Agenda Item 2.3	Review of New Information on Threats to Small Cetaceans Pollution and Hazardous Substances
Information Document 2.3	Organochlorine Contaminants and Reproductive Implication in Cetaceans: A Case Study of the Common Dolphin
Action Requested	Take Note
Submitted by	Murphy et al.

Note:
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Chapter 1

Organochlorine Contaminants and Reproductive Implication in Cetaceans: A Case Study of the Common Dolphin

Sinéad Murphy[1,2], Robin J. Law[2,3], Robert Deaville[2], James Barnett[4], Matthew W. Perkins[2], Andrew Brownlow[5], Rod Penrose[6], Nicholas J. Davison[5], Jonathan L. Barber[3], Paul D. Jepson[2]

[1]Galway-Mayo Institute of Technology, Galway, Ireland; [2]Zoological Society of London, London, United Kingdom; [3]Centre for Environment, Fisheries and Aquaculture Science, Lowestoft, United Kingdom; [4]University of Exeter, Penryn, United Kingdom; [5]SRUC Veterinary Services, Inverness, United Kingdom; [6]Marine Environmental Monitoring, Cardigan, United Kingdom

INTRODUCTION

Organochlorines (OCs) are known persistent organic pollutants (POPs) that both bioaccumulate and biomagnify within marine food webs. This chapter will focus on the legacy pollutants polychlorinated biphenyls (PCBs) and dichlorodiphenyltrichloroethane (DDT), which have been reported to have adverse effects on endocrine, reproductive, and immune functions in marine mammals (Hall et al., 2006a; Murphy et al., 2015; O'Shea et al., 1999; Reijnders et al., 1999; Vos et al., 2003). The chapter is divided into three sections, including an introduction to OCs and their effects, a review of the published cases of reproductive failure and dysfunction in cetaceans associated with exposures to OCs, and a new case study exploring the effects of PCBs on reproduction in short-beaked common dolphins (*Delphinus delphis*) in the Northeast Atlantic. Thus, this chapter provides a comprehensive overview of published and new information on OCs and reproductive implications in cetaceans.

PCBs were originally synthesized in the 19th century, but they came into widespread use in the 1930s. They were primarily used in mineral oils used as dielectric fluids in electrical equipment such as transformers and capacitors, but they were also used in a wide variety of other applications, including as flame retardants, in paints and lacquers, hydraulic fluids, caulks, and sealants (Diamond et al., 2010). A number of different products were produced, differing

Marine Mammal Ecotoxicology. https://doi.org/10.1016/B978-0-12-812144-3.00001-2

in the proportion of chlorine incorporated and the range of congeners comprising the product (e.g., Aroclor 1242, 1254 and 1260, manufactured by Monsanto: 42%–60% chlorine). Most of the PCB products were produced in the United States and Europe (Law and Jepson, 2017). In the mid-1960s, they were discovered as contaminants in fish from the River Viskan in Sweden, and later in other wildlife, highlighting their widespread environmental occurrence (Jensen, 1996; Jensen et al., 1969). Subsequently, it was discovered that PCBs are persistent and highly mobile, being transported to the Arctic by a process known as global distillation, or long-range atmospheric transport (Jepson and Law, 2016). Controls on production and use in both the United States and Europe, where over 1 million tons of PCBs were produced, began around the early 1980s.

Initially, marine environmental concentrations of PCBs declined rapidly following the ban in America and Europe in 1979 and 1985, respectively, but in some instances, this decline has stalled (Aguilar and Borrell, 2005; Borrell and Aguilar, 2007; Jepson et al., 2016; Law et al., 2012). Continued input into the marine environment through activities such as dredging of PCB-laden sediment and mariculture, as well as from land-based sources such as leakages from old landfills and PCB-contaminated buildings material are suspected (Jepson et al., 2016; Tornero and Hanke, 2016). Further, as large quantities of PCB-containing equipment still require disposal (CLEEN, 2005) and the half-life of some PCB congeners is up to 100 years (Hickie et al., 2007; Jonsson et al., 2003; Sinkkonen, 2000), the problems associated with these compounds will continue for decades to come. Traditional organochlorine pesticide compounds (e.g., DDT, aldrin, dieldrin) have been restricted or scheduled for elimination under the Stockholm Convention since 2004 (United Nations Environment Programme, 2001), and declines in some of these compounds, notably, DDT, have been reported in some marine mammal populations (e.g., European waters; Aguilar and Borrell, 2005; Borrell and Aguilar, 2007; Law et al., 2012). However, concentrations of DDT have been observed to increase again in tropical wildlife species, where use has been recommitted by the World Health Organization to tackle malaria (Alava et al., 2011).

As top predators with long life spans, cetaceans accumulate high concentrations of OCs in their lipid tissue, as these lipophilic compounds bind to fatty acids in the blubber (90%–95% of total body burden; Aguilar, 1985), and odontocetes through their higher trophic level status have a higher exposure to OCs compared to mysticetes (Houde et al., 2005). Blubber concentrations in male cetaceans increase with age, with reported annual PCB accumulation rates of 1.1 mg/kg in UK harbor porpoises (*Phocoena phocoena*) (Murphy et al., 2015) and 2.96 mg/kg in bottlenose dolphins (*Tursiops truncatus*) from Sarasota Bay, Florida (Hall et al., 2006b). In species such as killer whales (*Orincus orca*), a growth dilution phase was observed after weaning up to around 10 years in age, following which an increase in ΣPCBs was observed in males (Hickie et al., 2007). Once sequestered in blubber tissue, compounds are mobilized during times of fasting/starvation or intense energetic demand. In southern resident killer whales (*Orcinus orca*), concentrations of POPs, possibly mobilized from endogenous lipid stores,

were highest and had the greatest potential for toxicity during periods of low prey abundance (Lundin et al., 2016). During pregnancy and lactation, female cetaceans offload a high proportion of their lipophilic pollutant burden to offspring, particularly in lipid-rich milk. In bottlenose dolphins, up to c. 80% of OCs can be offloaded to firstborn calves during the first 7 weeks of lactation (Cockcroft et al., 1989). This is similar to long-finned pilot whales (*Globicephala melas*), where 60%–100% of their pollutant load is offloaded during lactational transfer, compared to just 4%–10% through placental transfer (Borrell et al., 1995), and in striped dolphins (*Stenella coeruleoalba*), 72%–91% of body burdens were offloaded during lactation and only 4%–9% during gestation (Fukushima and Kawai, 1981 reported in Yordy et al., 2010). For all cetacean species studied to date, gestational and lactational transfer of OCs has ranged from 3.5% to 15% and 67.6%–99.9%, respectively (Mongillo et al., 2016). DDTs are more easily transferred than PCBs, as transplacental and lactational transfer is easier for lower chlorinated compounds (Borrell and Aguilar, 2005). It is during these periods of mobilization of OCs that adverse health effects may occur, for example, exerting toxic effects on fetal growth and development.

Both PCBs and DDT have been reported as endocrine disruptors in marine mammals, though the latter has also shown direct lethal effects on wildlife. Endocrine-disrupting chemicals (EDC) are "an exogenous chemical, or mixture of chemicals, that interferes with any aspect of hormone action" (Zoeller et al., 2012). By hormone action, it is inferred to mean hormone receptor activation, i.e., interfering or interacting with the hormone receptors themselves, such as mimicking hormones or blocking hormone receptors, and also delivery (synthesis, release, transport including blood and across membranes, metabolism, or clearance) of hormones to those receptors (Zoeller et al., 2014). Thus, it is any inference with the endocrine system's role in maintaining homeostasis, as well as roles in sexual differentiation, development, metabolism, and stress responses. In marine mammals, it has been hypothesized that PCBs and DDT, or metabolites thereof, bind to hormone receptors and/or hormone carriers, or in some cases break down steroid hormones through increased OC metabolic-induced cytochrome (CYP) enzyme activity (Reijnders, 2003). EDCs differ somewhat from general toxicants as they (e.g., chemicals with hormone-like properties) have the ability to act at low doses, exhibit nonmonotonic dose responses (e.g., U-shaped curves), show varying effects over an individual's lifespan, delayed effects (of sexual dysfunction and physical abnormalities) that are not evident until later in life or until future generations, and have the potential to show combination effects when exposed to multiple pollutants (Bergman et al., 2013; Ingre-Khans et al., 2017).

The EDC effects of PCBs depends on the specific congeners in the compound, as some congeners have a dioxin-like mechanism mode of action, while other congeners and metabolites thereof have estrogenic and/or antiandrogenic or antiestrogenic effects (EEA Technical Report, 2012; Fossi and Marsili, 2003; Letcher et al., 2010). Both *p*,*p*′-DDT and *o*,*p*′-DDT, which comprise DDT,

promote estrogenic activity but have also been shown to have both antiestrogenic and antiandrogenic effects, while the breakdown product, *p,p′*-DDE, has been shown to exert a wide variety of effects (Fossi and Marsili, 2003). Hence, the toxic effects of OCs can be exerted by the parent compound or by their metabolites, and different cetaceans (and even different populations, depending on previous levels of exposure) have varying capacities to metabolize/biotransform OC compounds depending on the presence and activity of CYP enzymes (Houde et al., 2005; Muir et al., 1996). It is beyond the scope of this chapter to discuss the properties of OCs in detail; however, fully comprehensive reviews are provided elsewhere (Aguilar et al., 1999; Houde et al., 2005; Letcher et al., 2010; O'Shea et al., 1999; Reijnders et al., 1999).

