Veen and de Boer, 2012).

PBDEs, BB153 and HBCDD were the major FRs detected among monitored subpopulations, whereas other brominated FRs were infrequently detected (Letcher et al., 2018; McKinney et al., 2011b; Tartu et al., 2017b). However, relatively high concentrations of emerging brominated FRs were found in polar bear plasma samples from the Barents Sea (Harju et al., 2013; Sagerup et al., 2010). The average concentration of EH-TBB was 415 ng/g lipid weight in plasma sampled in 2008, and it was the only detected compound among 12 emerging brominated FRs analysed including DBDPE and BEH-TEBP (Sagerup et al., 2010). In plasma samples collected in 2012, the average concentrations of DBDPE were 775 ng/g lipid weight, which was ~50–70 times higher than average concentrations of BDE47 and BEH-TEBP in the same samples (Harju et al., 2013). Concentrations of 2,4,6-tribromophenol were also detectable in polar bear plasma (26 ng/g wet weight), however, this compound was not necessarily of anthropogenic origin as it also occurred naturally in the marine environment (Harju et al., 2013). Chlorinated FRs (Dechlorane 602, and Dechlorane Plus anti and syn isomers) have only been detected at trace levels in polar bear plasma from the Barents Sea (Schlabach et al., 2017).

Similar to other lipophilic compounds, concentrations of FRs have varied between individual polar bears, but the underlying reasons for individual variation have mainly been studied for PBDEs mostly due to infrequent detections of the other FRs. For East Greenland, concentrations of PBDEs were similar between males and females (Dietz et al., 2007) and did not show age-related accumulation (Dietz et al., 2007; Lippold et al., 2019; McKinney et al., 2011b; Muir et al., 2006; Tartu et al., 2017b). Conversely, concentrations of BB153 did increase with age in Hudson Bay polar bears, however the effect of subpopulation was more pronounced than age in the statistical models (Letcher et al., 2018). Studies from the Barents Sea indicated that concentrations of PBDEs in female polar bears were mainly determined by variation in body condition and diet (Lippold et al., 2019; Tartu et al., 2017b). Furthermore, PBDE concentrations were higher in spring compared to autumn, when the bears were at their thinnest, particularly after a winter with unfavorable sea ice conditions (Tartu et al., 2017b). Similarly, PBDE concentrations for East Greenland bears were higher in spring compared to the rest of the year (Dietz et al., 2007).

There have been numerous studies that have shown the environmental degradation of FRs, including in the Arctic (AMAP, 2017). However, only a handful of studies have examined PBDE and other FR metabolism in polar bears, even though they are clearly capable of FR biotransformation, which influences the tissue residue concentrations in exposed bears (McKinney et al., 2011a; Vetter et al., 2015). For example, in liver microsomal in vitro assays for polar bear, BDE209 was depleted by about 20%, while that of lower brominated BDE congeners was ≤3% (McKinney et al., 2011a). Polar bears were also able to deplete DBDPE by 60% in the same in vitro liver assays. The data suggested that BDE209 and DBDPE were not substrates for the same enzyme. No debrominated metabolites were detected, but it was noted that phenolic metabolites might have been formed, possibly in combination with multiple debrominations. In a study on four polar bears who swam from Greenland to Iceland between 2008 and 2011, the DDC-CO known as Dechlorane 602 and a potential hydrodechlorinated metabolite were identified in all samples (Vetter et al., 2015).

There are few reports of abiotic or biotic degradation of OPEs in the environment, and a dearth of information in Arctic biota (AMAP, 2017). Polar bear adipose samples from the Hudson Bay subpopulations collected in 2013–2014 were screened for a suite of 17 OPEs (Letcher et al., 2018), but only very low concentrations of tris(2-ethylhexyl) phosphate were quantifiable. Trace amounts of triphenyl phosphate, tris(2-chloroisopropyl)phosphate, tris(2-butoxyethyl)phosphate and tri-n-butyl phosphate were also found. These low levels of OPEs in tissues were consistent with the rapid in vitro metabolism reported for tris(1,3-dichloropropyl) phosphate, triphenyl phosphate, tri-n-butyl phosphate and tris(2-butoxyethyl) phosphate in polar bear liver microsomal assays (Strobel et al., 2018). Trace levels of triisobutyl phosphate, tris(2-chloroethyl)phosphate and tris(1,3-dichloro-2-propyl)phosphate have been reported for a few polar bears sampled from the Barents Sea (Hallanger et al., 2015).

For the present review, we collected current subpopulation-specific concentrations of PBDEs and HBCDD (Table S.1). PBDE concentrations measured in polar bear adipose tissue were available for the following subpopulations: southern and western Hudson Bay, East Greenland, Barents Sea, Kara Sea and Chukchi Sea, whereas HBCDD was analysed in Hudson Bay, East Greenland, and Barents Sea polar bears (Letcher et al., 2018; Tartu et al., 2017b; Riget et al., unpublished; Boltunov et al., unpublished). As mentioned in Section 2.1, subpopulation comparisons were not corrected for variation caused by any biological factors (Table S.1). ΣPBDE concentrations were highest in southern Hudson Bay, followed by the Barents Sea, East Greenland, and western Hudson Bay subpopulations (Fig. 1D). The lowest ΣPBDE concentrations were found in the Chukchi Sea and Kara Sea polar bears. HBCDD concentrations were higher in polar bears from East Greenland than from Barents Sea, and not detected in Hudson Bay bears (Fig. 1D). These results were in agreement with an earlier spatial assessment on PBDEs conducted on 11 polar bear subpopulations spanning from Alaska to the Barents Sea in 2005–2008. ΣPBDE showed higher levels in southern Hudson Bay followed by western Hudson Bay, East Greenland and the Barents Sea (McKinney et al., 2011b), which is in accordance with a previous spatial PBDE study on polar bears sampled in 1996–2002 (Muir et al., 2006). Higher levels of PBDEs in the southernmost polar bear subpopulation in North-America are likely related to the sites of production of these compounds. Penta- and octa-BDE mixtures, which contain similar compounds as found in polar bears, were produced at much higher quantities in U.S. than in Europe or Asia (Persistent Organic Pollutants Review Committee, 2006, 2008). HBCDD concentrations were clearly highest in the East Greenland and Barents Sea subpopulations, being 15–51 fold higher in the latter subpopulations compared to the

Canadian subpopulations (McKinney et al., 2011b). The spatial trend can be explained by higher use of HBCDD in Europe compared to other parts of the world (Persistent Organic Pollutants Review Committee, 2010).

Temporal trends of FRs have been studied in the Barents Sea, East Greenland and Hudson Bay subpopulations. For two studied PBDEs, concentrations of BDE47 in female polar bears from the Barents Sea were shown to have decreased by 3%/year during the last two decades, 1997–2017, whereas BDE153 concentrations were stable over time (Lippold et al., 2019). A study on subadult polar bears from East Greenland (1983–2010) indicated that BDE47 and BDE99 concentrations increased 6–8%/year until 2000–2004 after which they declined by 31% and 13%/year, respectively (the latter not significant) (Dietz et al., 2013a). In the same study, BDE100, BDE153 and HBCDD concentrations increased by 3–8%/year over the study period, while concentrations of the PBB congener BB153 did not change over time (Dietz et al., 2013a). As was reported for temporal trends in Western Hudson Bay polar bears, and at intervals over the period of 1991 to 2007, ΣPBDE levels increased by 13%/year and matched the increases in the four consistently detected congeners, BDE47, BDE99, BDE100 and BDE153 (McKinney et al., 2010). Although no trend was observed, in the same study total-(α)-HBCDD was only detected post-2000. BB153 showed no temporal change over the period of 1991 to 2007 (McKinney et al., 2010). Comparison of samples collected in 2013–2014 relative to those collected in 2007–2008 in the Hudson Bay area suggested that BB153 had declined, whereas BDE153 concentrations remained unchanged and changes in ΣPBDE concentrations did not show clear patterns (Letcher et al., 2018; McKinney et al., 2011b). The decline of BDE47 in Barents Sea and East Greenland polar bears reflects the phase-out of the production of penta-BDE mixture in Europe in late 1990s, whereas the mixture was phased out in the U.S. in the mid 2000s (Persistent Organic Pollutants Review Committee, 2006). Stable BDE153 concentrations in all studied subpopulations was likely related to recent emissions of deca-BDE, which may be degraded to lower brominated BDEs in the abiotic environment and biota. Production (but not import) of deca-BDE was phased out in EU in 1999, whereas the phase-out Persistent Organic Pollutants Review Committee, 2014, 2015a started a decade later in North-America (Persistent Organic Pollutants Review Committee, 2014, 2015a). Emissions of deca-BDE from China, the largest producer of the mixture in the world, have been relatively constant since early 2000s (Zhang et al., 2017; Persistent Organic Pollutants Review Committee, 2014, 2015a).

