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Health effects from contaminant exposure in Baltic Sea birds and marine mammals: A review

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ABSTRACT

Here we review contaminant exposure and related health effects in six selected Baltic key species. Sentinel species included are common eider, white-tailed eagle, harbour porpoise, harbour seal, ringed seal and grey seal. The review represents the first attempt of summarizing available information and baseline data for these biomonitoring key species exposed to industrial hazardous substances focusing on anthropogenic persistent organic pollutants (POPs). There was only limited information available for white-tailed eagles and common eider while extensive information exist on POP exposure and health effects in the four marine mammal species. Here we report organ-tissue endpoints (pathologies) and multiple biomarkers used to evaluate health and exposure of key species to POPs, respectively, over the past several decades during which episodes of significant population declines have been reported. Our review shows that POP exposure affects the reproductive system and survival through immune suppression and endocrine disruption, which have led to population-level effects on seals and white-tailed eagles in the Baltic. It is notable that many legacy contaminants, which have been banned for decades, still appear to affect Baltic wildlife. With respect to common eiders, changes in food composition,

Abbreviations: ΣPCB_{14}, Sum of 14 CB congeners; AHR, Aryl hydrocarbon receptor; ARNT, Aryl hydrocarbon receptor nuclear translocator; BSDC, Baltic Seal Disease Complex; CB-118, Chlorinated biphenyl-118; CB-149, Chlorinated biphenyl-149; CB-180, Chlorinated biphenyl-180; CYP-450, Cytochrome P450; DDE, Dichlorodiphenyldichloroethylene; DDT, Dichlorodiphenyltrichloroethane; DNA, Deoxyribonucleic acid; FT3, Free triiodothyronine; FT4, Free Thyroxine; GST, Glutathione S-transferase; H10N7, Avian influenza virus; Hg, Mercury; HSP70, Heat shock protein 70; MeHg, Methylmercury; mRNA, Messenger RNA; PBDE, Polybrodminated diphenyl ethers; PCBs, Polychlorinated biphenyls; PDV, Phocine distemper virus; PFAS, Per and polyfluoroalkyl substances; POPs, Persistent organic pollutants; PPARα, Transcription factor peroxisome proliferator-activated receptor; *p,p*'-d, *p,p*′-Dichlorodiphenyldichloroethane; *p,p*'-DDE, *p,p*′-Dichlorodiphenyldichloroethylene; *p,p*'-DDT, *p,p*'-Dichlorodiphenyltrichloroethane; TT3, Total Triiodothyronine; TT4, Total Thyroxine; TTR, Transthyretin; VSI, Virtual Special Issue

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quality and contaminant exposure seem to have population effects which need to be investigated further, especially during the incubation period where the birds fast. Since new industrial contaminants continuously leak into the environment, we recommend continued monitoring of them in sentinel species in the Baltic, identifying possible effects linked to climate change, and modelling of population level effects of contaminants and climate change.

1. Introduction

Determining the health status of wildlife including marine mammals is difficult as they are rarely observed and handled (Dietz et al., 2019; Letcher et al., 2010). Physiological monitoring and detection of altered physical states may be evaluated at various biological scales from the molecular to the individual, population and community, which evidently provide different measures of reproductive capacity and degree of change (Sonne, 2010). The strength in using a combination of organ-tissue endpoints (pathologies) and biomarkers lies in the ultimate provision of a comprehensive health status and linkages to external stressors (Sonne, 2010). This is the basis for an evaluation of population health and exposure to environmental stressors such as persistent organic pollutants (POPs) that may lead to significant population declines (Dietz et al., 2019).

The Baltic ecosystem has undergone drastic changes over the past century due to anthropogenic chemical stress caused by POPs. As is often the case, these changes have been most notably documented in selected wildlife species such as grey seals (*Halichoerus grypus*), ringed seals (*Pusa hispida*) and white-tailed eagles (*Haliaeetus albicilla*). These species have undergone massive population declines with POPs exposure as the major force behind the reduced health of Baltic wildlife and ecosystems. While the individual-level effects of POPs have been studied in Baltic sentinel species such as ringed and grey seal, harbour porpoise and white-tailed eagles (Roos et al., 2012; Helander et al., 2008; Siebert et al., 2006, 2007), little effort has been made to quantify population level effects. Rodriguez-Estival and Mateo (2019) have shown that one of the major challenges in wildlife ecotoxicology including marine mammals is to establish strong links between exposure to anthropogenic chemicals and adverse health effects. To manage and conserve wildlife populations, it is therefore crucial to quantify how pollution measured at the individual level propagates to population-level effects through impacts on mortality and reproduction, but also effects on fertility, energy allocation, immune and endocrine functioning (Harding and Härkönen, 1999; Sundqvist et al., 2012; Harding et al., 2015). This also requires a combination of *in vitro* dose-response studies as well as *in vivo* studies of key species in the Baltic as reference populations from pristine areas such as the Arctic when possible.