Using data on UK harbor porpoises from Murphy et al. (2015), we assessed the influence of metabolism and the degree of offloading of PCBs in females. PCBs were grouped into five structure activity groups (SAGs) based on their capacity for biotransformation as defined previously by Boon et al. (1994). Seven PCB congeners (PCB118, -138, -149, -153, -170, -180, and -187) contributed to 79% of the ΣPCB content in female harbor porpoises blubber samples (Fig. 1.1). PCB118, PCB170, and PCB180 are dioxin-like PCBs, whereas PCB138 and PCB153 are nondioxin-like, with the latter having estrogen-like activities. The top PCB congeners in the blubber of females were PCBs 153 > 138 > 149 > 180 > 187, accounting for 54% of the ΣPCB concentration. PCB congener profiles did not differ markedly among reproductive groups, and this is due to the persistence of some congeners and the lack of ability by cetaceans to metabolize those congeners. The highly persistent CB-153 ranged from 23% of ΣPCB concentration in pregnant females to 27% in resting females (neonates = 26%, immature = 26%).

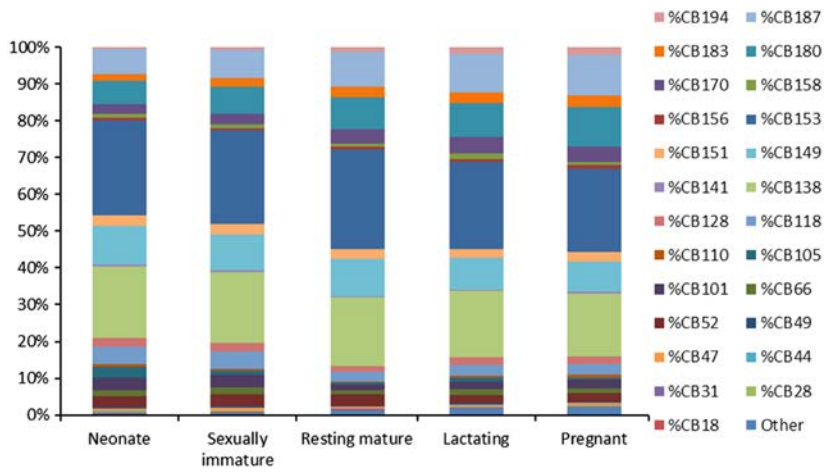

FIGURE 1.1 PCB congener profiles in 278 female UK harbor porpoises by reproductive status. Neonates $n = 14$, sexually immature $n = 145$, resting mature $n = 54$, lactating $n = 28$, and pregnant $n = 37$. *(Raw data taken from Murphy et al. (2015).)*

PCB153, -138, and -149 are SAG 1, 2, and 5 congeners, respectively, and are considered nonbiotransformable in cetaceans (Boon et al., 1994; Yordy et al., 2010). For SAG 3 congeners (PCB28, -31, -66, -105, -118, and -156) that are metabolized by CYP1A1-mediated enzymes in cetaceans (Boon et al., 1994; Yordy et al., 2010), relatively low concentrations were observed within the blubber tissue of all maturity groups. Other cetaceans have also shown an accumulation with age of metabolically refractory PCBs, but not for those PCBs that are subject to metabolism (e.g., bottlenose dolphins; Yordy et al. 2010).

There has been continued debate over the use of thresholds (below which no adverse effect occurs) in human studies, as not all people are equally sensitive to a particular dose, so a graded response is expected (Zoeller et al., 2014). Further, there are so many confounding factors that have to be taken into account in human toxicity studies that dose thresholds are impossible to prove or disprove (Zoeller et al., 2014). Namely, these are accounting for additive, synergistic, or nonadditive effects between pollutants, and also other stressors, which leads to difficulties in identifying chronic and sublethal responses for specific pollutants, particularly where adverse responses show delayed latent effects. Similar problems have been observed in marine mammal toxicity studies, so few attempts have been made at understanding the exposure-response relationship, and for the most part, proposed thresholds have relied on experimental studies on surrogate species. Kannan et al. (2000) proposed a toxicity threshold concentration of 17 mg/kg PCB lw (for Aroclor 1254; or 9 mg/kg for ΣPCBs determined by Jepson et al., 2016) for the onset of physiologic (immunological and reproductive) endpoints in marine mammals, and it was based on observed effects in experimental studies on seals, otters, and mink (Kannan et al., 2000). These endpoints (responses to a hazard) were for sublethal effects, causing morbidity, i.e., impairing the health of the animal through disruption of thyroid hormones, suppression of natural killer cell activity, etc. Higher-level exposure to certain PCBs may result in more severe immunosuppression, increasing risks of opportunistic infections that may ultimately lead to death (Hall et al., 2006a). Other studies that have applied this threshold to cetacean species noted that caution was warranted due to differing sensitivities among species; however, it did provide a benchmark for which to assess if PCB exposure was biologically significant (Hickie et al., 2007; Jepson et al., 2005, 2016; Murphy et al., 2015). It should be noted that threshold levels for adverse health effects during critical periods in development would be lower than those proposed for adults (Borrell and Aguilar, 2005), and Hall et al. (2006b) estimated a threshold of 10 mg/kg for calf survival in bottlenose dolphins from Sarasota Bay.

CASES OF REPRODUCTIVE FAILURE AND DYSFUNCTION ASSOCIATED WITH EXPOSURE TO OCs IN CETACEANS

The effects of EDCs may be expressed as infertility, cancer, or other types of diseases, and if EDCs interfere during critical periods of development, these

effects may not be observed until later in life (Bergman et al., 2013). Proposed reproductive toxicity endpoints for EDCs in animals and humans include spontaneous abortions, early puberty, disorders of lactation and ovulation, including polycystic ovarian syndrome and premature ovarian failure, ovarian and mammary gland tumors, and other reproductive tract disorders/diseases including endometriosis and uterine fibroids, as well as leiomyomas and vaginal adenocarcinomas (reviewed in Diamanti-Kandarakis et al., 2009).

Within marine mammals, few cases of reproductive failure and dysfunction have been associated with exposure to OCs, and even fewer in cetaceans. This is primarily due to confounding factors and difficulties in identifying the mechanism or mode of action for specific pollutants. For those cases of reproductive failure and reproductive dysfunction that have been documented, the etiologies of the observed conditions have usually been uncertain (Reijnders, 2003). In cetaceans, observed cases of reproductive failure that have been associated with high exposure to OCs include fetal and/or newborn mortality in harbor porpoises (Murphy et al., 2015) and increased firstborn calf mortality (stillbirths or neonate mortality) in bottlenose dolphins, where PCB-related risk of reproductive failure in primiparous females ranged from 60% to 79% among three populations (Schwacke et al., 2002; Wells et al., 2005). Evidence of reproductive abnormalities and disorders associated with exposure to OCs include the presence of ovarian luteinized cysts in striped dolphins (Munson et al., 1998) and the development of cancer of the reproductive system and hermaphroditism in beluga whales (*Delphinapterus leucas*) (Béland et al., 1993; De Guise et al., 1994a; Martineau et al., 2002).

Beluga whales inhabiting the St. Lawrence Estuary in Canada are one of the most heavily contaminated cetacean populations worldwide, exposed to a variety of chemicals, including PCBs and DDT, as well as polycyclic aromatic hydrocarbons (PAHs) (Martineau, 2012). This threatened (COSEWIC status 2004) population has the highest prevalence of cancer in cetaceans, and it is the second leading cause of death with tumors (primarily of the digestive tract) identified in 27% of sampled adult whales (Martineau et al., 2002; McAloose and Newton, 2009). Putative causes include environmental exposure to carcinogenic substances and/or reduced immune function due to limited genetic diversity (Martineau et al., 2002; Newman and Smith, 2006). Evidence of reproductive disease in females between 1983 and 1999 included three cases of ovarian tumors (see Table 1.1), and adenocarcinomas were observed in mammary gland tissue of a further three individuals and the uterus of another (Martineau et al., 2002). Two hermaphrodite cases were documented out of 94 animals examined. These include an atypical bilateral true hermaphrodite, which was attributed to hormonal disturbance in early pregnancy (De Guise et al., 1994a), and a male pseudohermaphrodite (Reijnders, 2003). A follicular cyst was found on the left ovary of the true hermaphrodite measuring 6 cm × 6 cm × 5 cm (De Guise et al., 1995). Cases of adrenal and thyroid proliferative and degenerative lesions (adenomatous hyperplasia and follicular cysts) were observed (reviewed

TABLE 1.1 Individual Cases of Ovarian Neoplasms in Cetaceans

Ovarian Neoplasms	Cetacean Species	Location	Reference
Dysgerminoma (*germ cell tumor*)	Dusky dolphin	Peru	Van Bressem et al. (2000)
Dysgerminoma[a]	Beluga Whale	St. Lawrence Estuary	De Guise et al. (1994b) and Martineau et al. (2002)
Granulosa cell tumor (*sex cord-stromal tumor*)	Harbor porpoise	German North Sea	Seibel et al. (2012)
Granulosa cell tumors	Beluga whale	St. Lawrence Estuary	Martineau et al. (1988)
Granulosa cell tumor	Beluga whale	St. Lawrence Estuary	De Guise et al. (1994b)
Granulosa cell tumor	Pilot whale	Japan	Benirschke and Marsh (1984)
Granulosa cell tumor	Fin whale	Antarctica	Geraci et al. (1987) and Rewell and Willis (1950)
Granulosa cell tumor	Fin whale	Antarctica, S. Georgia	Geraci et al. (1987) and Rewell and Willis (1950)
Granulosa cell tumor	Blue whale	Antarctica, S. Georgia	Geraci et al. (1987) and Rewell and Willis (1950)
Ovarian carcinoma (granulosa cell tumor?[b])	Fin whale*	Antarctica	Geraci et al. (1987) and Stolk (1950)
Mucinous cystadenoma (*epithelial tumor*)	Blue whale	Antarctic	Geraci et al. (1987) and Rewell and Willis (1950)

[a]*Originally classified as a granulosa cell tumor and reclassified as a dysgerminoma by Martineau et al. (2002).*
[b]*Reclassified as a (possible) granulosa cell tumor in Geraci et al. (1987).*

in Martineau, 2012), as well as incidences of mastitis (De Guise et al., 1995). Evidence of reproductive failure was also apparent in the population, as the proportions of calves and juveniles were lower than less polluted populations off Alaska (Martineau et al., 1987). Compromised milk production (inflammatory change and cancer) was reported in 41% of stranded females (Martineau et al., 1994), which may have impacted fecundity rates. For all cases of reproductive

failure and dysfunction, a contaminant-based etiology was proposed (Martineau, 2012; Martineau et al., 2002), although the mechanisms of action were not established. PAHs more so than PCBs may have been involved in the etiology of cancer in the observed cases (Martineau et al., 2002).