2.3. Perfluoroalkyl substances (PFASs)

PFASs have been produced and used in large quantities for a wide variety of industrial purposes (OECD, 2011). Two subgroups of PFASs are mainly found in marine biota: perfluoroalkyl sulfonates (PFSAs, including PFOS) and perfluoroalkyl carboxylates (PFCAs) (Houde et al., 2011). Both PFSAs and PFCAs have complex emission histories. PFOS and its precursors were produced at high quantities in Western countries from the 1970s until the early 2000s (Wang et al., 2017). Later, since the early 2000s, smaller scale production of PFOS-related compounds started in China and Brazil (Gilljam et al., 2016a, 2016b; Wang et al., 2017). Release of PFCAs also shifted from Western countries and Japan to continental Asia in the early 2000s, and today emissions of PFCA precursors increasingly contribute to PFCA loads in the environment (Wang et al., 2014a, 2014b). PFOS, its salts and a parent compound, perfluorooctane sulfonyl fluoride, were listed under the Annex B of Stockholm Convention in 2009, which means large restrictions, but not a complete ban on production and use of these compounds. Currently (2019), perfluorooctanoate and perfluorohexasulfonate (PFHxS) and closely related compounds are proposed for listing under the Convention (Persistent Organic Pollutants Review Committee, 2015b, 2017).

Ocean currents are the main transport route for PFASs, which are directly released into aquatic systems (Wania, 2007; Zhao et al., 2012), whereas volatile precursors of PFSAs and PFCAs undergo long-range atmospheric transport and degrade to PFSAs and PFCAs in the atmosphere and snow (D'Eon et al., 2006; Ellis et al., 2004; Martin et al., 2006; Taniyasu et al., 2013). PFASs may also originate from human activities in the Arctic. Elevated PFAS concentrations have been reported in meltwater in locations downstream from local settlements, as well as close to firefighting training sites (Kwok et al., 2013; Skaar et al., 2018). However, lake and sea water samples collected close to settlements in Svalbard had only very low levels of PFASs indicating that local PFAS sources do not significantly contribute to local marine and terrestrial pollution (Skaar et al., 2018). The PFASs, PFOS and C_{8-14} PFCAs in particular, biomagnify in Arctic marine food webs (Kelly et al., 2009).

PFASs are quantitatively the most abundant contaminants in polar bear plasma, at least for adult females from the Barents Sea, for which the average concentration ratio between PFASs and PCBs, and PFASs and OH-PCBs, were 16 and 6 on a wet weight basis (Tartu et al., 2017a, 2017b). In general, PFOS followed by PFHxS, and PFCAs with 9 to 11 carbons were quantitatively the most abundant PFASs in polar bear blood circulation and liver (Bytingsvik et al., 2012b; Letcher et al., 2018; Rigét et al., 2013; Tartu et al., 2017a). PFASs bind to proteins, and PFAS (and specifically PFOS and PFCA) concentrations were much greater in the liver followed by blood > brain > muscle ≈ adipose as reported for East Greenland polar bears (Greaves et al., 2012). Using the same samples, liver, blood, brain, muscle and adipose were analysed for linear PFOS (L-PFOS), as well as multiple mono- and di-trifluoromethyl-substituted branched isomers. L-PFOS accounted for 93% of total-PFOS isomer concentrations in the liver, whereas the proportion was significantly lower in blood (85%) (Greaves and Letcher, 2013). Branched isomers were quantifiable in the liver and blood, but not in the brain, muscle, or adipose tissue. No di-trifluoromethyl-substituted isomers were detectable in any of the tissues. It was suggested that these tissue-specific isomer patterns were due to isomer-specific pharmacokinetics, perhaps due to differences in protein affinities, and thus differences in protein interactions, as well transport, absorption, and/or metabolism in the body. PFASs were compared in eight brain regions of polar bears from East Greenland (Greaves et al., 2013). Blood–brain barrier transport of PFASs (PFSAs and PFCAs) occurred for all brain regions, although inner regions of the brain closer to incoming blood flow (pons/medulla, thalamus, and hypothalamus) contained consistently higher PFAS concentrations compared to outer brain regions (cerebellum, striatum, and frontal, occipital, and temporal cortices). PFOS and the longer-chain PFCAs (C_{10}–C_{15}) were significantly positively correlated with lipid content for all brain regions.

There are very few studies of emerging PFASs in polar bears. However, F-53B, a chlorinated polyfluorinated ether sulfonic acid, was detected at <0.1 ng/g concentrations in polar bear liver samples from East Greenland (Gebbink et al., 2016). Neither F-53B nor F53 was detected in polar bear plasma samples from the Barents Sea (Schlabach et al., 2017). Additionally, perfluoro-4-ethylcyclohexane sulfonic acid (a cyclic PFSA) and short chain PFSAs and PFCAs have been detected at low concentrations in liver or plasma samples from East Greenland, Hudson Bay and the Barents Sea (Gebbink et al., 2016; Letcher et al., 2018; Routti et al., 2017). Cyclic and unsaturated PFSA, ether-PFSAs, unsaturated ether-, cyclic ether and carbonyl PFSAs, and x:2 chlorinated perfluoroalkyl ether sulfonates were recently detected in polar bear serum from Hudson Bay and Beaufort Sea using non-target screening methods (Liu et al., 2018).

Polar bears can rapidly metabolize N-ethyl-perfluoro-1-octanesulfonamide to perfluorooctanesulfonamide (FOSA) in vitro, and likely are able to easily metabolize FOSA to PFOS, which suggests that at least a portion of PFOS accumulating in bears likely comes from PFOS precursor metabolism by the bear (Letcher et al., 2014). Furthermore, PFCA precursors such as FTOHs can be transported via atmospheric longrange transport and converted to PFCAs through biotransformation processes

that increase the concentrations of PFSAs and PFCAs as well as accumulating themselves.

Individual variation in blood concentrations of PFASs is mainly determined by diet and feeding/fasting state, and not by body condition (Tartu et al., 2017a). Polar bears feeding on a high trophic level marine diet, and those that are fasting, exhibit the highest PFAS concentrations (Tartu et al., 2017a). Also, females with young cubs have higher PFAS concentrations than solitary females, which is likely related to increased lipoprotein synthesis during lactation and the long fasting period preceding the emerging from dens (Routti et al., 2017; Tartu et al., 2017a). However, maternal transfer of PFASs is low compared to lipophilic compounds. That is, circulating PFSA and PFCA concentrations are a quarter or less in young cubs compared to their mothers (Bytingsvik et al., 2012b). No differences in PFAS concentrations between sexes have been shown, and age-related accumulation in adult females has not been observed (Letcher et al., 2018; Routti et al., 2017; Tartu et al., 2017a). In Hudson Bay bears, including adult and subadult males and females, there were small, but significant, positive associations of PFOS and ΣPFAS with age, but again subpopulation (location) was the dominant factor (Letcher et al., 2018).

For this review, we compared liver PFOS and PFCA concentrations between the following polar bear subpopulations from 2012 to 2016: southern and western Hudson Bay, East Greenland and the Barents Sea (Table S.1) (Letcher et al., 2018; Tartu et al., 2017a; Riget et al., unpublished). As PFAS data for the Barents Sea were only available for plasma, we converted plasma concentrations to liver concentrations (Table S.1). These comparisons indicated that PFOS concentrations were several times higher in Barents Sea polar bears compared to Hudson Bay and East Greenland polar bears (Fig. 1E). The subpopulation trends were similar although less pronounced for ΣPFCAs (Fig. 1E). Spatial trends of PFASs were assessed in polar bears sampled from seven regions spanning from Alaska to the Barents Sea between 1999 and 2002 (Smithwick et al., 2005). The results indicated that polar bears from southern Hudson Bay, East Greenland and the Barents Sea had higher PFOS concentrations compared to those from the western areas. Proportion of PFCAs varied between the eastern and western areas. The observed PFAS trends are likely related to spatial differences in oceanic and atmospheric input of PFASs to the Arctic (Wong et al., 2018; Yeung et al., 2017).

PFAS exposure can also be related to habitat use within subpopulations. Polar bears that used high quality sea ice habitat on the eastern side of Svalbard had higher PFAS concentrations compared to those that used more open water habitat on western Svalbard (Routti et al., 2017; Tartu et al., 2017a). Furthermore, PFAS concentrations were higher in the so-called "offshore" bears from the Barents Sea subpopulation compared to the coastal bears that stay in proximity to the Svalbard archipelago, and the concentrations increased towards eastern longitudes (Tartu et al., 2018). This spatial variation may be related to diet and/or larger home ranges and thus higher energy and contaminant intake and, possibly, to efficient uptake into food webs during sea ice melt (Tartu et al., 2017a, 2018).

Most recently, temporal trends have been studied for Barents Sea and East Greenland polar bears (Rigét et al., 2013; Routti et al., 2017). Concentrations of PFHxS and PFOS peaked in early 2000 for female polar bears from the Barents Sea and a few years later for East Greenland bears (Rigét et al., 2013; Routti et al., 2017). The short time-lag between the peaks and the cessation in worldwide production of PFOS precursors (and their shorter-chain homologues) indicated that peak exposure was mainly related to transport of precursors via air currents (Routti et al., 2017). The decrease of 9% to 14%/year in the Barents Sea continued only until 2009 after which the levels have been stable, likely due to continuous input of PFSAs by ocean currents (Routti et al., 2017). PFCAs with carbon chain lengths from C_9 to C_{13} increased ~2%/year in Barents Sea polar bears, and when these changes were adjusted to climate-related changes in feeding habits, the increase was slightly faster, ~3%/year (Routti et al., 2017). C_9-C_{11} PFCAs increased ~6%/year in East Greenland polar bears from 1984 to 2006 after which, the levels were stable (Dietz et al., 2008; Rigét et al., 2013). Published information of PFAS trends in the North American Arctic is scarcer. A study published over a decade ago (Smithwick et al., 2006) reported increasing PFOS and C_9-C_{11} PFCA concentrations in polar bears from two geographic locations in the North American Arctic, northern Baffin Island, Canada, and the region around Barrow, Alaska, collected from 1972 to 2002. FOSA showed decreasing concentrations over time at both locations, while the remaining PFASs showed no significant trends or were not detected in any sample. A more recent two time point comparison, 2012–2013 vs. 2002, suggested a decrease in PFOS concentrations and an increase in ΣPFCAs in polar bears from southern Hudson Bay (Letcher et al., 2018; Martin et al., 2004).