In the present paper, we review health effects from pollution on Baltic key species over the past seven decades including ringed seal, grey seal, harbour seal, harbour porpoises, white-tailed eagle and common eider (Fig. 1). Information about health effects in the seal species was comprehensive while fewer investigations are reported on harbour porpoise, white-tailed eagles and common eiders that spend most of their time in the Baltic despite migration out of the area is happening after end breeding season (Kjellén and Roos, 2000; Swennen et al., 1989). These species were selected as they represent sentinel high trophic indicator species in the Baltic regions that for decades have been used to biomonitor the environment. Due to the long-term monitoring over 7 decades, the Baltic Sea is an ideal ecosystem to study and related findings are extrapolated globally and used in the monitoring and assessment of for example the Arctic region (Dietz et al., 2019). The effects from other stressors such as infectious diseases on Baltic sentinel species is reported elsewhere in this virtual special issue (VSI) of Environment International.

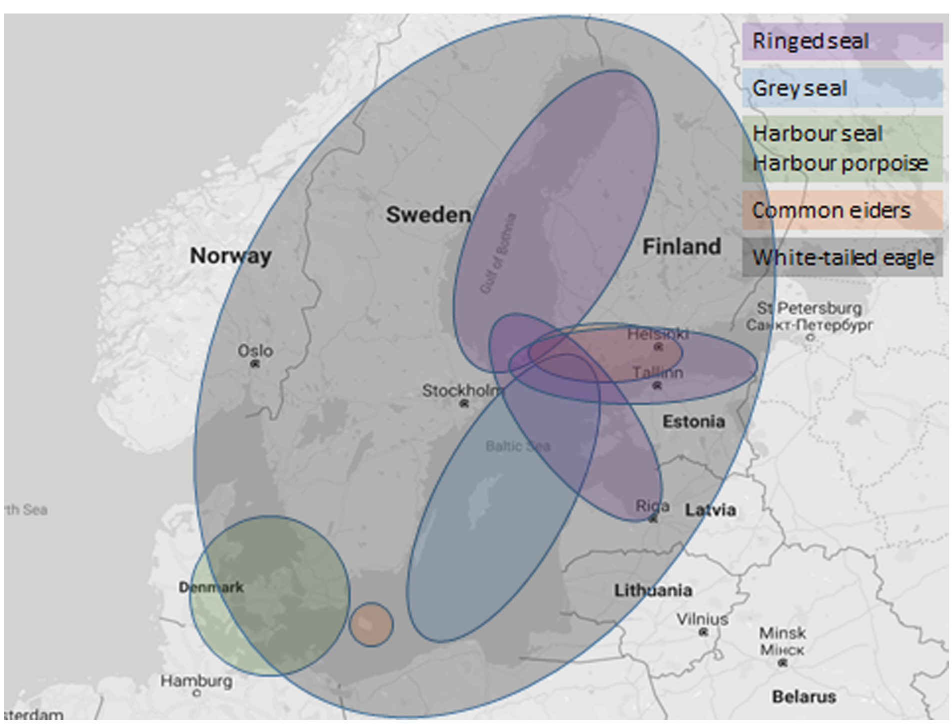

Fig. 1. Distribution and study sites of the six species included in the present review. Please also visit: http://www.helcom.fi/baltic-sea-trends/biodiversity/red-list-of-species/red-list-of-marine-mammals/.

2. Literature survey

From our own experience in the field, we identified and searched for environmental contaminants that are known to biomagnify in wildlife. In addition to these, we searched for effects from contaminants on specific organ-tissue health endpoints. We used ScienceDirect, PubMed, Google, Google Scholar, ISI Web of Knowledge/Web of Science and Springer Link to locate the peer-reviewed scientific articles and reports, using the following key words (either alone or in combination): eider, white-tailed eagle, harbour seal, grey seal, ringed seal, harbour porpoise, contaminants, POPs; persistent organic pollutants; PCBs, polychlorinated biphenyls, mercury, syndrome, organ, histopathology, bone, reproductive organs, reproduction, vitamins, hormones, endocrine system, cytokines, lymphocyte proliferation test, skeletal, bone density, immunology, immune system, skull, cancer, oxidative stress, DNA and CYP-450 (Table 1 and 2). We also used educational and scientific textbooks and references cited herein, apart from the selected articles retrieved by the above-mentioned efforts. Although we attempted to be systematic within the scope of the review, we acknowledge that this is not an exhaustive representation of all information that may exist in the scientific literature.

3. The baltic seal disease complex

The Baltic Sea is a unique marine region with low salinity while exposed to many anthropogenic factors such as industry activities, transport, cargo, military and fishing ships. A widely distributed pathological disease syndrome caused by exposure to POPs is reported among grey seals and ringed seals in the Baltic Sea, North Sea and German Bight from 1977 to 1983 and it may still occur to a lesser extent (Bergman and Olsson, 1985; Helle, 1980; Helle et al., 1976a; 1976b).