Multiple luteinized cysts were observed on the ovaries of four striped dolphins (out of 56 examined) that died during a morbillivirus epizootic (Munson et al., 1998). A mass die-off of more than 1000 striped dolphins occurred in the Mediterranean Sea between 1990 and 1992, and it was suggested that PCBs and other OC pollutants with the potential for immunosuppressive effects may have triggered the event, or enhanced its spread and lethality (Aguilar and Borrell, 1994). It is not known if the presence of ovarian luteinized cysts and lower fecundity, demonstrated by a high number of abortions, were caused by high PCB levels, the morbillivirus infection, or a combination of the two (Munson et al., 1998). Luteinized cysts occur when ovulation is impeded and were potentially caused by the effects of PCBs or morbillivirus on hypothalamic/pituitary function, or PCBs on ovarian responsiveness (Munson et al., 1998).

The Northeast Atlantic harbor porpoise population exhibits a lower pregnancy rate and longer calving interval than other conspecific populations, which could be resulting from PCB-mediated effects (Murphy et al., 2015). A decline in blubber ΣPCBs concentrations was observed in UK porpoises in the mid-1990s; however, this plateaued after 1998 (Jepson et al., 2016; Law et al., 2012), whereas levels of blubber ∑DDT showed a significant decline from the early 1990s onward, reflecting a lack of fresh input into the marine environment of this agricultural pesticide (Law et al., 2012). Murphy et al. (2015) assessed for evidence of reproductive failure and reproductive dysfunction in the population using samples and data collected over a 22-year period and from 329 female UK stranded porpoises. Twenty-five of 127 (19.7%) mature females showed direct observations of reproductive failure including fetal death, spontaneous abortion, dystocia, and stillbirth. Further, 16.5% (21 of 127) of mature females had infections of the reproductive tract or tumors of reproductive tract tissues that could contribute to reproductive failure. These included malignant tumors such as cervix squamous cell carcinoma, benign tumors such as leiomyoma, papilloma-like lesions and vaginal plaques, endometritis, and other infections and inflammations of the reproductive tract, some of which were previously reported as toxicity endpoints in animals and humans (Caserta et al., 2008; Diamanti-Kandarakis et al., 2009; Herbst et al., 1971; Murphy et al., 2015; Padmanabhan et al., 2010; Steinberg et al., 2008). Difficulties arose in showing casual associations between cases of reproductive dysfunction and ΣPCBs concentration due to the female's capability in offloading lipophilic pollutants (Murphy et al., 2015). However, 47% of females had ∑PCB concentrations above Kannan's threshold for the onset of adverse health effects, which included 52% of sexually immature and 53% of resting (not pregnant or lactating) mature individuals. Resting females were more likely to have higher ΣPCB burdens than other maturity groups (apart from sexually immature individuals), and where data

were available, these nonoffloading females were previously gravid, which suggests fetal or newborn mortality (Murphy et al., 2015).

Above all, these studies on cetaceans have not shown a cause-effect relationship related to a particular mechanism, nor a causal relationship between an observed disorder and exposure to certain OCs (Reijnders, 2003). A semifield experimental study on harbor seals (*Phoca vitulina*) did show a possible mechanism for reproductive failure following exposure to PCBs. Between the 1950s and 1970s, average pup production declined by c. 30% in harbor seals inhabiting the Dutch Wadden Sea, and PCB concentrations were significantly higher (by five to seven times) than contiguous populations (Reijnders, 1980). In an experimental setup, seals fed fish from the Wadden Sea showed a decreased reproductive rate (by 50%), and lower levels of oestradiol-17β around the time of implantation, compared to a control group (Reijnders, 1986). Mean PCB levels in the control group ranged from 5 to 11 mg/kg lw, compared to 25–27 mg/kg lw in seals fed contaminated fish (Pierce et al., 2008). Lower levels of estradiol could have impaired endometrial receptivity and prevented successful implantation of the blastocyst, and it was proposed that enhanced OC-induced CYP enzyme activity may have lowered circulating estradiol (Reijnders, 2003). Exposure to PCBs has also been linked to the development of genital cancer in California sea lions (*Zalophus californianus*). A metastatic genital carcinoma was reported in 18% (66 of 370 individuals) of stranded sexually mature individuals between 1979 and 1994 (Gulland et al., 1996; Lipscomb et al., 2000). The cause of urogenital carcinoma in the species is multifactorial, and possible potential causal factors include an otarine herpesvirus-1 (Buckles et al., 2006; King et al., 2002) and infection with β-haemolytic streptococci (Johnson et al., 2006), and it has been proposed that there is a genetic basis as a result of inbreeding depression (Browning et al., 2017). Exposure to pollutants may be an additional factor, as a higher mean concentration of OCs was reported in blubber tissue of females with genital carcinoma relative to those without genital carcinoma (>85% and 30% higher in relation to PCBs and DDT, respectively; Ylitalo et al., 2005). This demonstrates an association between OCs and carcinoma, through possibly affecting the prevalence of carcinomas by acting as immunosuppressive agents or by genotoxic mutation and tumor promotion (Ylitalo et al., 2005). A follow-up study suggested that OCs interact with steroid hormone receptors in the intraepithelial lesions and that alternations in the expression of p53 may also play a role (Browning et al., 2017; Colegrove et al., 2009).

CASE STUDY OF SHORT-BEAKED COMMON DOLPHIN IN THE NORTHEAST ATLANTIC

Within the Northeast Atlantic, a large proportion of necropsied short-beaked common dolphins presented with blubber PCB burdens exceeding Kannan's threshold level for the onset of adverse physiologic health effects (Murphy et al., 2010).

Similar to harbor porpoises in the region, the short-beaked common dolphin Northeast Atlantic population exhibits a lower pregnancy rate and longer calving interval than other conspecific populations, which could be resulting from PCB-mediated effects (Murphy et al., 2009, 2010).

Short-beaked common dolphins are widespread in the Northeast Atlantic, ranging from waters off Norway to Africa. One population has been reported to exist ranging at least from Scotland to Portugal, with a separate population in the Mediterranean Sea (Mirimin et al., 2009a,b; Murphy et al., 2009, 2013; Natoli et al., 2008). Common dolphins have been observed out to the Mid-Atlantic Ridge, but due to a lack of genetic sampling in offshore waters, the range of the Northeast Atlantic population is unknown (Murphy et al., 2013). The most recent abundance estimate from SCANS III suggests at least 467,673 dolphins (CV = 0.26) in continental shelf and adjacent waters (Hammond et al., 2017). Female common dolphins in the population attain sexual maturity at an average length of 188.8 cm and an average age of 8.2 years, with a maximum age of 30 years and a low annual pregnancy rate of 26% reported (Murphy et al., 2009, 2010).

Previous research assessing reproductive effects from exposure to POPs in the region reported that individual feeding history (proxied by blubber fatty acid profiles) was the most important variable explaining individual POP profiles (Pierce et al., 2008). This former EU Fifth Framework funded study called BIOCET analyzed samples collected from stranded and bycaught common dolphins in Irish, Scottish, French, and (Galician) Spanish waters during the period 2001–03. Common dolphins sampled in both French and northwestern Spanish waters had significantly higher PCB concentrations than Irish animals; however, the Galician common dolphin pollutant sample was mainly composed of sexually immature females that had not offloaded their pollutant burdens (>65%). Within the whole mature sample, incidences of pregnancy in individuals was negatively related to blubber PCB and polybrominated diphenyl ether concentrations, which may suggest that higher POP concentrations were inhibiting successful reproduction, though infertility due to other causes may have caused higher POP levels to bioaccumulate (Pierce et al., 2008).

Further analysis of BIOCET data revealed that ovarian corpora number (corpus luteum and albicans) significantly increased with PCB burdens in sexually mature *D. delphis* (Murphy et al., 2010). Approximately 83% of female common dolphins with PCB concentrations exceeding Kannan's threshold level for the onset of adverse physiologic health effects were resting mature individuals with high numbers of ovarian corpora. This suggests that due to high contaminant burdens, females were unable to successfully reproduce (offload) and thus continued ovulating; or some females were not reproducing for other reasons, either physical or social, and therefore accumulated higher levels of PCBs (Murphy et al., 2010). Within the BIOCET sample, 92% of sexually mature (all but two were resting) female common dolphins with PCB burdens above Kannan's threshold level and corresponding high corpora counts (≥15

scars) were obtained from a mass live stranding event of a nursery group at Pleubian, France, in February 2002. Genetic analysis of this nursery group did not reveal evidence for a matriarchal system, as a lack of genetic relatedness among mature individuals was reported (Viricel et al., 2008). The existence of nonreproductive females (based on high contaminant loads and high numbers of ovulations) within this nonmatriarchal female nursery group is remarkable; though, it should be noted that only 52 of the whole mass-stranded group was sampled for genetic analysis, and approximately 50 other individuals were released alive offshore (Viricel et al., 2008).