2.4. Hg

Hg emissions have recently been subject to regulation at the international level through the 2017 ratification of the Minamata Convention on Mercury. Nonetheless, biogeochemical modelling efforts have suggested that global emissions of Hg will need to be "aggressively reduced" even to just keep oceanic Hg at the current levels due to legacy anthropogenic burdens (Amos et al., 2013). To evaluate the effectiveness of emissions reductions in bringing about decreases in environmental Hg concentrations over time, both modelling and measurements are needed (Selin, 2014). One practical measurement approach that has been identified is continued monitoring of Hg concentrations in Arctic biota (Mallory and Braune, 2018). Within Arctic marine ecosystems, Hg is considered one of the key contaminants of concern with respect to health risks to biota (Dietz et al., 2013c; Scheuhammer et al., 2015). Like PCBs, a major pathway for emitted Hg into the Arctic Ocean may be riverine outflows (Zhang et al., 2015), although atmospheric, terrestrial, and oceanic inputs also occur (Braune et al., 2015). Generally, Hg pollution in the Arctic is considered to be a consequence of nonpoint source global emissions; however, the potential contribution of more local point sources has not been thoroughly evaluated. Deposited Hg is converted to monomethyl Hg (MeHg), a potent neurotoxin, in oxic surface seawater (Schartup et al., 2015). Once bacterially produced, MeHg then bioaccumulates and shows stronger biomagnification in Arctic marine food webs relative to those in warmer regions (Lavoie et al., 2013), resulting in levels of concern in high trophic position marine species, particularly the apex predator: polar bear. Indeed, concentrations of total Hg (THg, a suitable proxy for MeHg in polar bears) in polar bear liver may be an order of magnitude or more higher than the concentrations reported in the liver of their main prey, ringed seal (Brown et al., 2018).

Hg concentrations in polar bears have primarily been quantified in hair, but also in muscle, liver, kidney, brain, whole blood, and milk (Basu et al., 2009; Born et al., 1991; Dietz et al., 1995, 1998, 2000, 2006, 2009, 2013c; Knott et al., 2012; Knott et al., 2011a; Sonne, 2010). While Hg in polar bear hair reflects Hg concentrations in blood as well as those in liver, muscle, and kidney (Born et al., 1991; Cardona-Marek et al., 2009), the absolute concentration was orders of magnitude higher in hair (Cardona-Marek et al., 2009). Higher hair concentrations are thought to reflect a transfer of Hg into the hair as it grows (Bechshoft et al., 2015; Cardona-Marek et al., 2009; Dietz et al., 2013c), in effect offloading this toxic element into a tissue with limited bioavailability, thereby reducing exposure to some degree.

Hg concentrations in polar bear hair are suggested to be related to several biological factors, most of which are interconnected. Differences have been found between the sexes, with adult females having higher concentrations than adult males (Bechshoft et al., 2015; Cardona-Marek et al., 2009; St Louis et al., 2011). This is likely a consequence of age-related and sex-specific differences in growth rates, selection of prey species, and, origin of carbon and lipid sources and relative amount of protein in the diet (Bechshoft et al., 2008a; Derocher and Stirling, 1998; Knott et al., 2011a; Routti et al., 2012; St Louis et al., 2011). Age

is also an influential factor in determining a polar bear's Hg load, with increasing hair levels from cubs to yearlings and adults (Bechshoft et al., 2016). For adult females, Hg concentrations may also vary depending on their reproductive status (pregnant/denning/lactating), which affects their Hg intake as well as offloading (Knott et al., 2012). As Hg is essentially a dietary contaminant, individual diet - itself related to sex, age, body condition, and habitat use - has a significant influence on the exposure to this contaminant (Bechshoft et al., 2015; Galicia et al., 2015; McKinney et al., 2017b; Sciullo et al., 2017). For example, McKinney et al. (2017b) demonstrated THg concentrations were lower in bears with better body condition that consumed lower trophic position food items.

Hg exposure varies among the circumpolar subpopulations, but in a different pattern than that for PCBs. For this review, we compared THg concentrations from 2011 to 2016 in polar bear hair among the following polar bear subpopulations: southern Beaufort Sea, East Greenland, Barents Sea, Kara Sea and Chukchi Sea (Table S.1) (McKinney et al., 2017b; Boltunov et al., unpublished; Riget et al., unpublished; Routti et al., unpublished). These comparisons suggest that THg concentrations are several times higher in East Greenland compared to all other studied subpopulations (Fig. 1F). The present trends are somewhat different from earlier assessments. The latest published circumpolar assessment was based on samples collected in 2005–2008 (Routti et al., 2011). Consistent with earlier assessments (Braune et al., 1991; Norstrom et al., 1986; Rush et al., 2008), Routti et al. (2011) reported that concentrations of THg were most elevated in liver tissues of polar bears from the western North American Arctic, i.e., the southern and northern Beaufort Sea subpopulations (~30-60 μg/g wet weight). Similar spatial patterns have also been reported for ringed seals with higher Hg concentrations in the western Canadian Arctic compared to the eastern Canadian Arctic, Alaska, and Greenland (Brown et al., 2016; Wagemann et al., 1996). The reason for the observed changes in spatial trends seems to be linked to opposite temporal trends in southern Beaufort Sea and East Greenland subpopulations as discussed below.

A recent study on southern Beaufort Sea polar bears reported a decline of 13%/year for hair THg in adult males and females over 2004–2011 (McKinney et al., 2017b). This decline was linked to changing body condition and feeding patterns, e.g., feeding on prey occupying lower trophic positions, in this subpopulation because of increasing use of onshore habitats. Such a decreasing trend is not consistent with trends published for other Western and Central Arctic subpopulations. Hair THg concentrations increased by 2%/year in Northwest Greenland polar bears over 1987–2008 (Dietz et al., 2011) and had similar increases over 1892–1991 (Dietz et al., 2006). Conversely, THg concentrations declined by 0.8%/year over 1973–2001 in polar bears from East Greenland (Dietz et al., 2006). However, THg levels increased in the East Greenland subpopulation over the period of 1984 to 2008 (Braune et al., 2011) and seemed to be even higher in 2014–2017 (Table S.1) compared to the levels in polar bears sampled in 1999–2008 (Braune et al., 2011). Dietz et al. (2006) proposed that dissimilarities in the trends for polar bears in the Eastern Arctic relative to those in the Western and Central Arctic may be a consequence of declining emissions from North America and Europe over the past few decades, but rising emissions from Asia. Polar bear hair was also an important component in a literature review concerning the long-term changes of Hg in humans and selected Arctic marine mammals and birds of prey since pre-industrial times, i.e. before 1800 CE, to determine the anthropogenic contribution to present-day Hg concentrations and the historical timing of any changes (Dietz et al., 2009). The results revealed that trends of Hg in hard tissues hair, teeth, and feathers consistently showed that there had been an order-of-magnitude increase of Hg in Arctic marine food web-based animals that began in the mid- to late-19th Century and accelerated in the 20th Century. The median man-made contribution to present-day Hg concentrations was 92.4% ranging from 74.2 to 94.4%.

2.5. Emerging compounds

In previous sections, published studies on POPs are noted for polar bears, some of which are classified as contaminants of emerging Arctic concern (CEACs). As has recently been summarized in an AMAP report (AMAP, 2017), there are a broad range of CEACs that have not been previously studied in Arctic wildlife, but have been reported in other biotic or abiotic media. The AMAP report also lists specific chemicals and chemical groups that should be prioritized for future Arctic studies. These CEACs are comprised of about 150 individual compounds and in 18 groupings of chemicals including pharmaceuticals and personal care products, replacement and alternative PFASs, new FRs including brominated and chlorinated FRs and OPEs, the pesticide hexachlorobutadiene, siloxanes, by-product PCBs (e.g. PCB11), phthalates, halogenated natural products, new current-use pesticides and macro/microplastics. Several CEACs identified in previous AMAP assessments of POPs continue to be prominent and concentrations of some are present and/or increasing in Arctic air and wildlife (including polar bears), such as some PFASs, BDE209, HBCDD, other brominated FRs, polychlorinated naphthalenes (PCNs), SCCPs, and pentachloroanisole (PCA) and pentachlorophenol (PCP).

With respect to CEACs in polar bears, based on 2013–2014 collected tissue samples from Hudson Bay polar bears, a large and complex suite of 295 legacy and new halogenated compounds were reported (Letcher et al., 2018). A total of 210 compounds were detected and/or quantifiable with some frequency in all fat or liver samples. ΣPCBs followed by ΣCHL remained the most concentrated groups of contaminants in polar bear fat, and ΣSCCP and ΣPCN among the studied CEACs were detected at intermediate concentrations. OPEs, dicofols and PCP were detected at low frequencies or not at all (0–82%). SCCPs and medium chain chlorinated paraffins (MCCPs) were also detected in various species from the Barents Sea food web (Harju et al., 2013). The highest levels of SCCPs were found in polar bears and ringed seals, and ringed seals had higher concentrations of MCCP than polar bears (Harju et al., 2013).