Table 2 summarizes the POPs induced Baltic Seal Disease Complex (BSDC) and links each health effect to the sentinel species and shows whether it causes effects on the individual or population level or both. The complex included hyperplasia of adrenal glands, reduced bone density and skin changes, which altogether indicate elevated production of cortisol due to extreme physiological stress (Table 2). Elevated concentrations of PCBs (polychlorinated biphenyls) and *p,p'*-DDT (dichlorodiphenyltrichloroethane) were detected in these animals, and the chemicals were identified as the cause of the observed syndrome, closely resembling endocrine disruption of iatrogenic (caused by external factors) similar to Cushing's in dogs, or due to multiple chronic organ lesions secondary to the organochlorine caused lesions (Bergman, 2007; Cohn et al., 2007). The blubber threshold concentrations in seals at which the BSDC arose was around 100 μg/g lw (Σ_{PCB17} range: 27–390 μg/g lw; DDT [*p,p'*-DDE, *p,p'*-DDD and *p,p'*-DDT] range: 12–970 μg/g lw) being among the highest ever measured in wild phocids (Table 2) (Jensen et al., 1979; Letcher et al., 2010; Roos et al., 2012).

The prevalence of occlusions and stenosis of the uterus were as high as 30% and 70% in grey and ringed seals, respectively. In addition, tumours in the smooth muscle tissue of the uterine myometrium (leiomyomas) were found, but only in old grey seals indicative of benign neoplastic changes (Bergman, 1999). Bredhult et al. (2008) gathered material consisting of 257 Baltic grey seal females to study the statistical relationship between concentrations of PCBs and *p,p'*-DDT and leiomyoma from 1973 to 2007 (Table 2). The authors found neoplastic changes only in old specimens, 20–40 years of age, and with a prevalence of 65%. Likewise, skull and claw lesions and renal glomerulopathy (changes in glomerular structure and functioning of the kidneys), interstitial nephritis and tubular hyperplasia as well as intestinal ulcers and arteriosclerosis were reported (Bergman and Olsson, 1985; Bergman, 1999).

The following text provides an overview of endpoints associated with exposure to POPs including PCBs and *p,p'*-DDT used to investigate the health of Baltic Sea top predators over the past decades, sub-divided into pathological organ-system changes and biomarkers of exposure. Fig. 1 shows the distribution and study sites of the species included in the present review.

4. Ulcers and tumours

Since the 1970's, BSDC in Baltic grey seals have been associated with impaired reproduction and reduced health with the main causal factor being exposure to POPs (Table 2) (Bergman, 2007). Most of BSDC symptoms, especially in the reproductive tract, i.e. uterine occlusions, leiomyomas and uterine horn stenosis, started to decrease in the early 1990's in the Baltic environment following the reduction of PCB and *p,p'*-DDT ban in the mid 1970ies (Bergman, 1999; Bäcklin et al,. 2011). On the contrary, the prevalence of colonic ulcers in young (1–3 years

Table 1
Literature search strategy for the present review using search machines, taxa and key words. Each taxa was also used as keyword.

Search machines	Taxa	Keywords
ScienceDirect	Harbour seal	eider, white-tailed eagle, harbour seal, grey seal, ringed seal, harbour porpoise, contaminants, POPs, persistent organic pollutants, PCBs, polychlorinated biphenyls, mercury, syndrome, organ, histopathology, bone, reproductive organs, reproduction, vitamins, hormones, endocrine system, cytokines, lymphocyte proliferation test, skeletal, bone density, immunology, immune system, skull, cancer, oxidative stress, DNA and Cyp-450
Pubmed	Ringed seal	eider, white-tailed eagle, harbour seal, grey seal, ringed seal, harbour porpoise, contaminants, POPs, persistent organic pollutants, PCBs, polychlorinated biphenyls, mercury, syndrome, organ, histopathology, bone, reproductive organs, reproduction, vitamins, hormones, endocrine system, cytokines, lymphocyte proliferation test, skeletal, bone density, immunology, immune system, skull, cancer, oxidative stress, DNA and Cyp-450
Google	Grey seal	eider, white-tailed eagle, harbour seal, grey seal, ringed seal, harbour porpoise, contaminants, POPs, persistent organic pollutants, PCBs, polychlorinated biphenyls, mercury, syndrome, organ, histopathology, bone, reproductive organs, reproduction, vitamins, hormones, endocrine system, cytokines, lymphocyte proliferation test, skeletal, bone density, immunology, immune system, skull, cancer, oxidative stress, DNA and Cyp-450
Google Scholar	Harbour porpoise	eider, white-tailed eagle, harbour seal, grey seal, ringed seal, harbour porpoise, contaminants, POPs, persistent organic pollutants, PCBs, polychlorinated biphenyls, mercury, syndrome, organ, histopathology, bone, reproductive organs, reproduction, vitamins, hormones, endocrine system, cytokines, lymphocyte proliferation test, skeletal, bone density, immunology, immune system, skull, cancer, oxidative stress, DNA and Cyp-450
ISI Web of Knowledge/WoS	White-tailed eagle	eider, white-tailed eagle, harbour seal, grey seal, ringed seal, harbour porpoise, contaminants, POPs, persistent organic pollutants, PCBs, polychlorinated biphenyls, mercury, syndrome, organ, histopathology, bone, reproductive organs, reproduction, vitamins, hormones, endocrine system, cytokines, lymphocyte proliferation test, skeletal, bone density, immunology, immune system, skull, cancer, oxidative stress, DNA and Cyp-450
Springer Link	Common eider	eider, white-tailed eagle, harbour seal, grey seal, ringed seal, harbour porpoise, contaminants, POPs, persistent organic pollutants, PCBs, polychlorinated biphenyls, mercury, syndrome, organ, histopathology, bone, reproductive organs, reproduction, vitamins, hormones, endocrine system, cytokines, lymphocyte proliferation test, skeletal, bone density, immunology, immune system, skull, cancer, oxidative stress, DNA and Cyp-450