For animals that stranded as part of the Pleubian mass stranding event, there are no available data pertaining to assessments of previous gravidity or general health status. The possibility of either social or pollutant suppression of reproduction in common dolphins was investigated further using a control group composed of stranded and bycaught individuals collected in English and Welsh waters (Murphy et al., 2010). The control group was composed of "healthy" common dolphins, and in contrast to the BIOCET, common dolphin data results revealed a negative relationship between PCBs and DDT concentrations and increasing corpora number. This suggests that some "healthy" females may go through a large number of (infertile) ovulations prior to a successful pregnancy, birth, and survival of their firstborn offspring during early lactation, when females offload the majority of their OC burden (Murphy et al., 2010).

The current case study aims to further examine the effects of pollutants such as PCBs on reproduction in common dolphins in the Northeast Atlantic using stranded and bycaught animals sampled in English and Welsh waters. Evidence of reproductive failure and reproductive dysfunction, such as abnormalities and disorders, will be assessed, and their association with exposure to PCBs will be investigated.

Study Design

Stranded and bycaught common dolphins were collected and necropsied between 1990 and 2013 by the UK Cetacean Strandings Investigation Programme (CSIP). All animals were in fresh-to-moderate decomposition on necropsy. Cause of death (COD) was determined by specific diagnostic criteria (see Deaville and Jepson, 2011; Jepson et al., 2005), and individuals were categorized into three COD groups: infectious disease, trauma (bycatch, boat/ship strike, bottlenose dolphin attacks, and dystocia), and others (live stranding, starvation, neoplasia, and not established) (after Murphy et al., 2015). Age was determined by counting growth layer groups in the dentine of teeth samples (after Murphy et al., 2014).

Fixed ovarian samples were assessed externally for the presence of ovarian corpora then hand-sectioned into 0.5–2 mm slices and examined internally under a binocular microscope for the presence of additional corpora scars. Total numbers of corpora (number of ovulations) were counted, which was used as an

index of reproductive activity (after Murphy et al., 2010). Females were classified as sexually mature if one or more ovarian corpora (corpus luteum or albicans) were present. Pregnancy was established by the presence of an embryo/fetus and an active (nonregressing) corpus luteum, confirmed by histological assessment. Mammary glands were examined for evidence of lactation via gross examination and, in some individuals, histological assessment of mammary gland tissue. Females were classified into five reproductive states: (1) sexually immature, (2) pregnant (fetus present), (3) pregnant and lactating, (4) sexually mature and lactating, and (5) resting mature (not pregnant or lactating) (after Murphy et al., 2010).

The reproductive tracts were assessed for abnormalities and evidence of sterility and infertility, including tumors, uterine stenosis, occlusions and leiomyomas, endometriosis, and vaginal calculi. Ovaries were examined for ovarian cysts and tumors through gross and histopathological assessment. The sample was also assessed for evidence of hermaphroditism and other disorders of genital development. Ovarian lesions and other abnormalities were measured, and shape, color, texture, and position were recorded. Assessment of previous gravidity in mature females and cases of reproductive failure (including fetal death, dystocia and stillborn, recently aborted and aborted, and her calf did not survive) followed classifications outlined in Murphy et al. (2015). Incidences of disease and infection of the reproductive system were confirmed by bacteriology, virology, and histopathology assessments.

Dorsal blubber samples were analyzed by the Centre for Environment, Fisheries, and Aquaculture Science Laboratory for quantification of hexane extractable lipid and wet weight concentrations of 25 individual chlorobiphenyls, and the sum of the concentrations of these chlorobiphenyl congeners (ΣPCB mg/kg lw) was determined (see Jepson et al., 2016; Law et al., 2012; Murphy et al., 2015 for further information). Two toxicity thresholds were applied to the pollutant data, after Jepson et al. (2016). Toxicity threshold concentration was 9 mg/kg lw (as ΣPCB; determined by Jepson et al., 2016) for the onset of physiologic (immunological and reproductive) endpoints in marine mammals (Kannan et al., 2000), and one of the highest PCB toxicity thresholds reported in marine mammal toxicology studies, 41 mg/kg lw (determined for ΣPCB by Jepson et al., 2016 and based on 77 mg/kg for *Clophen 50*), was associated with profound reproductive impairment in Baltic ringed seals (*Pusa hispida*) (Helle et al., 1976). A high prevalence of reproductive tract lesions were observed in Baltic seals, including both ringed and grey seals (*Halichoerus grypus*), during the 1970s and 1980s. These lesions included occlusions and stenosis of the uterine horns (42% of grey seals) and benign uterine leiomyomas (53% of grey seals >4 years) (Bergman, 1999; Bredhult et al., 2008; Helle et al., 1976), which rendered females partially or completely sterile for life (Reijnders, 2003). As some females retained fetal membranes aligned to stenosed sections of the uterine horns, obtrusions may have developed as a result of PCB (or PCB metabolites) induced abortions, or fetal death (Bergman, 2007; Bergman and Olsson,

1985; Helle et al., 1976), and in some seals presenting with obtrusions, purulent endometriosis was also reported (Bergman, 2007). However, unequivocal evidence for a cause-effect relationship was not provided (Reijnders, 2003). Follow-up work using an exposure index indicated that PCBs, more than DDT, were associated with the increased incidence of uterine leiomyomas in Baltic grey seals (Bredhult et al., 2008).

Incidences of Reproductive Abnormalities and Disorders in Common Dolphins

A sample of 107 female common dolphins that stranded along the English and Welsh coastlines were assessed for evidence of reproductive failure and dysfunction. Samples included those from animals that died during a mass live stranding event that occurred in the southwest of the United Kingdom in 2008 ($n=13$ females; Jepson et al. 2013) and a control group of "healthy" female *D. delphis* ($n=43$) collected between 1992 and 2004 along the southwest of the United Kingdom (previously assessed by Murphy et al., 2010). The control group was composed of stranded females whose COD was attributed to incidental capture in fishing gear. Routine general health status assessments revealed that individuals were not suffering from any infectious or noninfectious diseases that might inhibit reproduction (Murphy et al., 2010). The remaining dolphins stranded between 1990 and 2013 ($n=51$) had causes of death that were attributed to trauma ($n=17$), infectious disease ($n=2$), other ($n=26$), or were not established ($n=6$).

Of the 107 animals, 44 were sexually immature and 63 were sexually mature. No incidences of uterine stenosis, occlusions, or leiomyomas were observed within the common dolphin sample (reproductive toxicologic endpoints previously reported in Baltic seals) (Bergman, 1999; Helle et al., 1976). However, 18 proposed cases (16.8% of the whole sample) of reproductive system pathologies were identified. Six females presented within vaginal calculi (5.6%), six females exhibited suspected precocious mammary gland development (5.6%), and there were three possible cases of ovarian tumors (2.8%) (see Table 1.2). The three cases of ovarian neoplasms include a possibly fibroma, a well-differentiated granulosa cell tumor, and a rare case of either a mesothelioma or Schwannoma tumor. In addition to the preceding, females presented with an ovarian cyst, atrophic ovaries, and the first reported case of an ovotestis in a cetacean species. In the majority of cases of reproductive dysfunction, available blubber ΣPCB data were above the toxicity threshold concentration of 9 mg/kg lw (Table 1.2). The only other study assessing evidence of disease and lesions of the reproductive tract in common dolphins was undertaken on the long-beaked common dolphin (*D. capensis*) in the southeast Pacific. Within a sample of 24 bycaught females (14 mature and 10 immature), one case of reproductive dysfunction was observed, which was a case of ovarian cysts (a prevalence of 4.2% of the whole sample; Van Bressem et al., 2006).

TABLE 1.2 Abnormalities and Dysfunction of the Reproductive System in 107 UK Female *D. delphis* Sampled Between 1990 and 2013

Abnormality	Code	COD	Body Length (cm)	Age (year)	Maturity Status	Corpora Scar No.	Previously Gravid	ΣPCB lw
Reproductive Tract								
Vaginal calculi	SW1993/43	BY	195	7	Immature	0	No	27.5
Vaginal calculi	SW1995/4	NE	207	>7	Resting mature	13	NA	NA
Vaginal calculi	SW1996/98	NE	201	>18	Resting mature and lactating	23	Yes	NA
Vaginal calculi	SW2004/131	BY	205	>10	Resting mature	c.34	Yes	41.1
Vaginal calculi	SW2004/336	LS	196	25.5	Resting mature	19	Yes	NA
Vaginal calculi	SW2005/65	LS	196	>10	Resting mature	21	Yes	49.5
Suspected precocious mammary gland development	SW1994/160	BY	177		Immature	0	No	39.2
Suspected precocious mammary gland development	SW2008/94.3	LS	163	3	Immature	0	No	17.6
Suspected precocious mammary gland development	SW2008/94.4	LS	185	5	Immature	0	No	19.4

Precocious mammary gland development	SW2008/94.15	LS	169	7	Immature	0	No	5.72
Precocious mammary gland development	SW2011/562	LS	183	NA	Immature	0	No	14.7
Suspected precocious mammary gland development	SW2013/594	LS?	143	1	Immature	0	No	13.44
Ovary								
Possible granulosa cell tumor	SW1994/24	NE	174	2	Immature	0	No	22.6
Possible fibroma	SW1994/147	BY	192	c. 14	Resting mature	12	Yes	NA
Mesothelioma or Schwannoma tumor	SW1998/148	LS	209	24	Resting mature	26	Yes	48.5
Ovarian cyst	SW2005/2	LS	195	19	Resting mature	27	Yes	26.1
Ovotestis	SW2006/298a	NE	191	6	Immature	0	No	NA
Atrophic ovaries	SW2008/94.11	LS	206	18	Immature	0	No	45.4

BY, bycatch; *COD*, cause of death; *LS*, live stranding; *NA*, not available; *NE*, not established.