2.6. Marine litter

Marine litter including microplastics is present in Arctic sea water, sea ice, sediment and biota with the highest concentrations reported for Greenland and Barents Seas (Cózar et al., 2017; Peeken et al., 2018; Tekman et al., 2017; Trevail et al., 2015). Interactions between polar bears and marine litter, including plastic shred in the mouth of adults and cubs as well as a net from fishery entangled around the neck or ear tag, have been documented at Svalbard (Bergmann et al., 2017; Hallanger and Gabrielsen, 2018). Most of the plastics present in the oceans occur as microplastics or nanoplastics (Peeken et al., 2018). Furthermore, small plastic particles adsorb hydrophobic organic compounds, such as PCBs and DDE, from the water column (Mato et al., 2001), and thus ingestion of plastic particles may act as a vector for POP uptake (Carbery et al., 2018), although such a pathway of amplified contaminant exposure is currently under debate (Lohmann, 2017).

Although micro- and nanoplastics are likely not important vectors for POP uptake in animals, studies mostly based on fish and lower trophic level species have indicated that microplastics themselves may accumulate from prey to predator in marine food webs (Carbery et al., 2018). A recent study on captive grey seals (*Halichoerus grypus*) fed on Atlantic mackerel (*Scomber scombrus*) further suggested that trophic transfer is potentially the major, although indirect, pathway of microplastics for marine top predators that consume whole prey (Nelms et al., 2018). However, as polar bears feed mainly on seal blubber and often abandon the rest of the carcass (Stirling and McEwan, 1975), it is unlikely that they are exposed to considerable amounts of microplastics through their prey. This hypothesis is also supported by a recent modelling study that indicated microplastics do not bioaccumulate in polar bears (Diepens and Koelmans, 2018). The

same study also modelled biomagnification of contaminants adsorbed on microplastics. The results suggested that inert PCBs biomagnify to a lesser extent in polar bears when microplastics are ingested because bioaccumulation from ingested plastic is weaker than from food. However, there is a lack of experimental evidence regarding the extent to which contaminants sorbed in microplastic particles may be transferred in the marine food web up to apex predators (Carbery et al., 2018).

3. Effects of contaminants

Adverse effects of contaminants in polar bears have mostly been investigated using correlative approaches based on field samples. Studied end-points, including endocrine disruption and metabolism, immunotoxicity, neurotoxicity and pathological changes, have been shown to vary between subpopulations and according to the availability of samples (Bechshoft et al., 2017). An increasing number of in vitro studies, studies on surrogate species as well as risk assessment studies have been published during recent years. Correlative studies have high environmental relevance, but are often challenged by confounding factors and do not test cause-effect relationships. In vitro methods using molecules/cells from the species in question can provide insights into species-specific sensitivities to toxicological effects and assess specific modes of actions for contaminant-mediated effects. This type of information is needed for more accurate extrapolation and risk assessment (Celander et al., 2011) as currently, risk assessment studies in polar bears are based on extrapolations from toxicity studies on other mammalian species. Studies on surrogate species can evaluate possible causality between effects and exposure, but do not account for differences in species sensitivities. It should be emphasized that none of the approaches alone can answer whether polar bears are affected by contaminants or not, but these studies can collectively provide a weight of evidence. Although effects may be observed, it should be also noted that polar bears may have endogenic physiological compensation mechanisms that enable them to physiologically adapt to exposure to contaminants.

3.1. Immune system and pathogens

The Arctic has long been considered a low disease environment due to cold climates acting to limit the viability of infectious agents (Kirk et al., 2010). Polar bears and other Arctic wildlife are therefore relatively immunologically naïve, being exposed to few pathogens during their lifetime. Low genetic diversity in the immunologically important, major histocompatibility complex supports the tenet that polar bears are poorly equipped to resist disease (Weber et al., 2013), and consequently maladapted to face the increased threat of pathogens in a rapidly warming and changing Arctic. Polar bear exposure to several pathogens has been confirmed through serological surveys and has been recently reviewed (Fagre et al., 2015). Documented pathogen exposure thus far has included *Brucella* spp., antimicrobial resistant *Escherichia coli*, morbillivirus, rabies virus, canine adenovirus, calicivirus, *Toxoplasma gondii*, *Coxiella burnetii, Francisella tularensis*, *Neospora caninum*, and *Trichinella* spp. (Atwood et al., 2017; Fagre et al., 2015), but long term studies are needed to monitor the trends in disease prevalence and identify exposures to emerging pathogens in vulnerable subpopulations.

Given that a warming climate will likely increase the risk of infectious disease in polar bears, understanding the immune system and its vulnerability to contaminants is very timely. In their study of nearly 200 polar bears in the southern Beaufort Sea, Kirk et al. (2010) presented hematological reference ranges, i.e. immune cell counts, for different age and sex classes, thus adding important insight into baseline immune parameters for future health studies. Nonetheless, there have only been four studies published directly that have investigated the immunological effects of contaminants (Bernhoft et al., 2000; Desforges et al., 2017; Lie et al., 2004, 2005). These studies have shown that environmental contaminants, particularly PCBs and OCPs, can negatively affect circulating levels of immunoglobulin class G (IgG), impair the production of specific viral antibodies, and suppress the proliferation of T and B lymphocytes. Desforges et al. (2017) applied in vitro techniques to evaluate the concentration-response relationship between blubber-derived contaminants and polar bear immune function. It was revealed that there was a clear suppression of lymphocyte proliferation above 0.1 μg/mL PCBs, but no effects on natural killer cell activity at similar exposure levels. Finally, Sonne et al. (2010) reported similar immunological effects of PCBs and OCPs on cellular and humoral immunity in sledge dogs (*Canis familiaris*), which were used as surrogate species for polar bears.

Only a single histology study has been conducted on immune tissues from polar bears including samples of axillary and inguinal lymph nodes ($n = 54$ and 45, respectively), spleen ($n = 60$), thymus ($n = 11$) and thyroid tissue ($n = 5$) from a total of 82 polar bears collected in East Greenland from 1999 to 2002 (Kirkegaard et al., 2005). The study reported a negative association between secondary follicles in spleen and lymph nodes versus POPs including $\sum$PCB levels. This may indicate that the higher POP concentrations, the lower the immune activity, which may lead polar bears to be more susceptible to infections.

3.2. Neurochemistry and -epigenetics

In humans (*Homo sapiens*), one of the earliest indicators of neurotoxic disease is the disruption of brain neurochemistry resulting in effects on the control of movements, motivation, and cognition (Arias-Carrion and Poppel, 2007; Grandjean and Landrigan, 2006; Manzo et al., 2001; Stamler et al., 2005). Three studies investigated the effects of Hg on polar bear brain neurotransmitters or epigenetics (Basu et al., 2009; Krey et al., 2014; Pilsner et al., 2010) and two studies investigated the effects of PFASs on neurotransmitters (Pedersen et al., 2015, 2016). A study on 82 East Greenland polar bears reported that *N*-methyl-D-aspartate glutamate receptor levels were negatively related to THg and MeHg concentrations in brain stem tissue (oblongated medulla), whereas several other neurotransmitters were not related to Hg concentrations (Basu et al., 2009). Furthermore, among three studied neurochemical enzymes, the activity of monoamine, which is involved in metabolism of neurotransmitters including serotonin and dopamin, was negatively related to THg concentrations in 24 brain samples from polar bears collected from Nunavik, Canada (Krey et al., 2014). Related in vitro experiments, however, demonstrated that Hg can also inhibit cholinesterase activity and muscarinic acetylcholine receptor binding (Krey et al., 2014). Correlations between PFASs and three neurochemical enzymes and the densities of three central neuroreceptors were further studied across several brain compartments of East Greenland polar bears ($n = 6$–9), and both positive and negative relationships were reported (Pedersen et al., 2015). The authors concluded that it is unknown whether these alterations are related to negative effects on neurochemistry in the studied bears. Furthermore, concentrations of several steroid hormones, which also behave like neurotransmitters (Rudolph et al., 2016), were positively related to PFAS concentrations in different brain compartments from East Greenland polar bears ($n = 4$–10) (Pedersen et al., 2016). Although based on a very limited number of individuals, the study highlighted the urgent need for a better understanding of the consequences of PFAS exposure for the neuroendocrine system in polar bears (Pedersen et al., 2016). Finally, Pilsner et al. (2010) analysed DNA methylation in 47 East Greenland polar bears as a measure of epigenetic toxicity from Hg exposure. The study showed that the percentage of global DNA methylation tended to decrease, though not statistically significantly, with increasing total Hg concentration in the brain stem.

3.3. Corticosteroids

Corticosteroids, a class of steroid hormones that includes corticosterone, aldosterone and the main stress hormone cortisol, have a number

of physiological functions, including regulation of metabolism and maintenance of growth and development (Sjaastad et al., 2003). Overall, corticosteroids, regulated by the hypothalamic-pituitary-adrenal axis, function to optimize the behavioural and physiological changes needed for an animal to increase their chances of survival and to maintain homeostasis during stressful periods of environmental disturbance (Romero, 2004; Sjaastad et al., 2003). Hypothalamic-pituitary-adrenal axis is well adapted to dealing with short-term stressors by temporarily minimizing or shutting down those biological functions deemed non-essential for the specific situation. However, chronic activation of the axis, e.g. due to prolonged fasting, can result in negative health effects, including on the reproductive and immune systems and energy balance (Dobson and Smith, 2000; Peck et al., 2016).