Table 2
Health endpoint and biomarkers of exposure that in Baltic key species have been associated with exposure to concentrations of persistent organic pollutants i.e. the organochlorines p,p'-DDE, ΣPCB and ΣDDT (*p,p'*-DDE, *p,p'*-DDD and *p,p'*-DDT) and BSDC. Concentrations in Baltic white-tailed eagles and marine mammals is for egg and blubber, respectively. I: Individual level effect. P: Population level effect. ▼: decrease; ▲: increase; ►: No change; Yes: indications of organ-system impacts. Blanks: data not available. References given in the text.

	POPs			Biomarkers of exposure							
	ΣPCB (μg/lw)	ΣDDT (μg/g lw)	p,ṕ-DDE (μg/g lw)	CYP-450	Thyroid hormones	Testosterone	Cortisol	Blood biochem-istry	DNA lesions	Liver vitamin A	Blood vitamin A
Level of effects				I	I	I	I	I		I	I
Ringed seal	27–390	31–770		▲	▲▼	▼	▼	Yes		▼	▼►
Grey seal	47–320	68–970		▲	▼▲	▼	▲	Yes		►▼	▲
Harbour seal	28–110	12–82			▼			Yes			▼
Harbour porpoise					▼		▲				
White-tailed eagle	260–1500		70–1300								
Common eider								Yes	▲	▲	

	Biomarkers of exposure				Organ-system health endpoints						
	Vitamin B	Liver vitamin E	Blood vitamin E	Liver vitamin D	Kidney histopa-thology	Liver histopa-thology	Intestinal pathology	Thyroid histopa-thology	Bone pathology/density	Reproducti-ve organs	Immune system
Level of effects	I,P	I	I	I	I	I	I	I	I	P	P
Ringed seal		▲	▲	▲	Yes		Yes			Yes	
Grey seal		▼▲	►▲	▼▲	Yes	Yes	Yes		Yes	Yes	Yes
Harbour seal								Yes	Yes		Yes
Harbour porpoise								Yes			Yes
White-tailed eagle										Yes	
Common eider	▼						Yes				

old) grey seals increased significantly from 15% (1977–1986) to 53% (1987–1996) (Bergman, 1999). These colonic alterations, ulcers and thickened intestinal walls still occur and are commonly associated with the parasite *Corynosoma* spp. Acanthocephala infection (Bergman 1999, 2007). Exposure to POPs leads to immunosuppression across marine mammal species and may explain the colonic alterations and chronic infections continuously observed in Baltic grey seals (Bergman, 2007; Desforges et al., 2016; Jepson et al., 2016).

The prevalence of colonic ulcers also increased in 4–20 years old grey seals in the Gulf of Bothnia between 1997 and 2006 and their prevalence is persistently high (Bäcklin et al., 2011; Norrgren et al. 2012). In grey seals in the Gulf of Bothnia investigated from 2002 to 2007, the prevalence of intestinal ulcers increased with age from 24% (1–3 years old) to 74% (11–20 years old) in hunted males (Bäcklin et al., 2011). Colonic ulcers were a notable cause of mortality, when perforating the intestinal wall, especially near the head of the caecum, opposite the ileocolic orifice (Bergman, 1999). There is only one known case of intestinal ulceration in non-Baltic grey seals (Baker, 1980). In a recent study of Atlantic grey seals, no colonic alterations were found which again support that these types of lesions predominantly affect Baltic grey seals (Bäcklin et al., 2013; ÓNeill et al. 2002).