Cases of ovarian neoplasms in cetaceans are infrequently reported, with the majority being granulosa cell tumors, the archetypal feminizing sex cord-stromal tumor with cells resembling those of follicular granulosa or luteinized variants (Russell et al., 2009) (see Table 1.1). Other cases of reported cetacean ovarian neoplasms include a dysgerminoma and a mucinous cystadenoma, originating from germ and epithelial cells, respectively. In the current study, a possible ovarian fibroma, benign sex cord-stromal tumor, was observed in SW1994/147. The tumor measured 20 mm × 25 mm and consisted of reddish/black tissue resembling splenic tissue in gross appearance. The ovoid mass was attached to the hilus of the right ovary by a band of mesothelial connective tissue. Fibrous stroma, comprising the core of the mass, was moderately vascular and composed of spindle-shaped or more ovoid and irregular fibroblastic cells frequently orientated at random. These cells were densely packed toward the periphery of the mass and more loosely arranged centrally. Tissue autolysis and poor staining made final diagnosis uncertain. The individual in question was a bycaught 14-year-old resting mature female in moderate nutritional condition.

SW1994/24, a 2-year-old female common dolphin, presented with a well-differentiated granulosa cell tumor in one ovary. The ovarian stroma had many primary follicles and a few secondary follicles, and it contained a vaguely wedge-shaped zone of tissue opposite the hilus that showed irregular tubule-like structures lined with a single layer of polygonal to columnar cells (Murphy et al., 2018b). The tumor was unilateral, as a transverse cross-section of the contralateral ovary revealed only normal follicular development within the ovarian stroma. A third ovarian neoplasm was reported in SW1998/148, a resting mature female that live stranded in moderate nutritional condition. The ethology of the observed tumor on the left ovary remains ambiguous due to few typical histological features and atypical immunostaining patterns, which are common for very poorly differentiated tumors (Murphy et al., 2018b). Results from histological examination and the presence of psammoma bodies indicates either a mesothelioma or Schwannoma tumor, though other tumors types were not ruled out (Murphy et al., 2018b).

The first reported case of an ovotestis in a cetacean species was observed within the sample. A 6-year-old sexually immature female (external phenotype and female reproductive tract) common dolphin (SW2006/298a) that was found stranded on the southwest coast of the United Kingdom was diagnosed as a true hermaphrodite (Murphy et al., 2011). The individual in question had one ovotestis containing both ovarian follicles and testicular tubular elements and a contralateral ovary. Ovarian portions of the ovary appeared normal, demonstrating follicular development, but the testicular tissue tubular elements observed in the medulla (6.8 mm × 5.5 mm) presented with hypoplasia and degeneration (Murphy et al., 2011). COD for this female was not fully established due to scavenger damage, though incidental capture in fishing gear was not ruled out. It is not known if this disorder of genital development was due to abnormalities of genetic or chromosomal origin or inappropriate hormone exposure: blubber samples were not available for retrospective pollutant analysis.

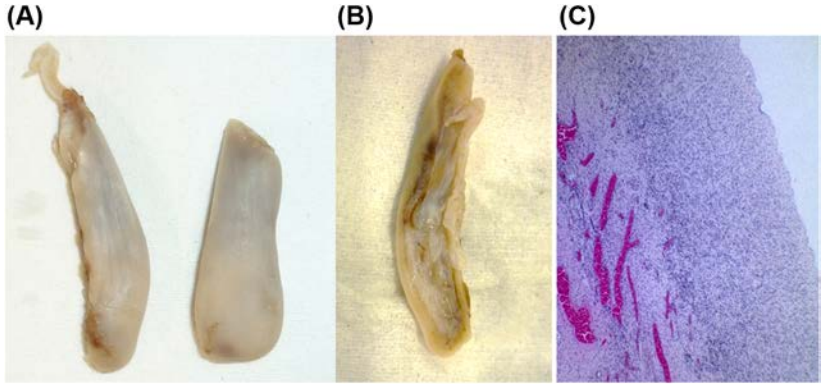

FIGURE 1.2 (A and B) Atrophic ovaries in a 17-year-old common dolphin (SW2008/94.11) that stranded as part of a mass live stranding event in 2008. Note a lack of follicles in the stroma in image (C).

A female common dolphin (SW2008/94.11) from the mass live stranding event sample presented with atrophic ovaries, with only a few follicles present in both ovaries (Fig. 1.2). Although the female was 18 years old, the lack of follicles was not attributed to reproductive senescence, as no ovarian corpora (corpus luteum or albicans) were present. This sexually immature individual was in good nutritional condition and health status, though it presented with a ΣPCB burden of 45.4 mg/kg, which is greater than the threshold for profound reproductive impairment in Baltic ringed seals. Reproductive senescence is rarely observed in cetaceans (Hohn et al., 2007), and not in common dolphins (Murphy et al., 2009). Studies on cetaceans have rarely reported a lack of ovarian follicles or pathologic changes that would result in senescence (Hohn et al., 2007).

A large, thin-walled fluid-filled cyst was noted on the lateral aspect of the left ovary of SW2005/2 (Fig. 1.3). The right ovary exhibited signs of hypostasis with noted congestion, which may be due to the live stranding event. The maximum length of the cyst was c. 47 mm, while the maximum length of the left ovary was only 43 mm, and ovaries presented with a corpora count of 24. This 19-year-old resting mature dolphin was in good nutritional condition, though live stranded in the month of January, i.e., outside the mating period. Nothing abnormal was detected in the uterus or vagina upon gross assessment. The prevalence of ovarian cysts in the mature sample was 1.7%. Ovarian cysts, such as follicular and luteinized cysts (though mainly the former), have been reported in the ovaries of the striped dolphin, long-beaked common dolphin, dusky dolphin (*Lagenorhynchus obscurus*), Pacific white-sided dolphin (*Lagenorhynchus obliquidens*), short-finned pilot whale (*Globicephala macrorhynchus*), and southern minke whale (*Balaenoptera bonaerensis*), among others (Lockyer, 1987; Marsh and Kasuya, 1984; Munson et al., 1998; Robeck et al., 2009; Van Bressem et al., 2000). In cattle, deviation of the preovulatory

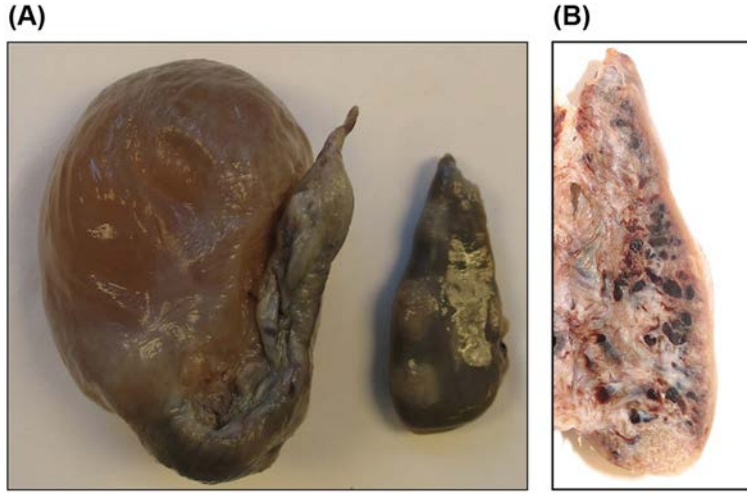

FIGURE 1.3 (A) Lateral fluid-filled ovarian cyst on the left ovary of live stranded common dolphin SW2005/2; cyst measured 47 mm in length; (B) cross-section of congested right ovary.

surge of luteinizing hormone, either the absence or mistiming of the surge, is thought to cause follicular cysts (Kennedy and Miller, 1993; McEntee, 1990; Van Bressem et al., 2006). Though the cyst observed in the current study was not luteinized, luteinized cystic follicles have been known to produce estrogen and progesterone (Robeck et al., 2001).

Of the 107 female common dolphins assessed within the current study, six presented with vaginal calculi within their reproductive tracts (see Table 1.2). These included one sexually immature, four resting mature, and one sexually mature and lactating individual. Corpora count numbers ranged from 13 to 34 in mature individuals presenting with calculi. As common dolphins can possibly ovulate up to five times within one estrus period and have a reproductive lifespan of between 10 and 20 years (Murphy, 2004; Murphy et al., 2009, 2010), this suggests that reproductive dysfunction (large number of ovulations without fertilization) may have occurred in some individuals, conceivably due to the relative size of the calculi (100–490 g within the same) causing an occlusion of the reproductive tract. Some vaginal calculi in cetaceans are believed to represent an incomplete abortion, with retention of part or all of a fetus that subsequently crystallized and coalesced (Benirschke et al., 1984; Woodhouse and Reinne, 1991). Others are possibly produced by a fetal bone that acted as a nidus for calcium phosphate deposition (Benirschke et al., 1984; Woodhouse and Reinne, 1991).

SW2004/131, a bycaught resting mature female who presented with a calculi and evidence of previous gravidity, had the highest corpora count within the whole sample. This bycaught female was in good nutritional condition and health status, though it exhibited adrenal cysts (bilateral). ΣPCB burden in this

individual was high at 41.1 mg/kg, suggesting this mature female may never have offloaded her pollutant burden via transplacental and lactational transfer. In SW1996/98, the anterior vagina contained five highly polished faceted calculi that could be assembled into an egg-shaped mass, and analysis revealed they were mainly composed of phosphate salts. Baker (1992) noted a vaginal calculus in a UK common dolphin collected prior to 1992, which was also composed of phosphate salts. Within the current study, a sexually immature female common dolphin (SW1993/43) bore a calcified body within her vagina. This 7-year-old bycaught individual was in good nutritional condition, though it had a high ΣPCB burden (27.3 mg/kg), and its ovaries were heavily congested. This is not the first study to report a vaginal calculus in a sexually immature cetacean. Van Bressem et al. (2000) observed a struvite (not calcium phosphate) calculus in an immature Peruvian dusky dolphin, and suggested an infectious etiology. McFee and Osborne (2004) also reported that a urinary tract infection might have been the underlying cause of a struvite (magnesium-ammoniumphosphate hexahydrate) calculus observed in the vagina of a sexually immature 4-year-old bottlenose dolphin. The presence of struvite calculi (>30) was also reported in a 1-year-old harbor porpoise, which was attributed to mucosal hyperplasia of the distal urogenital tract (Norman et al., 2011).