To date, only a small number of polar bear studies have examined corticosteroids, with all focusing on the connection between cortisol and endocrine disrupting chemicals (Bechshoft et al., 2012, 2015; Oskam et al., 2004). The relationships between PCBs and pesticides, and plasma cortisol concentrations were studied in male and female Svalbard polar bears (Oskam et al., 2004). 95% confidence intervals for ΣPCBs and pesticides in plasma ranged from 49 to 273 and 5.5–53 ng/mL, respectively (Oskam et al., 2004). Results showed that the picture was complex, in that ΣOCPs were negatively related to cortisol concentrations, whereas the relationship with ΣPCBs was positive. A similar scenario was observed in a later study on East Greenland polar bears (8 males, 15 females) (Bechshoft et al., 2012), focused on assessing the relationship between hair cortisol, whole blood thyroid hormones, and POPs measured in adipose tissue. The authors found that some of the individual contaminants: BDE99, PCB180, PCB201, BDE153, and PCB170/190, were negatively related to cortisol concentrations, while others: PCB66/95, α-HCH, heptachlor epoxide, Dieldrin, BDE47, and *p,p'*-DDD, were positively related to cortisol levels. The thyroid hormone triiodothyronine, T3, also had a positive association with cortisol. However, it should be noted that circulating and hair cortisol levels are likely highly affected by the acute stress related to capture (Cattet et al., 2003, 2014; Champagne et al., 2018).

While Hg is a well-known neurotoxin, its role as an endocrine disruptor in wildlife has been studied less (Franceschini et al., 2009; e.g., Freeman et al., 1975; Jayasena et al., 2011; Tan et al., 2009). In hair from western Hudson Bay male polar bears, Bechshoft et al. (2015) found a significant relationship between Hg and cortisol concentrations. However, here also the relationship was complex, in that hair cortisol was not only influenced by Hg, age, and body condition, but also by interactions between Hg and year, Hg and fatness, and year and fatness. Recent research, describing validated methods for analysing not only cortisol but also two other key polar bear glucocorticoids, corticosterone and aldosterone, will undoubtedly help expand on our knowledge of how anthropogenic pollutants affect polar bear corticosteroids (Bechshoft et al., 2011; Weisser et al., 2016).

3.4. Sex hormones and reproductive organs

Steroid hormones are crucial in vertebrates for numerous physiological processes, including regulation of reproduction, growth, and development (Evans-Storms and Cidlowski, 1995; Hadley, 1996). These lipophilic, endogenous hormones are mainly produced and secreted from steroidogenic glands such as the gonads (ovary and testis), adrenals and the placenta (Hadley, 1996). In addition, several steroids such as pregnenolone may be synthesized in high concentrations in the brain, and these neurosteroids are involved in the regulation of sexual behaviour, feeding, aggressiveness, locomotion and stress (Baulieu, 1997; Do Rego et al., 2009). The production and secretion of most sex hormones are controlled by neurons and negative hormone feedback regulation involving the hypothalamic-pituitary-gonadal axis (HPG axis) (Hill et al., 2008). This regulation of steroid hormones is linked to biological factors such as sexual maturity and body size, but toxic chemicals may impair the endocrine system (Klaassen, 2008). Disruption of the ovarian steroidogenesis may prevent normal ovulation and implantation and cause harmful effects on fertility and survival in females (Craig et al., 2011; Waye and Trudeau, 2011). Thus, contaminants acting on the steroid hormone homeostasis may be an anthropogenic threat to population dynamics in Arctic animals, such as polar bears (Jenssen, 2006; Jenssen et al., 2015).

One of the first studies of sex hormone concentrations in polar bears, which sampled individuals from Svalbard reported increasing plasma progesterone concentrations with increasing ΣPCB concentrations in females with offspring (n = 54) (Haave et al., 2003). Thus, PCBs, which ranged from 1392 to 18,210 ng/g lipid weight in plasma, could disrupt feedback mechanisms of the major gonadotropins, the follicle-stimulating hormone and luteinizing hormone, and thereby preventing normal ovulation and impacting reproductive success (Haave et al., 2003). It should be mentioned, however, that the negative feedback system may be able to adjust steroid levels by increasing or decreasing the production of gonadotropins, thereby compensating or perhaps even slightly over-compensating for endocrine effects, as indicated by a recent study on sledge dogs (Sonne et al., 2014). Indeed, Haave et al. (2003) did not find correlations between ΣPCBs and 17β-estradiol in any of the groups of polar bears, or between ΣPCBs and progesterone in female polar bears that did not have offspring. Therefore, it was concluded that PCBs may affect progesterone levels in female polar bear even though the study was based only on statistical associations.

Circulating concentrations of nine steroid hormones were further investigated in the serum of female polar bears (n = 15) from Svalbard by gas chromatography–tandem mass spectrometry (GC–MS/MS) (Gustavson et al., 2015a, 2015b). Inverse correlations were found between circulating levels of pregnenolone and androstenedione, and circulating levels of OH-PCBs in females, which ranged from 59 to 260 ng/g wet weight in plasma. This suggests that OH-PCBs may interfere with the steroid homeostasis, but it should be noted that the result was based on a small number of individuals. Also, three females, which appeared to have inflamed and swollen genitals, had higher progesterone and lower androstenedione concentrations than the remaining females. In addition, two OH-PCBs tended to be higher, though not statistically significant, in the individuals with inflamed and swollen genitals. Although the number of individuals was small, the authors suggested that the enzyme CYP17 may be a potential target for OH-PCBs. This suggestion is in accordance with the data obtained by Haave et al. (2003) and Oskam et al. (2004) since an inhibition of the CYP17, in particular the lyase reaction, by PCBs and/or their hydroxylated metabolites, will not only decrease androgens, but also increase progestagens (Haave et al., 2003) and stimulate corticosteroid production (Oskam et al., 2004). However, interactions between contaminants and polar bear CYP17 and possible consequences on steroid metabolism should be tested in vitro.

Gustavson et al. (2015a) also suggested that previously reported pseudohermaphroditism (enlarged clitoris) in female polar bears (Wiig et al., 1998), could be related to high body burdens of OH-PCBs that inhibits CYP17 activity and thus causes rises in circulating levels of progesterone and reduced circulating levels of androstenedione. Enlarged clitoris in polar bears has however been debated for decades. Observation of enlarged clitoris in two polar bear yearlings was first suggested to be related to androgen producing tumours in their mother or endocrine disruptive effects of contaminants (Wiig et al., 1998). However, histological examination of an enlarged clitoris from an adult bear in East Greenland suggested that the enlargement in this case was due to inflammation (Sonne et al., 2005a). There have also been reports of enlarged clitoris in polar bears housed in zoological gardens related to reproductive cycling and/or urine dermatitis (Erin Curry pers. comm.).

In male polar bears, the ratio between androgens and estrogens significantly depended on their sexual maturity, with androgen/estrogen ratios being approximately 60 times higher in adult males than in subadult males (n = 23) (Ciesielski et al., 2017). Relationships between

plasma testosterone and contaminants were first studied in 121 male polar bears from Svalbard, which included males from cubs to adults (Oskam et al., 2003). Testosterone concentrations were negatively related to plasma PCB and OCP concentrations in all males combined during different seasons as well as in a subset of reproductively active males during the mating season. The authors concluded that the continuous presence of high concentrations of organochlorines in male polar bears (e.g. 95% confidence intervals for ΣPCBs in plasma ranged from 49 to 273 ng/g wet weight) throughout their life could possibly potentiate any reproductive toxicity that may have occurred during early life stages. However, it should be noted that testosterone–contaminant relationships may be confounded by body condition. Body condition has been shown to be negatively related to plasma contaminant concentrations (Tartu et al., 2017b), whereas positive relationships between plasma testosterone concentrations and body condition have been reported in adult (n = 17) male polar bears from Svalbard (Ciesielski et al., 2017). In addition, Ciesielski et al. (2017) analysed nine steroid hormones with GC–MS/MS and reported negative relationships between several PCBs, BDE154, β-HCH and HCB, and dihydrotestosterone based on results from multivariate statistics taking into account biometric variables. Consequently, POPs and body condition may potentially affect the endocrine function of steroids, including development of reproductive tissues and sex organs and the general condition of male polar bears from Svalbard (Ciesielski et al., 2017).

As mentioned in 3.2. Pedersen et al. (2016) investigated correlations among concentrations of eleven steroid hormones in eight brain regions of 4 to 10 polar bears in East-Greenland and the concentrations of PFASs in the corresponding tissues. Correlative analyses showed significant positive associations between PFASs, including ∑PFSA and ∑PFCA, and 17α-hydroxypregnenolone (OH-PRE), and PFCAs and testosterone across brain regions. In the occipital lobe, significant positive correlations between PFCAs and steroids were observed for pregnenolone, progesterone, OH-pregnenolone, dehydroepiandrosterone, androstenedione and testosterone. The authors concluded that it was presently not possible to determine whether alterations in brain steroid concentrations arise from interference with de novo steroid synthesis or via disruption of peripheral steroidogenic tissues mainly in gonads and feedback mechanisms controlled by the brain (Pedersen et al., 2016).

