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Immunologic, reproductive, and carcinogenic risk assessment from POP exposure in East Greenland polar bears (*Ursus maritimus*) during 1983–2013

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ABSTRACT

Polar bears (*Ursus maritimus*) are among the world's highest trophic level marine predators and as such have some of the highest tissue concentrations of organohalogen contaminants (OHCs) among Arctic biota. In this paper we present the results of a three decade (1983–2013) risk assessment of OHC exposure and effects on reproduction, immunity, and cancer (genotoxicity) in polar bears from Central East Greenland. Risk of adverse effects are evaluated using a risk quotient (RQ) approach with derivation from measured OHC concentrations in polar bear tissue and critical body residues (CBR) extrapolated for polar bears using physiologically-based pharmacokinetic modelling (PBPK). The additive RQs for all OHCs in polar bears were above the threshold for all effect categories (RQ > 1) in every year, suggesting this population has been at significant and continuous risk of contaminant-mediated effects for over three decades. RQs peaked in 1983 (RQ > 58) and again in 2013 (RQ > 50) after a period of decline. These trends follow ΣPCB levels during that time, and contributed almost all of the risk to immune, reproductive, and carcinogenic effects (71–99% of total RQ). The recent spike in RQs suggests a major shift in polar bear contaminant exposure from climate related changes in food composition and hereby the increased risk of adverse health effects. In the context of lifetime exposure ΣPCB and PFOS levels showed the interactive importance of year of birth, age, and emission history. In conclusion, the results indicate that East Greenland polar bears have been exposed to OHC levels over the period of 1983–2013 that potentially and continuously affected individual and theoretically also population health, with a peaking risk in the more recent years.

1. Introduction

Through complex environmental and bioaccumulation/magnification processes, wildlife are exposed to a suite of potentially toxic chemical substances, including most notably organohalogen contaminants (OHCs). OHCs include the legacy persistent organic pollutants (POPs) such as polychlorinated biphenyls (PCBs) and dichlorodiphenyltrichloroethane (DDT) as well as the more recent emerged POPs including brominated flame retardants (BFRs, e.g. polybrominated diphenyl ethers; PBDEs) and per-/poly-fluoroalkyl substances (PFASs, e.g. perfluorooctane sulfonate (PFOS)). Despite clear cause-effect relationships between OHC exposure and various health endpoints determined in controlled laboratory experiments (Lund et al., 1999; Seed, 2000; Case et al., 2001; Beach et al., 2006), ecotoxicologists struggle to interpret the potentially disruptive effects of complex contaminant mixtures of potentially agonistic and/or antagonistic pollutants in environmentally exposed wildlife.

We have previously summarized the effects of OHCs on polar bears and other species in a number of reviews and assessments (e.g. Sonne 2010; Letcher et al., 2010; Jenssen et al., 2015; Dietz et al., 2018). According to these findings OHC concentrations were associated with alterations of vitamin and steroid hormone concentrations, reduction in size of sexual organs, changes in various immune and endocrine related biomarker responses and histopathological lesions, reduction of bone mineral density, and effects on growth and reproduction. This weight of evidence supports the hypothesis that current levels of OHCs in polar bear tissues can affect various physiological and biochemical endpoints. However, recently improvements of effects studies have been

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conducted for cetaceans using individual-based model (IBM) coupled to a Leslie matrix population model modelling survival and disease mortality to determine population effect predictions of PCBs on cetacean populations including humpback whales (*Megaptera novaeangliae*), common bottlenose dolphins (*Tursiops truncatus*), and killer whales (*Orcinus orca*) (Desforges et al., 2018; Hall, 2006; Hall et al., 2017).

We recently used a polar bear-specific physiologically-based pharmacokinetic (PBPK) model coupled to a critical body residue (CBR) approach to evaluate the possible linkages between exposure to OHCs and effects on reproduction, the immune system and carcinogenicity (genotoxicity) in various polar bear subpopulations using the most recent OHC geographical trend data available (Dietz et al., 2015; McKinney et al., 2011). Our risk quotient (RQ) analysis revealed considerable risk (RQ > 1) from OHC exposure in all subpopulations, particularly East Greenland polar bears, for effects on all three health endpoints. While that study confirmed results, where effects have been observed for various health endpoints in polar bears, it however, ignored the long history of contaminant exposure in these long lived animals.

In the present study we investigated the historical OHC exposure in East Greenland polar bears and employed our previously developed PBPK-RQ approach to evaluate the risk of adverse health effects over the past several decades (Dietz et al., 2015; Sonne et al., 2009, 2014, Sonne et al., 2015a, 2015b). Polar bears in East Greenland are assumed to constitute a subpopulation which to a large extent is separate from neighbouring subpopulations at Svalbard and in West of Greenland (PBSG, 2010, 2017). The focus in this study is on East Greenland polar bears as this is the population previously determined to be most at risk from OHC-mediated effects, and contaminant levels are well documented for this subpopulation through long term biomonitoring programs. In this study we report on RQs for immune, reproductive, and genotoxic effects from exposure to mixtures of OHCs measured in polar bear tissues collected from 1983 to 2013. This extended time period also allowed us to explore lifetime cumulative exposure in polar bears, a metric we discuss as a potentially useful indicator for exposure and effects.