Six sexually immature females presented with precocious mammary gland development, with individuals ranging in age from 1 to 7 years. Interestingly, three of these dolphins (SW2008/94.3, SW2008/94.4, SW2008/94.15) mass live stranded together in 2008, possibly due to naval activity in the region causing an acoustic disturbance (Jepson et al., 2013). A small quantity of yellow viscous (colostrum-type) milk was present in the mammary glands of all three females, and histological examination revealed mature and minimally lactating mammary gland tissue in the 7-year-old SW2008/94.15, not assessed in the other two dolphins. Premature mammary gland development has been linked to (gestational) pollutant exposure in other animals, including precocious mammary gland development in immature female rats (Fenton, 2009; Moon et al., 2007). Although not all individuals were fully assessed, three cases of mastitis were observed in the sample. SW1996/114, a sexually immature female, presented with mild, multifocal, subacute-chronic mastitis. SW2002/224, another immature individual, presented with enlarged mammary glands and purulent mastitis arising from an infection near the mammary gland tissue. Finally, multifocal chronic inflammation of the lactiferous ducts (mastitis) was observed in a nonlactating mature common dolphin (SW1999/15).

Effects of Contaminants on Reproduction in Common Dolphins

Within the control group of "healthy" bycaught females, all ovarian corpora (lutea and albicantia) were assessed, counted, and where uncertainties existed, verified through histological examination, so the reproductive status of some females has been updated since Murphy et al. (2010). The sample of 43

"healthy" females was composed of 20 immature, 11 resting mature, 1 primiparous pregnant (ovaries contained only one corpus, which was a corpus luteum), 2 pregnant and lactating, 7 mature and lactating, and 2 nonlactating primiparous females that had recently miscarried/aborted. Histological examination of corpora lutea of pregnancy in both females that had recently miscarried/aborted showed clear evidence of regression, with a reduction in luteal cells and an increase in fibrotic connective tissue. Animals had recently miscarried/aborted during what would have been their second trimester based on a mean date of conception of the 19th July and a gestation period of 0.99 years for common dolphins in the Northeast Atlantic (Murphy et al., 2009).

All sexually immature (nulliparous) females (range 10.5–52.9 mg/kg lw), the "primiparous" pregnant female (44.8 mg/kg lw), and the two primiparous females that had recently miscarried/aborted (range 19.1–28.3 mg/kg) had blubber ΣPCB concentrations above the threshold level of 9 mg/kg lw for the onset of adverse health effects (Fig. 1.4A). Other "healthy" females with ΣPCB burdens above this threshold were resting females. Sexually mature females with levels above the 41 mg/kg threshold in the control sample where were either resting ($n=3$) or pregnant ($n=1$), and all three resting females had been previously gravid; and based on the high PCB burden, these females either aborted or their newborn offspring did not survive during early lactation. In common dolphins, an assessment of transfer rates of OC compounds was undertaken on one mother-calf pair, and it was estimated that 41.48% of total PCBs (and 55.41% of total DDT) were offloaded during the first half of lactation, and that complete transfer of the OC burden would possibly occur by the end of lactation (Borrell and Aguilar, 2005). All nine lactating females (i.e., females who successfully reproduced and offloaded) had ΣPCB concentrations ≤10.5 mg/kg, and eight of those females presented with concentrations ≤5.8 mg/kg. A negative relationship was observed between ΣPCB concentration and increasing corpora number in the control group of "healthy" females (see Fig. 1.4A), which suggests that some females may successfully reproduce and offload their pollutant burden after many unsuccessful ovulations/miscarriages and/or early calf mortality.

The noncontrol pollutant sample ($n=19$) comprised nine sexually immature, four resting, five lactating, and one primiparous pregnant female. In contrast to the control sample, a positive relationship was observed between ΣPCB concentration and increasing corpora number (see Fig. 1.4B), which were comparable results to the earlier BIOCET/Pleubian mass stranding pollutant study. What data in the current study suggest, however, is that PCBs may be impacting fetal/newborn survival, similar to that proposed for UK harbor porpoises (Murphy et al., 2015), and high ΣPCB burdens are not due to reproductive suppression of nonbreeding females. All four resting females in the noncontrol sample had a high number of ovarian corpora scars and ΣPCB concentrations ≥26 mg/kg; and of these individuals, three females presented with ΣPCB concentrations ≥41 mg/kg. Pollutant data suggest that these four resting females had not successfully reproduced (offloaded) in the past, though all were previously gravid. Further,

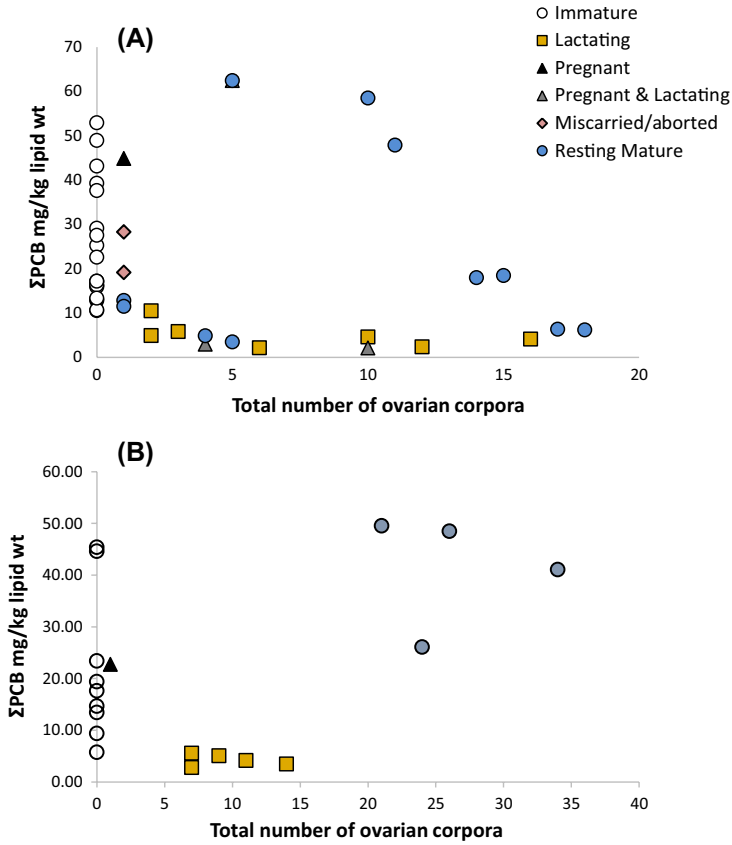

FIGURE 1.4 Blubber Σ25PCBs lipid weight as a function of ovarian corpora number in (A) *D. delphis* control group sample ($n=43$ bycaught individuals) and (B) *D. delphis* noncontrol sample ($n=19$).

all four resting females presented with reproductive system pathologies, including an ovarian tumor ($n=1$; SW1998/148), ovarian cyst ($n=1$; SW2005/2), and vaginal calculi ($n=2$; SW2004/131, SW2005/65); the calculi observed in these mature females may have impeded reproduction. The primiparous pregnant female (SW2011/295) was 6 years old and had a ΣPCB pollutant burden of 22.7 mg/kg lw. She presented with a male fetus measuring 88 cm in length in the left uterine horn and a dilated cervix. The female live stranded in the month of July, which may have been associated with an attempt to give birth to a full-term fetus.

Of the 13 females that mass live stranded together in Cornwall in 2008, blubber samples from 10 individuals were processed for pollutant analysis. The sample comprised five sexually immature and five sexually mature females. All five mature females were heavily lactating and presented with low ΣPCB

pollutant burdens (<6 mg/kg lw). Three of the immature females presented with suspected precocious mammary gland development and blubber ΣPCB concentrations ranging from 5.7 to 19.4 mg/kg. A fourth immature female was 18 years in age and presented with atrophic ovaries and a high ΣPCB burden of 45.5 mg/kg. Thus, 31% of females assessed from this mass stranding event sample presented with suspected reproductive system pathologies.

PCB and Reproductive Implications for Common Dolphins

16.8% (18 out of 107) of female common dolphins presented with reproductive system pathologies. As 40% of the sample was composed of a control group of "healthy" bycaught animals, the incidences of abnormalities and disorders reported here may be somewhat lower than what is occurring within the wider population. Even so, the current study reported a higher incidence of reproductive system pathologies than observed for other small cetacean species elsewhere. One such similar study assessed for evidence of genital diseases in 264 Peruvian female dusky dolphins. Eleven mature females (4.1% of the whole sample) presented with an ovarian tumor, ovarian cysts, and uterine tumors, and a further three individuals (1.1% of whole sample) presented with vaginal calculi. A vaginal mass was also observed close to the left ovary in another mature female containing the skull of a fetus (Van Bressem et al., 2000). Van Bressem et al. (2000) attributed some of their cases of genital disease in dusky dolphins to reproductive senescence, as animals were large in size: age data were not available for all individuals.