Polar bears have a low reproductive rate of two cubs every third year on average, therefore a decrease in reproductive output may have consequences for population viability (Derocher and Stirling, 1994; Sonne, 2010). Considering that the average life-span of female polar bears is likely around 25 years, and that they in some subpopulations may become reproductively senescent at age 15–20, a female can probably only produce six surviving cubs over her entire life-span (Larsen, 1985). It is therefore important to monitor and assess the health of the reproductive organs of polar bears.

Sonne et al. (2006) investigated the relationship between size of reproductive organs and OHC concentrations of 99 polar bears, including 55 males and 44 females, from East Greenland. Overall, testis and baculum size and bone mineral density in the baculum were negatively correlated with contaminants and a similar relationship was found for ovary/uterus size. These results suggested that there may be an impact of POPs on the size on the sexual organs and thereby potential function due to reduced sperm and egg quality/quantity and uterus and penis size/robustness. In addition, testicular multifocal fibrosis, atrophy, hyalinisation of basement membranes and inflammation was also found in the testes of 37% of the male bears. The reasons for this may be age, season and likely also contaminant exposure through testicular dysgenesis syndrome (Ahmad et al., 2003; Facemire et al., 1995; Guillette et al., 1994; Skakkebaek et al., 2001). Similar to size of baculum, bone mineral density was also negatively correlated with OHC concentrations. In the studies by Sonne et al. (2015) and Daugaard-Petersen et al. (2018a), significantly lower bone mineral density were reported in bacula of East Greenland polar bears compared to those in Canada, but the two studies showed conflicting results on the correlations with contaminants. The reasons for this are unknown, however, it is likely a function of contaminant exposure, genetics, and/or nutritional composition (see also Section 3.9).

3.5. Thyroid system

Thyroid hormones (THs) are involved in almost all metabolic processes and affect a variety of physiological processes during foetal development and throughout the lifetime of animals. They are important for regulating basal energy costs and are involved in temperature regulation, moulting and growth of fur, as well as in reproduction (Hulbert, 2000; McNabb, 1992). Thus, maintenance of normal thyroid function is important for proper development and maintenance of good health in polar bears.

In polar bears, several studies have shown statistically significant relationships between plasma concentrations of THs and concentrations of various POPs. The overall findings are that there are negative relationships between concentrations of environmental contaminants in blood and THs in polar bears (Bechshoft et al., 2012; Bourgeon et al., 2017; Braathen et al., 2004; Bytingsvik et al., 2013; Gabrielsen et al., 2015; Knott et al., 2011b; Sandau, 2000; Skaare et al., 2001; Villanger et al., 2011). Although statistical associations between contaminant levels and response variables are not direct evidence of causal effects, these findings are consistent with controlled experimental studies on other mammalian species linking hypothyroid effects to thyroid disrupting compounds (Boas et al., 2012; Gutleb et al., 2016). Histopathological changes have also been observed in polar bear thyroid glands (Sonne et al., 2011). Among the 20 East Greenland bears examined, in which concentration ranges for ΣPCBs and pesticides were 3556–28,670 and 9–3403 ng/g lipid weight in adipose tissue, respectively, 40% had C-cell proliferations, nodular hyperplasia or interstitial fibrosis, but no differences in POP concentration was found between individuals with and without lesions. The observed lesions in polar bears were, however, similar to those found in POP exposed laboratory animals and other highly contaminated wildlife and were likely the combined result of POP exposure, autoimmunity, and infections (Sonne et al., 2011).

It is important to note that many factors may confound observed relationships between THs and contaminants. Levels of THs may vary throughout the lifetime of animals, but also in relation to external abiotic factors, such as ambient temperature, ecological factors, such as food intake, and internal biological factors, such as reproductive status. For example, circulating thyroxine (T4) concentrations were higher in spring than in autumn in female polar bears irrespective of their reproductive status, whereas T3 concentrations were higher in spring only in solitary females, i.e. females without offspring (Bourgeon et al., 2017). As contaminant concentrations in polar bears may also vary according to season, ecological and internal biological factors (Polischuk et al., 2002; Tartu et al., 2017b), it is of high importance to take these factors into account when studying relationships between thyroid-related parameters and contaminants in polar bears (Bourgeon et al., 2017). For example, relationships between THs and POP were more pronounced in females with offspring than in single females without offspring, and the least pronounced in males (Braathen et al., 2004). Furthermore, THs were negatively related to POPs in female polar bears (n = 112) sampled in spring but not in autumn (Bourgeon et al., 2017).

The effects of POPs on THs and thyroid function may be induced by several mechanisms including disruption in TH transport in plasma. Due to the structural similarity of some contaminants, in particular OH-PCBs, with THs, these compounds compete with THs, primarily T4, for binding sites on plasma transport proteins for THs, such as transthyretin (TTR) and albumin. Gutleb et al. (2010) reported that one of the most abundant OH-PCBs found in polar bear plasma has a higher affinity towards polar bear TTR than its natural ligand T4. The authors suggested that TTRs in free-ranging polar bears are completely saturated by OH-PCBs. Further, Simon et al. (2011) extracted a broad range of POPs in polar bear plasma and tested their binding potency

towards human TTR. The method was further used to demonstrate that OH-PCBs and branched nonylphenol extracted from plasma of polar bear cubs fully explained TTR-binding activity (Bytingsvik et al., 2013; Simon et al., 2013). Ranges for penta- to heptachlorinated OH-PCBs, octachlorinated OH-PCBs and branched nonylphenol were 42–187, 1.3–164.3 and 2.5–6.2 ng/mL, respectively (Bytingsvik et al., 2013; Simon et al., 2013). Based on the results from the above mentioned studies, several compounds present in plasma of polar bear cubs have a very high affinity to TTR and they can occupy all circulating TTRs leaving no place for T4. Because of the small molecular size of free T4 in plasma, it will be excreted by biliary clearance, and both protein-bound and free concentrations of T4 in plasma will thus decrease (Bastomsky, 1974). As described below, lower concentrations of bioavailable T4 in plasma will also decrease the concentrations of the biologically active TH, which is T3, because T4 is the substrate of deiodinases.

Contaminants may also affect the function of enzymes called deiodinases that metabolize THs in tissues and organs (Shimizu et al., 2013; van der Spek et al., 2017). The primary role of type 1 deiodinase (D1) in vivo is to degrade inactivated TH, whereas type 2 deiodinase (D2) mainly converts T4 to its active form T3 (van der Spek et al., 2017). In East Greenland polar bears (n = 7) activity of D1 in muscle, liver or kidney tissues correlated positively with some individual PCBs, OH-PCBs and PBDEs, and negatively with OCPs, whereas D2 in muscle tissue showed positive correlations with PCB18, and negative with one OH-PCB (Gabrielsen et al., 2015). T4 concentrations in plasma and muscle tissue correlated negatively with some PCBs and OH-PCBs (Gabrielsen et al., 2015). Possibly, mechanisms of action with respect to TH disruption are specific to different groups of organic pollutants, but it should be noted that the sample size was small (2 males, 5 females) and confounding factors may thus have been an issue.

Currently, physiological consequences of the relationships between THs and POPs as well as TTR occupied by contaminants are not known. However, given the important role of THs in growth and development, including the development of the brain and nervous system (Porterfield, 1994; Zoeller, 2010; Zoeller et al., 2002, 2007), thyroid disruption in young polar bear cubs raises concern for potential effects on neurological development (Jenssen et al., 2015). Also, as THs are involved in temperature regulation, lipid metabolism, and adaptation to fasting, it is not unlikely that contaminants can affect the capacity of polar bears to adapt adequately to the climate changes currently reported in the Arctic, for example, to prolonged fasting periods (Jenssen et al., 2015). However, it is important to be aware that no studies have linked exposure to contaminants, and the following thyroid disruptive effects, to effects on reproduction and survival at the individual level and effects at the population level in polar bears.

3.6. Energy metabolism

Polar bears undergo extreme body fat variations and have evolved a unique metabolism that enables them to deal with a lipid-rich diet to adequately build and burn lipids (Liu et al., 2014; Welch et al., 2014). In mammals, the regulation of lipid metabolism is the result of the concomitant action of the central nervous system and several organs (e.g. liver, muscles, adipose tissue, thyroid) via hormonal messengers. Thyroid hormones, for instance, are involved in the synthesis, mobilization and degradation of lipids (Pucci et al., 2000). At the cellular level, in white adipocytes, fatty acid (FA) transport, synthesis, uptake and lipid hydrolysis are controlled by several genes mostly regulated by the nuclear receptor, peroxisome-proliferator activated receptor gamma (PPARG) (Lefterova et al., 2014). Amid the contaminants detected in polar bears, several have been described as having metabolic disrupting properties in rodents and humans (e.g. PCBs, OCPs, PFASs and FRs) (Nadal et al., 2017). As discussed in the previous section (Section 3.5), exposure to several compounds has been related to altered levels of THs, but only few studies have investigated the effects of contaminants on lipid metabolism in polar bears.