5. Reproductive impairment

5.1. Grey seals

The population of grey seals and ringed seals decreased dramatically in the 1960′s and 1970′s in the Baltic Sea due to reproductive impairment. High hunting pressure and contaminant-induced sterility of females resulted in a population crash prior to the 1960 s, and contaminants further hindered population recovery thereafter (Harding and Härkönen, 1999; Harding et al., 2007). Roos et al. (2012) showed that the pregnancy in grey seals increased over the period 1990–2010, while the prevalence of uterine occlusions and stenosis and uterine tumours decreased. This is an ongoing tendency supported by findings that the reproductive rate of grey seals is normal at present and that birth rate in Finnish waters is 88% (mean for 2013–2018, no uterine occlusions observed) (Kauhala et al., 2017). Today, adult animals only show minor renal BSDC symptoms due to the relatively low POP levels (Bäcklin et al., 2013; Bergman et al., 2001). Bergman (1999) reported on the temporal distribution of the syndrome covering the period 1977–1996 and found that gynaecological pathology had improved while the concentration of environmental contaminants had decreased (Bjurlid et al., 2018).

5.2. White-tailed eagles

The Swedish population of white-tailed eagles almost crashed over the period 1960–1990 due to eggshell thinning and reproductive failure from egg exposure to *p,p'*-DDE and ΣPCB_{22} concentrations of 70–1300 and 260–1500 µg/g lw, respectively (Table 2) (Helander et al., 2002; Helander et al., 1982). Helander et al. (2008) did a comprehensive review of the biomonitoring of pollution and health effects in Baltic white-tailed eagles showing that the Scandinavian subpopulations have recovered since the 1980's after regulation of the contaminants including *p,p'*-DDT took place (Bignert and Helander, 2015; Helander et al., 2002; Scharenberg and Struwe-Juhl, 2006). Following the publications on the collapse of the white-tailed eagle population in the 1960–90's, Roos et al. (2012) reviewed and updated the reproductive health of white-tailed eagles in the Swedish part of the Baltic for the period 1990–2010. The analyses showed that the reproduction of white-tailed eagles increased over the study period and these changes in reproduction correlated closely with temporal declines in the concentrations of PCBs and *p,p'*-DDT. This further strengthens the causal association between these chemicals and observed reproductive impairment in seals and eagles in the 1960–1980 s (Bergman, 1999; Roos et al., 2012). Although PCBs have been consistently detected at higher levels than *p,p'*-DDT, *p-p'*-DDT, they are considered to have less of an effect on the reproduction of white-tailed eagles compared to *p,p'*-DDE (Helander et al., 2002).

6. Skeletal pathology

Pathology of the skeletal system was also a major contributor to the BSDC. Reports of pathology include fluctuating asymmetry, changes in bone mineral density, and severe periodontitis and *peri*-alveolar inflammation and disease in ringed and grey seals (Table 2) (Bergman and Olsson, 1985). Bergman et al. (1992) showed that, by comparing grey seal skull lesions collected prior to 1950 and after 1960, periodontitis with loss of alveolar bone was the highest in the post 1960 period as well as having high concentrations of environmental contaminants such as PCBs and *p,p'*-DDT. Again, the lesions were similar to those in hyperadrenocorticism and the major cause being POPs was supported by a study of Baltic harbour seals by Mortensen et al. (1992). Mortensen et al. (1992) showed that the highest prevalence of alveolar bone loss and exostosis occurred in Baltic seals compared to those from the Swedish west coast which is generally less polluted.

Lind et al. (2003) reported that bone mineral density increased with increasing PCB concentration. That BMD is increasing with increasing PCB concentrations suggests that bone rebuilding is undergoing changes due to endocrine disruption which does not necessarily mean better quality or stronger bone but rather an indication of impaired bone quality. This impaired quality is reflected in decreased bone bending strength and collagen mass. The individual effects are obviously a risk of fractures and osteoporosis as well as mandibular functioning i.e. chewing of food (Sonne, 2010).

Schandorff (1997) and Zakharov and Yablokov (1990) reported on the stability of foetal and neonatal development reflected by metric and non-metric (foramina) asymmetry of 361 harbour seal skulls from the Baltic region. The study also analysed the prevalence of exostosis, periodontitis, and loss of alveolar bone structure. The study showed that a reduction in the developmental stability (i.e. increase in fluctuating asymmetry and prevalence of pathology) was the highest, with high levels of environmental contaminants in the Baltic Sea, following World War II. The developmental stability increased and pathology decreased in the period after 1988 and this was likely associated with decreasing concentrations of environmental contaminants in the Baltic region. Using 380 skulls and 141 mandibles in harbour seals from the waters surrounding Denmark, Pertoldi et al. (2018) showed a significant increase of pathological lesions from 1981 to 2014, and that skulls with lesions had higher asymmetry. One hypothesis is that these increasing trends could be linked to immune suppression from cumulative stress of multiple factors such as increasing PFAS (per and polyfluoroalkyl substances) concentrations and decreases in the quality and quantity of food resources (Sonne, 2010).