Overall, there have been a relatively low number of reported incidences of neoplasms in cetaceans, resulting from either not being assessed due to autolytic changes or other reasons, animals dying without pathologic investigations, or individuals dying before attaining an older age, namely when most cancers occur (Newman and Smith, 2006). In humans, cancers increase in occurrence with age due, in some cases, to cellular changes and damage (DeGregori, 2012). The age profile of individuals assessed within the current study ranged from neonates to 30 years ($n=77$), though 87% were ≤20 years old. Of the female common dolphins showing evidence of ovarian lesions, individuals ranged from 2–24 years in age. However, many pathologies were reported in sexually immature females, including an ovarian granulosa cell tumor, ovotestis, atrophic ovaries, and precious mammary gland development, which suggests inherited and/or environmental causes.

As noted earlier in the chapter, a recent study on harbor porpoises in UK waters reported that at least 16.5% of females assessed had infections of the reproductive tract or tumors of reproductive tract tissues (Murphy et al., 2015). The number of cases of reproductive system pathologies was only a minimum estimate, as the study did not include occurrences of ovarian tumors and other ovarian disorders that were under investigation. Apart from ovarian abnormalities and lesions, vaginal calculi, precious mammary gland development, and

mastitis, no other infections, diseases, or lesions of the reproductive tract were observed in female common dolphins in the current study. Results differing somewhat to harbor porpoises in the same region where cases of endometriosis, vaginitis, lesions of the vagina, uterus, and clitoris, as well as malignant tumors of the reproductive tract (such as squamous cell carcinoma of the cervix, uterine adenocarcinoma, and metastasizing adenocarcinoma) and benign tumors (including clitoral and vaginal papilloma-like lesions, vaginal epithelial plaques, and vaginal wall leiomyoma) were observed (Murphy et al., 2015). In contrast, lesions of the reproductive system were very rare in female harbor porpoises sampled from German waters, with one case of suppurative endometritis reported (Siebert et al., 2001).

High ΣPCB burdens were not inhibiting ovulation, conception, or implantation in common dolphins, as (all except one sexually immature [nulliparous] female and) the four primiparous females in the control and noncontrol samples had ΣPCB levels above the threshold level for the onset of adverse health effects (Murphy et al., 2010; current study). PCBs, however, may be impacting fetal and newborn survival, as some previously gravid resting females had not successfully offloaded their pollutant burdens. After removing the possible effects from stressors such as nutritional and immune issues (93% of individuals were regarded as "healthy" and were overall in good to moderate nutritional condition (Murphy et al. (2010)), evidence of reproductive failure was assessed both directly (e.g., through observations of fetal death/abortion) and indirectly by using individual ΣPCB burdens, after Murphy et al. (2015). Using these data, results suggested that reproductive failure could have occurred in approximately 30% (7 of 23) of mature females sampled in the control study. This was based on that fact that all lactating females (control and noncontrol samples) had ΣPCB burdens ≤10.5 mg/kg. Thus, resting females with pollutant loads >10.5 mg/kg more than likely had not successfully offloaded in the past, and where data were available, these females were previously gravid. Additionally, 8.7% of mature females in the control study showed evidence of recent miscarriage/abortion during their second trimester. The association between higher contaminant burdens in these females and incidence of miscarriage/abortion during the second trimester cannot be discounted.

ΣPCB concentrations in previously gravid resting females ranged from 17.9 to 62.4 mg/kg ($n=9$) in both the control and noncontrol samples, and six of these females had ΣPCB burdens greater than the 41 mg/kg threshold. The presence of vaginal calculi in five resting females may further signify reproductive failure, if they result from an incomplete abortion. Elevated ΣPCB levels may impact uterine and placental health in cetaceans and, subsequently, fetal health and survival (Hohn et al., 2007; Murphy et al., 2010). Further, higher (gestational and lactational) exposure to PCBs in firstborn offspring may increase incidences of mortality in those individuals (Wells et al., 2005). In mink (*Mustela vison*), although ovulation, conception, and implantation occurred, similar to the current study, PCBs (as Clophen A50)

increased fetal mortality through causing pathologic changes in the maternal vasculature in the placenta and degenerative changes in the trophoblast and fetal vessels (Bäcklin et al., 1997, 1998). A more recent experimental study focusing on effects from dietary consumption of Aroclor 1268 (dioxin-like PCBs were less prevalent, and it was the most highly chlorinated Aroclor manufactured) on mink reported that mean litter size, kit growth, and kit survival were the main reproductive and growth endpoints that were affected (Folland et al., 2016). As previously documented, female mink continued to reproduce, even at higher exposure concentrations to the chemical mixture. Whereas in harbor seals, experimental studies have shown that the effects from PCB exposure on reproduction occur at the stage of implantation, while the follicular, luteal, and postimplantation phases were not affected (Reijnders, 2003). Since pinnipeds experience delayed implantation/embryonic diapause, they may be more vulnerable than cetaceans at this stage of the reproductive cycle (Murphy et al., 2010).

Common dolphins are not as heavily parasitized as harbor porpoises in the Northeast Atlantic (Jepson, 2005; Pierce et al., 2008), and they did not show a change in nutritional condition during the period 1990–2006 (Murphy et al., 2009). Harbor porpoises are relatively small cetaceans, and individual health status often presents energetic "knife-edge" conditions that can be exacerbated by adding further health complications caused by exposure to anthropogenic pollutants (Murphy et al., 2015). For example, a significant positive association was observed between PCB levels and the number of gastric nematodes in UK harbor porpoises with blubber PCB concentrations >25 mg/kg (ΣPCB) (Bull et al., 2006). As noted earlier, a high incidence of reproductive failure was observed in UK harbor porpoises, with reproductive failure reported to occur in 39% or more of mature females sampled (calculated based on direct evidence such as fetal death and indirectly by using individual PCB burdens). Female health status played an important role in reproductive failure, as 86% of cases of fetal death/spontaneous abortion were observed in females that died from infectious disease or other causes such as starvation and neoplasia. PCBs may be impacting reproduction function indirectly in porpoises through lowering their immunity and increasing susceptibility to diseases (Jepson et al., 2005; Murphy et al., 2015). Terminations during late gestation can incur severe health and reproductive costs, and all reported cases of fetal death/spontaneous abortion in UK harbor porpoises occurred after the first semester (Murphy et al., 2015), similar to the current study. PCBs have been proposed to impact immune function in UK harbor porpoises (Jepson et al., 2005), where the average increase in risk of infectious disease mortality was 2% for each 1 mg/kg increase in blubber PCBs, with a 50% increase in risk occurring around 45 mg/kg lw (Hall et al., 2006a). Female UK harbor porpoises with higher PCB concentrations died due to ill health, as 92% of stranded individuals with ΣPCB concentrations >20 mg/kg died as a result of infectious disease or "other" causes such as starvation (Murphy et al., 2015).

When applying the toxicity thresholds to all available ΣPCB data for common dolphins in the Northeast Atlantic sampled between 1990 and 2013 ($n = 183$), 76% of sexually immature males and females had ΣPCB levels above the 9 mg/kg threshold for onset of adverse health effects in marine mammals, and 17% had levels greater than one of the highest toxicity thresholds for marine mammals, 41 mg/kg. ΣPCB ranged from 1.1 to 95.9 mg/kg in sexually immature individuals. Fifty percent of mature males (five out of ten) had blubber ΣPCB concentrations above the 41 mg/kg threshold for profound reproductive effects in female seals (Fig. 1.5). Although the sample size for mature males was small, mean ΣPCB was 45.8 mg/kg, and concentrations ranged from 7.0 to 119.8 mg/kg lw: the highest ΣPCB concentrations were observed in a male stranded in 1992. Males were unable to rid themselves of their lipophilic pollutant burden and accumulated high PCB concentrations, the effect of which is not fully understood in male cetaceans, as very few studies have been undertaken and none on *D. delphis*. One such study reported a negative correlation between testosterone levels and tissue concentrations of DDE in Dall's porpoise (*Phocoenoides dalli*) (Subramanian et al., 1987). It has been suggested that EDCs can cause male disorders such as reduced semen quality, urogenital tract abnormalities (e.g., cryptorchidism, hypospadias, testicular cancer), and altered timing of puberty (reviewed in Diamanti-Kandarakis et al., 2009). Observed effects of OCs on male

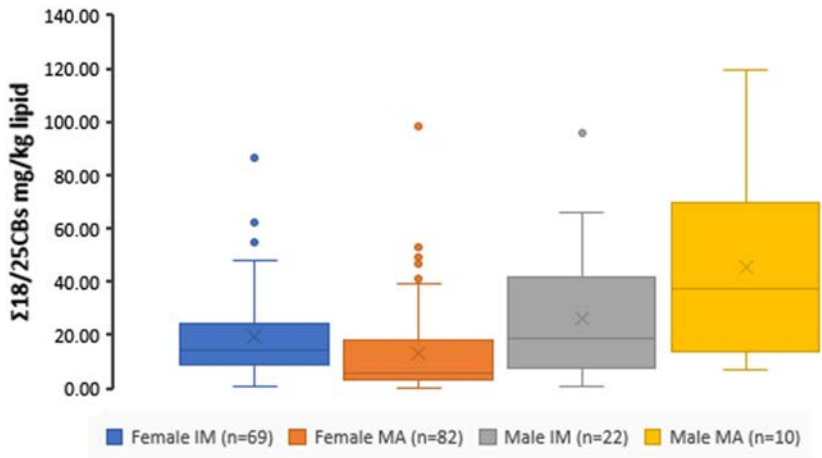

FIGURE 1.5 *Box* plots of male and female common dolphin reproductive status (*IM*, sexually immature; *MA*, sexually mature) and ΣPCB from stranded and bycaught common dolphins (1990–2013, $n = 183$). The *dark horizontal line* indicates the median, *x markers* indicate the mean, and outliers are highlighted by *circles*. *(Data obtained from Law (1994), Law et al. (2006), Pierce et al. (2008), Murphy et al. (2010), Jepson et al. (2013);* the current study and Murphy et al. (unpublished data)*)*

rats include decreased spermatogenesis and fertility and delayed puberty (Diamanti-Kandarakis et al., 2009).