One recent project was designed to acquire knowledge on the effects of contaminants on lipid metabolism in polar bears. Svalbard female polar bears (n = 112) were live-captured during two different seasons, in spring when individuals were thin but actively feeding, and in autumn when individuals were fat, but fasting (Bourgeon et al., 2017; Tartu et al., 2017a, 2017b). In adipose tissue samples, the abundance profiles of nine lipid-related genes and fatty acid (FA) synthesis and elongation indices were quantified, while in plasma, thyroid hormones and lipid-related variables, including cholesterol, triglycerides, high-density lipoprotein, were analysed in addition to the plasma non-targeted metabolome and lipidome (Bourgeon et al., 2017; Tartu et al., 2017c). The metabolome and lipidome comprise low molecular weight endogenous water- and lipid-soluble metabolites, respectively, and they are considered as final downstream products of gene transcription (Bundy et al., 2009).

PCBs, BDE153 and oxychlordane measured in polar bear adipose tissue were positively related to increased transcript levels of genes involved in the accumulation of triglycerides via glucose and utilization of free FA (Tartu et al., 2017c). Moreover, trans-nonachlor and the dioxin-like PCB118 were related to an increase of transcript levels of genes involved in FA transport, oxidation and insulin utilization (Tartu et al., 2017c). Relationships between plasma PFAS concentrations and biomarkers of lipid metabolism, including THs, lactate and lipid related parameters in plasma, and transcription levels of a gene related to lipid synthesis and accumulation in adipose tissue, suggest that a PFAS-mediated disruption of the hypothalamic-pituitary-thyroid axis could lead to higher levels of plasma lipids and lower lactate concentrations, respectively (Bourgeon et al., 2017; Tartu et al., 2017c). De novo synthesis of FAs was negatively related to BDE153 concentrations, whereas FA elongation index showed an opposite relationship with the same compound. Finally, although the polar bear metabolome and lipidome generally clustered according to sampling season rather than contaminants concentrations, some compounds of the lipidome were associated with contaminants (Tartu et al., 2017c). The above-mentioned relationships between lipid metabolism and pollutant concentrations were more pronounced during periods with little sea ice. This suggests that sea ice decline and contaminants exposure may have synergistic negative effects on polar bear lipid metabolism.

Metabolomics have also been studied in Hudson Bay polar bears. A targeted, quantitative metabolomics platform (219 metabolites) was evaluated in muscle and liver of polar bears from the southern and western Hudson Bay subpopulations (Morris et al., 2018). Five metabolites discriminated the hepatic profiles of southern Hudson Bay males and females, while 15 discriminatory metabolites, primarily phospholipids, contrasted the livers of males from the two subpopulations. An expansion of this study reanalyzed the combined metabolomics-contaminants profiles, which included POPs and THg (Letcher et al., 2018; Morris et al., 2019). PFASs, PBDEs, *p,p′*-DDE and some highly chlorinated *ortho*-PCB congeners were greater in the southern Hudson Bay bears (concentrations shown in Fig. 1), and were inversely correlated with the covarying discriminating metabolites in the liver. Some major OCP contaminants were greater in western Hudson Bay bears and were directly correlated with discriminatory metabolites. Overall, the results suggested that the arachidonic acid, glycerophospholipid and some amino acid pathways were potentially impacted, but dietary variation was also an important factor in the differences observed between the subpopulations. Overall, the results suggested linkages between components of the hepatic metabolome, particularly lipid-related compounds, and differential contaminant exposure in Hudson Bay polar bears (Morris et al., 2019).

Parallel to the field studies, effects of contaminants on polar bear energy metabolism have been investigated using in vitro and in silico approaches (Routti et al., 2016). A luciferase reporter assay was constructed to study activation of polar bear peroxisome proliferator-

activated receptor gamma (PPARG) by environmental contaminants and their mixtures. PPARG is the major regulator of adipogenesis and promoter of lipid stores in fat tissue (Feige et al., 2006). The major lipophilic POPs in polar bear adipose tissue antagonized polar bear PPARG at environmentally relevant concentrations (Routti et al., 2016). The antagonistic effect of POP mixtures is likely mediated by PCB153, since it is the PCB congener found at the highest concentrations in the mixture and a full antagonist of polar bear PPARG (Routti et al., 2016). Interestingly, lipid accumulation was not affected by the same POP mixtures in polar bear adipose tissue-derived stem cells or murine preadipocytes, but contaminant extracts from polar bear tissues enhanced adipogenesis in both cell types (Routti et al., 2016). This discrepancy is likely due to the presence of emerging chemicals, such as phthalates, tonalide and nonylphenol, in the extracts (Routti et al., 2016). Furthermore, Lille-Langøy et al. (2015) constructed a luciferase assay expressing polar bear pregnane X receptor, also known as steroid xenobiotic receptor (PXR/SXR). PXR, highly expressed in liver, is involved in metabolism of glucose and lipids, in addition to its role in detoxification (Mackowiak et al., 2018). Two-thirds of the tested 51 emerging and legacy contaminants, including PCBs, OCPs, brominated FRs, siloxanes and alkylphenols, activated polar bear PXR (Lille-Langøy et al., 2015). Although the study demonstrated that structurally diverse compounds are capable of activating polar bear PXR, toxicological relevance of the activation in vitro is difficult to evaluate (Lille-Langøy et al., 2015).

3.7. Liver and kidney histopathology

The liver is an initial target organ during exposure to xenobiotoxic substances, and multiple studies of contaminants, liver toxicity, and histopathology have therefore been conducted on laboratory animals and Arctic wildlife (Curtis, 2013; Sonne, 2010). When conducting histopathology, it is not possible to distinguish histopathological lesions due to age from those caused by exposure to POPs, PFASs, and Hg in polar bears. In East Greenland polar bears, organohalogen contaminants such as ΣHCH, HCB, CHL, PBDE, and Hg, as well as age, have been associated with morphological changes in polar bear liver and kidney including immune cell accumulation, bile duct changes, and lipid accumulation pointing towards chronic infections and toxic exposure (Letcher et al., 2010; Sonne, 2010). Comparison of polar bear tissue concentrations of PCBs, Hg, and PFASs to established thresholds for toxic effects, suggests that polar bears may be at increased risk for developing histological lesions (Sonne, 2010). Previous controlled studies of organohalogen compounds (OHC) exposed foxes and sledge dogs have shown that 2–14% of the liver lesions and 7–37% of the renal lesions in polar bears may be due to exposure to OHCs, Hg, and PFASs (Sonne, 2010).

3.8. Blood clinical-chemical parameters

Three studies have reported blood clinical-chemical parameters in plasma of polar bears (Ciesielski et al., 2018; Knott et al., 2011b; Tryland et al., 2002). Tryland et al. (2002) investigated 28 different parameters in 20 males and 15 females from Svalbard. This study provided the first baseline values of blood clinical-chemical parameters for free-living polar bears. However, it should be noted that the bears were tranquilized from a helicopter, and both the helicopter chase, the tranquillizers as well as injuries related to capture may have affected some of the parameters (Cattet et al., 2003; Ramos et al., 2013; Vandermeulen et al., 1991). The results were compared to values reported in Greenland sledge dogs (Sonne et al., 2008), and aspartate aminotransferase, creatine kinase and lactate dehydrogenase exceeded normal values in the dogs by 2 to 6 fold in one or more bears. Nevertheless, it is hard to draw conclusions from the relevance of these relationships to clinical health and contaminant exposure, as the differences in these liver enzymes and lipase among polar bears and sledge dogs could be due to species-differences in metabolism and diet.

In a more recent study from Svalbard, 12 blood clinical-chemical parameters were analysed in 20 female and 18 male polar bears captured (tranquilized from a helicopter) in spring 2007 to investigate the relationship between those parameters and POPs, including potential confounders such as age, body condition, biometrics, plasma lipid content and geographical location (Ciesielski et al., 2018). In general, the values corresponded to those reported by Tryland et al. (2002). In females, multiple POPs were found to be significantly correlated with hematocrit and high-density lipoproteins, while in males, POPs (individual or summed) were significantly correlated with hematocrit, aspartate aminotransferase, γ-glutamyltransferase and cholesterol when the relationships were corrected for confounding factors. When correcting for these, hematocrit was suggested as a simple cost-efficient biomarker of POP exposure in polar bears. Furthermore, decreasing high-density lipoprotein concentrations and increasing cholesterol concentrations with increasing POP concentrations may indicate responses related to increased risk of cardiovascular disease. Finally, albumin concentration was analysed in a total of 58 free-ranging (31 males, 27 females) polar bears from the southern Beaufort Sea in relation to PCBs, selenium and Hg and thyroid status (Knott et al., 2011b). Concentrations of selenium and albumin were greater in males than females and albumin concentrations were negatively related to concentrations of Σ_7PCBs. The data suggest that female polar bears were more susceptible to changes in blood-based biomarkers of selenium and thyroid status than males and that further classifications of the physiologic states of polar bears and repeated measures of individuals over time are needed to accurately assess the biological impact of combined toxicant exposures. It should be noted that based on the two latter studies (Ciesielski et al., 2018; Knott et al., 2011b), it is not possible to conclude on any cause-effect relationships between the POPs and the blood clinical-chemical parameters, as the correlations also may be due to physico-chemical interactions between the POPs and hematocrit, high-density lipoproteins, cholesterol and albumin. In conclusion, there are large inter-individual differences in blood clinical-chemical parameter values in polar bears, and factors such as sex, age, body condition, capture and handling are important confounding factors that need to be accounted for in future studies.