7. Immune system

7.1. Harbour seals

A well-functioning immune system is pivotal for animal health as it protects against infectious diseases and cancerous growths. The southern Baltic and neighbouring seas have been the site of major viral outbreaks in harbour seals, occurring in 1988, 2002 and 2014. Here, mass mortalities of tens of thousands of individuals, mostly at the Baltic border towards the North Sea, were caused by phocine distemper virus (PDV) and Avian Influenza Virus (H10N7) (Harding et al., 2002; Härkönen, 2006; Zohari et al., 2014; Bodewes et al., 2015). Immune suppression owing to contaminant exposure was suggested as an important factor adding to the poor environmental status of Baltic seals, and a captive feeding study with harbour seals was carried-out to investigate this linkage (Ross et al., 1996) (Table 2). Feeding seals with fish from contaminated Baltic waters resulted in significant immune suppression relative to seals fed with less contaminated fish, based on diminished T-cell function, delayed-type hypersensitivity, antibody responses, and natural killer cell activity (Ross et al., 1996). This feeding study was the first to show conclusively that environmental contaminants could significantly modulate the immune system of exposed marine mammals and established an effect threshold at 17 μg g^{-1} lw PCBs in blubber.

To complement the study by Ross et al. (1996) that focused on POPs, blood samples from Baltic marine mammals were used to isolate immune cells for *in vitro* dose-response studies using metals. Nickel, chromium, aluminium and lead stimulated lymphocyte proliferation in harbour seals while cadmium and different forms of mercury caused significant immune suppression (Das et al., 2008; Kakuschke et al., 2005, 2009). A recent study evaluated the *in vitro* immune responses from various marine mammal species against a wide range of concentrations of a realistic POPs mixture extracted from marine mammal blubber (Desforges et al. 2017a). This study showed clear immune suppressive effects of the POP mixture in several species of cetaceans and seals, and revealed effect thresholds much lower than observed when testing individual contaminants. In addition, Desforges et al. (2016) reviewed the literature including seals from the Baltic and showed that threshold levels for suppression of lymphocyte proliferation is 0.001–10 μg/g for PCBs, 0.002–1.3 μg/g for Hg and 0.009–0.06 μg/g for MeHg and 0.1–2.4 μg/g for cadmium in several pinniped and cetacean species. Similarly, thresholds for suppression of phagocytosis were 0.6–1.4 and 0.08–1.9 μg/g for PCBs and mercury, respectively. Altogether, these studies are timely and have important implications for future risk assessments as highlighted by Lehnert et al. (2018).

7.2. Harbour porpoise

Studies of the immune system in Baltic predators are either *in vivo* examinations of immune health and disease burden or *in vitro* techniques to investigate the effects from specific contaminant compounds and groups. For *in vivo* studies, necropsy findings from Baltic harbour porpoises have provided evidence that regional contamination of the environment with POPs and metals (e.g. mercury) is associated with increased incidence of bacterial and parasite infections (Wunschmann et al., 2001). This also included pathology of lymphoid and other infected tissues as revealed through comparison with specimens from less contaminated Arctic regions (Beineke et al., 2005; 2007; Siebert et al., 1999).

Immunological investigations of animals from German Baltic waters held in rehabilitation centres have provided opportunities to assess new diagnostic tools potentially useful for wildlife health assessments. These molecular tools have been used in free-ranging Baltic marine mammals to link contaminant stress to cytokine gene expression (Beineke et al. 2007; Lehnert et al., 2014; Routti et al. 2010; Weirup et al. 2013). Heat shock protein (HSP70) and receptors related to POP exposure including AHR (aryl hydrocarbon receptor), ARNT (aryl hydrocarbon receptor nuclear translocator) and PPARα (transcription factor peroxisome proliferator-activated receptor) have also been used (Lehnert et al. 2014). A significant decrease in xenobiotic markers AHR and ARNT transcription was found in grey seal pups after weaning rehabilitation due to POP exposure during lactation reinforced by maternal fasting and adipose tissue mobilization (Lehnert et al. 2014).