2. Materials and methods

2.1. Samples

A total of 323 polar bears were sampled from 1983 to 2013 in the Ittoqqortoormiit/Scoresby Sound region in Central East Greenland between ca. 69° to ca. 74° N (see Fig. 1, Supplementary information Table S1). Adipose samples were collected during the Greenlanders' subsistence hunts. Tissue samples were kept frozen outdoors until returned to Ittoqqortoormiit and eventually the Department of Bioscience Specimen Bank (Roskilde, Denmark) where they were stored at −20 °C until further processing (Dietz et al., 2013a, 2013b).

2.2. Age determination

Ages were determined by counting annual growth layer groups (GLGs) in the cementum of the lower right I3 using decalcification, thin sectioning (14 μm) and staining described by Dietz et al. (2004). Age classifications were as follows: adult males ≥6 years of age, adult females ≥5 years, and subadults consisted of all other bears (Rosing-Asvid et al., 2002). These three age/sex classes were used for calculation of mean OHC levels and Risk Quotients (RQs) as was previously done (Sonne et al., 2009; Dietz et al., 2013a, 2013b, 2015).

2.3. Chemical analyses

Organohalogen compound (OHC) concentrations in polar bear subcutaneous adipose were previously reported in two recent temporal trend studies of legacy and recently emerged OHCs (Dietz et al., 2013a, 2013b) from which details on the analytical methods can be obtained. PFOS data from liver tissues were obtained from Dietz et al. (2008) and Rigét et al. (2013) where analytical methods are likewise described in detail. Data on OHCs and PFOS up to 2013 were added using the same methods and labs.

2.4. PBPK and RQ modelling

We used the same approach for estimating critical body residue (CBR) data as was used in Dietz et al. (2015). In brief, CBRs were calculated based on critical daily doses (CDDs) determined in studies on rats (*Rattus rattus*) and extrapolated to polar bears using a physiologically-based pharmacokinetic (PBPK) model developed by Cahill et al. (2003) (Table 1, Table S2). CDDs were not always available from the exact same chemical congener mixture so here the closest chemical substance/congener was used (Table S1). Sonne et al. (2015a, 2015b) recently validated a similar PBPK model in a controlled experiment on captive Greenland sledge dog (*Canis familiaris*) fed minke whale (*Balaenoptera acutorostrata*) blubber for 500–635 days. Here the PBPK modelled POP concentrations in adipose, liver, kidney and plasma were mostly within a factor 2 of actual measured tissue concentrations. A similar convincing verification for the use of PBPK modelling for Arctic ecosystems was conducted for 118 middle age Greenlandic Inuit people from four cities in West Greenland (Sonne et al., 2014).

Another benefit of using risk quotients is that these are considered to be additive for mixed contaminant exposures, addition of toxic units as well as hazard quotients (e.g. Cassee et al., 1998; Kortenkamp et al., 2009; European Union, 2012).

Annual calculated RQs for each age class were used in an exploratory model for cumulative risk assessment. This model followed annual RQs for a theoretical male polar bear born in 1983, 1993 and 2003 by simply applying the observed RQ (calculated previously) for the appropriate year and age class depending on the modelled age of the bear. Since data was only sufficiently available for broad classification into subadult and adult males, our model could only apply two different RQs: all bears under the age of 6 received the same RQ and bears over 6 received another RQ for each year of the analysis (i.e. subadult vs adult). Thus, cumulative RQ were calculated by adding the annual RQ for each year of the bears life, which was a function of birth year and age (max age = 30 years).

3. Results and discussion

3.1. Samples

About half of the samples (n = 175/330) were obtained from subadult bears (mean age: 2.9 years) covering 26 years within the 31 year sampling period (1983–2013; Table 2; Figs. 2–4; Tables S3–S5). There were 90 samples from adult males (mean age: 10.8 years) from 19 of the 25 years (1989–2013) and 65 adult female samples (mean age: 11.5 years) obtained from 21 of the 30 years (1984–2013) (Tables S1; S6–S11; Figs. S1–S6). Due to the large sample size (more years and more samples collected per year) from subadult bears with more convincing temporal trends as documented by Dietz et al. (2013a, 2013b), the contaminant and RQ analysis in this article is focused strictly on results for subadult polar bears; nonetheless, results for adult male and female bears, which show similar patterns, are provided in the Supplementary Information.

3.2. Contaminant loads

Concentrations of legacy organochlorines in East Greenland subadult polar bears showed a number of increasing and decreasing trends over the 31 year time period (Table 3). Most of the legacy organochlorines showed a significant annual declines of 4.3 to 10.1% during the period between 1983 and 2001/2009 ($P < 0.001$). The only