3.9. The skeletal system

The skeletal system of polar bears is important for various reasons. This system acts to maintain body stature, to produce and control red and white blood cells, and to maintain calcium homeostasis (Ganong, 2005). The studies of polar bear skull and skeletal material can be divided into two categories. The first reports were on developmental instability and density measured as fluctuating asymmetry and later reports on size and density were published for Canadian, Greenland, and Barents Sea subpopulations. Fluctuating asymmetry has been studied in polar bear skulls from East Greenland and the Barents Sea in relation to contaminant exposure both by using correlative approaches as well as comparing the pre-pollution period to the time since pollutants have been present (Bechshoft et al., 2008b, 2008c, 2009; Pertoldi et al., 2012; Sonne et al., 2005b, 2007). Collectively, the results suggest that there is no association between contaminant exposure and skull morphology. Rather, changes in skull morphometrics were related to age, sex and likely to genetic differences among subpopulations (Pertoldi et al., 2012; Sonne et al., 2007).

Several investigations of East Greenland and Barents Sea polar bear skulls have dealt with changes in size and bone mineral density over the period 1892–2015. The reason for this is the fact that bone density may reflect dietary changes and contaminant related stress (Ganong, 2005; Lind et al., 2003, 2004; Sonne, 2010; Talbott et al., 2001). That is, a change in the hypothalamic-pituitary-adrenal/gonadal/thyroid axis leads to increased thyroid, parathyroid and cortisol hormone secretion and decreases in testosterone and estrogen concentrations, which in turn decrease bone formation and increase bone resorption

(Colborn et al., 1993; Ganong, 2005; Selye, 1973; Tung and Iqbal, 2007). Three studies have investigated skull size and bone mineral density in East Greenland polar bears collected over a period of more than a century (Daugaard-Petersen et al., 2018b; Sonne et al., 2004, 2013). Collectively, the studies indicate that skull bone mineral density has declined in male and subadult polar bears from East Greenland from the late 19th century until 2002–2015. Skull bone mineral density in females did not change over time (Daugaard-Petersen et al., 2018b; Sonne et al., 2004, 2013) likely due to their robustness related to fasting and gestation (Sonne, 2010). Skull bone mineral density correlated negatively with lipophilic POPs in polar bear samples collected in 1999–2001 (Sonne et al., 2004), whereas later studies have reported positive associations between bone mineral density and skull size and POPs (Daugaard-Petersen et al., 2018b; Sonne et al., 2013). Contrasting results have also been reported for relationships between baculum bone mineral density and contaminant exposure. Baculum bone mineral density was lower in polar bears from the East Greenland subpopulation with high contaminant levels than in Canadian subpopulations with lower contaminant levels (Daugaard-Petersen et al., 2018a; Sonne et al., 2015). In contrast, baculum bone mineral density in samples collected from East Greenland in 1999–2015 increased with increasing contaminant concentrations (Daugaard-Petersen et al., 2018a). Overall these reports suggest that environmental changes and exposure to POPs may affect bone mineral density and skull size in polar bears, but also other factors such as nutritional, endocrine and genetic parameters may play a role (Daugaard-Petersen et al., 2018a, 2018b; Sonne, 2010; Sonne et al., 2015).

3.10. Risk assessment and population level effects

Several studies have assessed health risk or population level effects of POPs to polar bears by extrapolating critical doses for experimental animals or humans to polar bears (Dietz et al., 2015, 2018; Pavlova et al., 2016a, 2016b; Sonne et al., 2009; Villa et al., 2017). The outcome of these studies should be interpreted with caution because the methods rely on extrapolation of toxicity threshold data from other mammals to polar bears. Toxic outcomes may vary dramatically even in closely related mammalian species (Boutros et al., 2008), and furthermore for example different rat (*Rattus rattus*) strains exhibit dramatic heterogeneity in their transcriptional responses to contaminants (Yao et al., 2012). Also, risk assessment studies assume that effects of different compounds are additive, which is an oversimplification, but cumulative risk of exposure to multiple chemicals is very challenging (Wilkinson et al., 2000).

Critical daily doses of POPs determined for rats were converted to critical body residues in polar bears using physiologically-based pharmacokinetic modelling (Dietz et al., 2015, 2018; Sonne et al., 2009). Estimates from these studies suggest that the concentrations of the sum of POPs in 11 polar bear subpopulations (from Alaska to Svalbard) exceeded the threshold levels for affecting reproduction, immune health and causing carcinogenicity (Dietz et al., 2015). A temporal study on East Greenland polar bears suggests that the subpopulation has been at risk for contaminant effects for several decades and the risk quotients peaked in early 1980s and again in 2013 (Dietz et al., 2018). In both studies, PCBs were the main contributors to the risks (Dietz et al., 2015, 2018). In another study, daily intake of POPs was calculated for polar bears based on literature data, and compared the values to acceptable daily intake of POPs for humans (Villa et al., 2017). The authors concluded that the risk of contaminant mixtures for adult polar bears is very high and even higher for polar bear cubs. Possible impact of PCB contamination on population growth and/or male reproductive success was studied in Svalbard polar bears using an individual-based model (Pavlova et al., 2016b). Thresholds for PCB effects on sperm quality and link between sperm quality and fertility were derived from mice studies. The authors concluded that PCB-related infertility of males may possibly lead to reduction in population growth via an Allee effect. Population level consequences of PCB exposure were also studied in East Greenland polar bears using individual-based models (Pavlova et al., 2016a). Thresholds for abortion and cub survival were derived from experimental studies on minks (*Mustela vision*) (Pavlova et al., 2016a). The authors concluded that PCB exposure is unlikely to lead to any effect on population growth in East Greenland polar bears through increased rate of abortions or increased cub mortality.

In a meta-analysis on circumpolar polar bears, Nuijten et al. (2016) examined the effects of several groups of POPs and other anthropogenic stressors, including ice cover as a proxy of climate change, human population density, and harvest rate, on population-level characteristics, including polar bear subpopulation density, mean litter size and adult female survival rate. The results suggested that a model containing only POPs, or, POPs and human population density, as predictors were among the best models explaining the variance in polar bear density among subpopulations. However, none of these variables significantly explained polar bear densities. Additionally, adult female survival was negatively affected by low September sea ice cover (Nuijten et al., 2016). Sea-ice-related demographic declines have been reported in some subpopulations of polar bears (Bromaghin et al., 2015; Lunn et al., 2016; Regehr et al., 2007, 2010), suggesting that loss of ice habitats in the polar basin will have population level consequences in polar bears (Durner et al., 2009). Further studies on the cumulative and interactive effects of multiple anthropogenic and natural stressors are needed to identify and assess the specific contributions of various stressors in polar bears.

4. Conclusions and future perspectives

The present review summarizes the current exposure, fate and effects of contaminants in polar bears from the circumpolar Arctic. Overall, results suggest that legacy POPs including PCBs, CHLs and PFOS are still the main contaminants to which polar bears are exposed. Also, other PFASs, such as PFCAs and PFHxS, which are current-used compounds, and brominated FRs are found at relatively high concentrations. Most contaminants of emerging Arctic concern have been detected only at trace levels in polar bears. Concentrations of several legacy POPs that have been banned for decades in most parts of the world, have generally declined in polar bears, but recent studies suggest increased concentrations in certain subpopulations. Also PFCAs are currently increasing in some subpopulations. Current circumpolar spatial trends vary largely between compounds. PCB concentrations were the highest in East Greenland and Kara Sea subpopulations, whereas PFAS was more elevated in Barents Sea bears compared to East Greenland and the North American Arctic. Conversely, the highest Hg concentrations were detected in East Greenland polar bears.

Future studies on exposure and fate of contaminants should focus on interactions of climate change and contaminant exposure in polar bears. Climate change is likely to affect transport, secondary emissions, food web structures, body condition influenced by changes in food availability, as well as movement patterns of polar bears. All of these factors may subsequently affect contaminant concentrations in polar bears. Also, it is of high importance to monitor both legacy and emerging compounds in polar bears to understand how Arctic ecosystems respond to changing emissions of contaminants.

Numerous studies have investigated effects of contaminants in polar bears using different approaches. Weight of evidence from correlative field studies, supported by in vitro studies suggests that contaminant exposure disrupts circulating levels of THs as well as lipid metabolism in polar bears. Polar bear immune systems seem to be affected by contaminants based on correlative field studies, in vitro studies and risk assessment approaches. Furthermore, both correlative field studies as well in vitro studies have suggested that neurochemistry is altered by contaminant exposure in polar bears. Conversely, contaminant-related effects on glucocorticoid and sex steroid concentrations, the skeletal

system (skull asymmetry and bone mineral density), liver and kidney pathology, blood clinical-chemical parameters and the size of reproductive organs have only been investigated using correlative approaches, and in some cases the relationships are not clear. Finally, several of the correlative studies have concluded that confounding factors may be present.

We recommend that future field studies investigating effects of contaminants use a sufficient number of samples, and take into account possible confounding factors (breeding status, feeding/fasting status, body condition). Whenever possible, power analyses should be used to determine the number of samples needed. In addition, in vitro methods specific to polar bears should be used to complement field studies to study, for example, activation of nuclear receptors by contaminants. This will also help modelling exercises to take into account species-specific differences in toxicity. Last, there is a need for studies that consider the potential for cumulative adverse effects of environmental change and contaminant and pathogen exposures on population vital rates. High quality studies using different approaches would be essential to improve our still very limited understanding of population level risks and effects of contaminants in polar bears.

Author contributions

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Appendix A. Supplementary data

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