8. Thyroid hormones

8.1. Ringed and grey seals

Hormones are produced by endocrine glands and play an important role as signal compounds in the thalamic-hypothalamic-pituitary pathway controlling physiological processes (Letcher et al. 2010; Sonne 2010). Routti et al. (2010) compared the status of thyroid hormones of ringed seals from the Baltic Sea with the less polluted Svalbard north of Norway. The POP levels of the Baltic seals were tenfold higher than in those from the Arctic (Routti et al. 2008a, 2009). The contaminated Baltic seals had higher plasma concentrations of free triiodothyronine, and higher hepatic mRNA expressions of deiodinase-I and thyroid hormone receptor β. The ratio of free and total T3 were also positively correlated to contaminant metabolites, suggesting that POPs interacted with transport proteins like transthyretin (TTR) in Baltic ringed seals that may affect both the imuune and reproductive system as well as bone disease (Routti et al. 2010). Likewise, Sørmo et al. (2005) examined thyroid hormones in Baltic grey seal pups from various areas in relation to organochlorine pollutants. The investigations showed no differences in plasma concentrations of FT4 and TT4 between the Baltic and Arctic seals. However, there seems to be a modifying effect on the transformation of thyroxine to triiodothyronine. The low TT3 and FT3 in plasma were noticeable in Baltic grey seal pups. The most influential pollutants identified in that study were CB-118, CB-149, CB-180, ΣPCB_{14} and *p,p'*-DDT.

8.2. Harbour porpoises

A multivariate statistical analysis showed that the increase of connective tissue in the thyroid of harbour porpoises was mainly correlated to the higher PCB, PBDE, *p,p'*-DDE and *p,p'*-DDT concentrations in the blubber (Das et al. 2006). Replacement of thyroid follicles by connective tissue results in severe impairment of thyroid function, which supports the hypothesis that thyroid fibrosis may be caused by contaminants (Schumacher et al. 1993). In these studies, it was postulated that thyroid colloid depletion and fibrosis in harbour seals, and to a lesser degree in harbour porpoises, may be linked to high tissue concentrations of PCBs. The study by Das et al. (2006) examined thyroid glands from 57 harbour porpoises and showed statistical relationships between thyroid fibrosis and various organochlorines and PBDEs; however, the pathways for the toxicity of environmental contaminants could not be determined.

9. Vitamins

Vitamins are essential compounds for the proper functioning of physiological processes. Vitamin D is of endogenous as well as dietary origin while vitamins A, C and E are purely dietary antioxidants (Canter et al. 2007). The vitamins most often included in wildlife studies are vitamins A, E and D (Routti et al. 2005). Analysis of vitamins in Baltic ringed seals and grey seals were collected in the period 1996–1998 and compared to reference seals from Svalbard (ringed seals) and Canada (grey seals) (Table 2) (Nyman et al. 2003). Vitamin A and E levels were found to be reliable biomarkers of exposure for exposure to PCBs and *p,p'*-DDT based on significant negative correlations. A later follow-up study found that Baltic seals had upregulated hepatic mRNA expression of the vitamin A receptor (retinoic acid receptor α) and lower plasma vitamin A levels (retinol) as compared to the lesser contaminated Arctic population (Routti et al. 2010).

The biomagnification of contaminants (PCBs and *p,p'*-DDT) as well as vitamins A and E in the food web of grey and ringed seals in the Bay of Bothnia were also studied and compared with reference seals from more pristine regions of Svalbard and Canada (Routti et al. 2005). PCBs were higher in grey seals than ringed seals, while *p,p'*-DDT was similar in both species in the Baltic Sea. Routti et al. (2008a) suggested that the bone lesions (and reproductive failures) seen in Baltic seals during the period of high environmental contamination in the Baltic, was likely associated with reduced concentrations of vitamin D and increased concentrations of thyroid hormones. Increased cortisol and disruption of circulating sex steroids have also been linked to bone absorption, pathology and changes in bone density (Letcher et al. 2010; Sonne 2010).

9.1. Vitamin B

Thiamine (Vitamin B_1) deficiency has been suggested as a factor in the mortality of marine birds in the Baltic. Sylvander et al. (2013) reported decreasing levels of thiamine with increasing trophic level across species in the Baltic Sea ecosystem (Table 2). A disease named 'paralysis syndrome' caused sea bird population declines around the Baltic Sea between 1990 and 2010. It was characterized by paralysis of the wings, followed by complete paralysis and death of the birds (Balk et al. 2009). Sonne et al. (2012) reviewed these cases and concluded the cause to be a multifactorial disease complex involving exposure to environmental contaminants e.g. mercury, lead, PCBs etc. as well as toxins, vitamin deficiencies and may be infectious diseases.

The Baltic Sea population of common eiders has declined dramatically during the last two decades and changes in food web dynamics and contaminant exposure affecting survival and reproduction are likely some of the causes. Morner et al. (2017) proposed that the decline could be due to thiamine deficiency being one of the multiple causes as discussed further by Sonne et al. (2012). Recently, widespread episodic thiamine (Vitamin B_1) deficiency has been demonstrated in feral birds and suggested to contribute significantly to the declining populations. The decline of the common eider population in the Baltic is paralleled by high mortality of the ducklings a few days after hatch, partly owing to thiamine deficiency and probably thereby associated abnormal behaviour resulting in high gull and white-tailed eagle predation (Morner et al. 2017). Together with exposure to environmental contaminants and also limited food access, these factors likely affect the population declines and dynamics of the Baltic common eider (Sonne et al., 2012; Garbus et al. 2018, 2019).

10. DNA lesions and liver enzymes

Fensted et al. (2016a, 2016b) investigated oxidative stress and DNA double-strand breaks in Baltic and Svalbard eider ducks and showed that Baltic eiders had higher concentrations of antioxidants, suggesting a possible upregulation in response to oxidative stressors such as PCBs (Table 2). Importantly, they hypothesize that such upregulation may incur considerable energetic costs. The analyses of DNA breaks did not reveal a link to POPs, however, positive correlations were found with mercury. Environmental contaminants as well as endogenous compounds undergo biotransformation in the body, which can lead to bioactivation of metabolites and/or facilitated excretion. Biotransformation of contaminants involves xenobiotic-metabolizing Phase I (cytochrome P450; CYP) and conjugating Phase II enzymes (glutathione S-transferase; GST). Routti et al. (2008b) investigated concentration of PCBs, liver phase I and 11 enzymes and formation of PCB metabolites in ringed seals from the Baltic Sea and the less contaminated Svalbard peninsula (Table 2). The analyses showed that PCBs upregulated Phase I enzymes and GST activities, increasing the biotransformation of specific PCBs. Altogether, such inductions could lead to increases in the concentrations of bioactive PCB metabolites and to metabolism of endogenous hormones causing possible endocrine disruption.

11. Considerations

Given the severity of contaminant exposure and other stressors in the Baltic, pathological organ-system changes and biomarkers of exposure are of particular importance to detect population level effects. This is in contrast to the Arctic and other regions where the impacts of stress may be more subtle and severe population declines due to contaminant exposure have not been reported. It is notable that many legacy contaminants, which have been banned for decades, still appear to affect Baltic wildlife. Given the multiple stressors in the Baltic Sea, new techniques are needed to integrate various health impacts and extend these to the population level and reported elsewhere in the Special Issue (Cervin et al., in review; Silva et al., in review). Modelling approaches utilizing bioenergetics and individual and agent based models are required to provide the basis for extrapolating effects from the molecular to the individual and eventually the population level (Desforges et al. 2017b, 2018; Martin et al. 2013) The combined effect from slightly reduced fecundity, increased suceptibiilty to infectious disease and anthropogenic stressors such as by-catches can bring the slowly recovering Baltic marine mammal populations to a new area of population declines and near extinction as accompanying studies in the current Special Issue illustrate (Cervin et al., in review; Silva et al., in review). With respect to common eiders, little information is available on contaminants exposure and population effects and that should be investigated further especially during incubation where the birds fast and climate change seem to limit food resources further prior to start of incubation (Balk et al. 2009; Garbus et al. 2018, 2019; Sonne et al., 2012). In relation to that, food-web changes and quality of eider prey should be mapped, as energetics is a major factor for eider duck reproduction. With respect to white-tailed eagles, and despite the Baltic population having re-established itself, it is still important to monitor the health, reproduction and population dynamics of this important sentinel apex predator.

12. Conclusions

Our review shows that POP exposure affects the reproductive system and survival through immune suppression and endocrine disruption which have led to population-level effects on seals and white-tailed eagles in the Baltic. It is notable that many legacy contaminants, which have been banned for decades, still appear to affect Baltic wildlife. With respect to common eiders, changes in food composition, quality and contaminant exposure seem to have population effects which need to be investigated further especially during incubation where the birds fast. Since new industrial contaminants continuously leak into the environment, we recommend to continue the monitoring of sentinel species in the Baltic and to continue model development to also include the possible effects linked to climate change.

CRediT authorship contribution statement

Christian Sonne: Conceptualization, Methodology, Writing - original draft, Writing - review & editing, Data curation. **Ursula Siebert:** Writing - review & editing. **Katharina Gonnsen:** Writing - review & editing. **Jean-Pierre Desforges:** Writing - review & editing. **Igor Eulaers:** Writing - review & editing. **Sara Persson:** Writing - review & editing. **Anna Roos:** Writing - review & editing. **Britt-Marie Bäcklin:** Writing - review & editing. **Kaarina Kauhala:** Writing - review & editing. **Morten Tange Olsen:** Writing - review & editing. **Karin Harding:** Writing - review & editing. **Gabriele Treu:** Writing - review & editing. **Anders Galatius:** Writing - review & editing. **Emilie Andersen-Ranberg:** Writing - review & editing. **Stephanie Gross:** Writing - review & editing. **Jan Lakemeyer:** Writing - review & editing. **Kristina Lehnert:** Writing - review & editing. **Su Shiung Lam:** Writing - review & editing. **Wanxi Peng:** Writing - review & editing. **Rune Dietz:** Writing - review & editing.

Declaration of Competing Interest

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

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Appendix A. Supplementary material

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