CONCLUSIONS

A low reproductive rate of 26% was reported for common dolphins in the Northeast Atlantic for the period 1990–2006 (Murphy et al., 2009). Significantly higher pregnancy rates of 47% and 40.2% were reported in *D. delphis* inhabiting the Eastern Tropical Pacific and *D. capensis* off South Africa, respectively (Danil and Chivers, 2007; Mendolia, 1989; Murphy et al., 2009). In cetaceans, low reproductive rates have been attributed to density-dependent compensatory responses when populations are close to carrying capacity, small population size causes inbreeding depression, interference, and resource competition, or long-term ecosystem change causes a decline in the prey base, leading to nutritional stress, cryptic effects of fishery interactions, such as separation of mother and calves or decreased fecundity due to stress effects, disease, marine biotoxins, and impacts of endocrine disrupting chemicals/anthropogenic pollutants (Cramer et al., 2008; Geraci and Lounsbury, 2009; Geraci et al., 1999; Gerrodette and Forcada, 2005; Murphy et al., 2009, 2015; Reeves et al., 2001). For common dolphins in the Northeast Atlantic, exposure to anthropogenic pollutants may be contributing to the low observed reproductive output (Murphy et al., 2009, 2010).

This study has reported evidence of reproductive failure and reproductive dysfunction in common dolphins inhabiting UK waters, which may be possibly linked to exposure to PCBs. Reproductive failure could have occurred in 30% or more of mature females in the control sample. Where pollutant data were available, all observed cases of reproductive tract pathologies in both control and noncontrol samples were reported in females with ΣPCB burdens >22 mg/kg lw (Table 1.2). However, there could be combined effects from exposure to multiple pollutants, including (low doses of) DDT and other legacy and emerging pollutants, which requires further investigation. One of the main anthropogenic threats to the Northeast common dolphin population is incidental capture in fishing gear (ICES Advice, 2016; Murphy et al., 2013). If bycatch rates are as high as predicted in the region, any suppression of reproduction will limit the population's ability to recover. There has been no evidence of a decline in the common dolphin population in the Northeast Atlantic in recent years (Hammond et al., 2017). Results from the recent SCANS III aerial and shipboard surveys undertaken by Hammond et al. suggest large-scale movements of animals into continental shelf and adjacent waters—possibly from offshore or more southern waters—so more dolphins are now exposed to anthropogenic pollutants in western European waters (Murphy et al., 2018a). Mean levels of ΣPCB in common dolphins are lower than that those observed in bottlenose dolphins, striped dolphins, and killer whales in European waters (Jepson et al., 2016). However, the effects of exposure to lower doses of EDCs may not be of

a magnitude less, particularly when exposure occurs during critical periods of development. In humans, observed disorders are more than likely to result from chronic exposure to low amounts of mixtures of chemicals, as these can produce synergistic and additive effects, which may be coupled with generational epigenetic effects (Diamanti-Kandarakis et al., 2009). Consequently, the continued exposure to legacy anthropogenic pollutants such as PCBs and new emerging pollutants raises concerns about the current and future population-level pollutant effects on Northeast Atlantic common dolphins.

ACKNOWLEDGMENTS

We thank Bob Reid, Tony Patterson, Harry Ross, Jason Barley, John Baker, Thijs Kuiken, Simon Northridge, and Christina Lockyer and the staff of the AHVLA at Polwhele (Truro), as well as the volunteers of the Cornwall Wildlife Trust Marine Strandings Network, for their contributions to data collection. This research was supported by a Marie Curie International Outgoing Fellowship within the Seventh European Community Framework Programme (Project Cetacean-stressors, PIOF-GA-2010-276145 to SM and PDJ). Additional funding was provided through the Agreement on the Conservation of Small Cetaceans of the Baltic, North East Atlantic, Irish and North Seas (ASCOBANS) (Grants SSFA/2008 and SSFA/ASCOBANS/2010/5 to SM). Samples examined in this research were collected under the collaborative Cetacean Strandings Investigation Programme (http://ukstrandings.org/), which is funded by the Department for Environment, Food and Rural Affairs (Defra) and the UK's Devolved Administrations in Scotland and Wales (http://sciencesearch.defra.gov.uk/Default.aspx) (grants to PDJ, RD). UK Defra also funded the chemical analysis under a service-level agreement with the Centre for Environment, Fisheries and Aquaculture Science (grants to RJL, JB).

REFERENCES

Aguilar, A., 1985. Compartmentation and reliability of sampling procedures in organochlorine pollution surveys of cetaceans. Residue Reviews 95, 91–114.

Aguilar, A., Borrell, A., 1994. Abnormally high polychlorinated biphenyl levels in striped dolphins (*Stenella coeruleoalba*) affected by the 1990-1992 Mediterranean epizootic. Science of the Total Environment 154, 237–247.

Aguilar, A., Borrell, A., 2005. DDT and PCB reduction in the western Mediterranean from 1987 to 2002, as shown by levels in striped dolphins (*Stenella coeruleoalba*). Marine Environmental Research 59, 391–404.

Aguilar, A., Borrell, A., Pastor, T., 1999. Biological factors affecting variability of persistent pollutant levels in cetaceans. In: Reijnders, P.J.H., et al., (Eds.), Chemical Pollutants and Cetaceans. In: Journal of Cetacean Research and Management, vol. Special Issue 1, pp. 83–116.

Alava, J.J., Salazar, S., Cruz, M., Jiménez-Uzcátegui, G., Villegas-Amtmann, S., Paéz-Rosas, D., Costa, D.P., Ross, P.S., Ikonomou, M.G., Gobas, F.A.P.C., 2011. DDT strikes back: galapagos sea lions face increasing health risks. Ambio 40, 425–430. https://doi.org/10.1007/s13280-011-0136-6.

Bäcklin, B.-M., Madej, A., Forsberg, M., 1997. Histology of ovaries and uteri and levels of plasma progesterone, oestradiol-17β and oestrone sulphate during the implantation period in mated and gonadotrophin-releasing hormone-treated mink (*Mustela vison*) exposed to polychlorinated biphenyls. Journal of Applied Toxicology 17, 297–306.

Bäcklin, B.-M., Persson, E., Jones, C.J.P., Dantzer, V., 1998. Polychlorinated biphenyl (PCB) exposure produces placental vascular and trophoblastic lesions in the mink (*Mustela vison*): a light and electron microscope study. APMIS 106, 785–799.

Baker, J., 1992. Causes of mortality and parasites and incidental lesions in dolphins and whales from British waters. Veterinary Record 130, 569–572.

Béland, P., DeGuise, S., Girard, C., Lagacé, A., Martineau, D., Michaud, R., Muir, D.C.G., Norstrom, R.J., Pelletier, É., Ray, S., Shugart, L.R., 1993. Toxic compounds and health and reproductive effects in St. Lawrence beluga whales. Journal of Great Lakes Research 19, 766–775. https://doi.org/10.1016/s0380-1330(93)71264-2.

Benirschke, K., Marsh, H., 1984. Anatomic and pathologic observations of female reproductive organs in the short-finned pilot whale, *Globicephala macrorhynchus*. International Whaling Commission (Special Issue 6), 451–455.

Benirschke, K., Henderson, J., Sweeney, J., 1984. A vaginal mass, containing bones, in a common dolphin, *Delphinus delphis*. Reports of the International Whaling Commission (Special Issue 6), 457–458.

Bergman, A., 1999. Health condition of the Baltic grey seal (*Halichoerus grypus*) during two decades. Gynaecological health improvement but increased prevalence of colonic ulcers. Acta Pathology Microbiology and Immunology of Scandinavia 107, 270–282.

Bergman, A., 2007. Pathological Changes in Seals in Swedish Waters: The Relation to Environmental Pollution. Tendencies during a 25-year Period. Swedish University of Agricultural Sciences, Uppsala, p. 102.

Bergman, A., Olsson, M., 1985. Pathology of Baltic gray seal and ringed seal females with special reference to adrenocortical hyperplasia: is environmental pollution the cause of a widely distributed disease syndrome? Finnish Game Research 44, 47–62.

Bergman, Å., Heindel, J.J., Jobling, S., Kidd, K.A., Zoeller, R.T., 2013. State of the science of endocrine disrupting chemicals - 2012. In: WHO (World Health Organization)/UNEP (United Nations Environment Programme).

Boon, J.P., Oostingh, I., van der Meer, J., Hillebrand, M.T.J., 1994. A model for the bioaccumulation of chlorobiphenyl congeners in marine mammals. European Journal of Pharmacology: Environmental Toxicology and Pharmacology 270, 237–251. https://doi.org/10.1016/0926-6917(94)90068-X.

Borrell, A., Aguilar, A., 2005. Mother-calf transfer of organochlorine compounds in the common dolphin (*Delphinus delphis*). Bulletin of Environmental Contamination and Toxicology 75, 149–156. https://doi.org/10.1007/s00128-005-0731-y.

Borrell, A., Aguilar, A., 2007. Organochlorine concentrations declined during 1987–2002 in western Mediterranean bottlenose dolphins, a coastal top predator. Chemosphere 66, 347–352. https://doi.org/10.1016/j.chemosphere.2006.04.074.

Borrell, A., Bloch, D., Desportes, G., 1995. Age trends and reproductive transfer of organochlorine compounds in long-finned pilot whales from the Faroe Islands. Environmental Pollution 88, 283–292.

Bredhult, C., Bäcklin, B.-M., Bignert, A., Olovsson, M., 2008. Study of the relation between the incidence of uterine leiomyomas and the concentrations of PCB and DDT in Baltic gray seals. Reproductive Toxicology 25, 247–255. https://doi.org/10.1016/j.reprotox.2007.11.008.

Van Bressem, M.F., Van Waerebeek, K., Siebert, U., Wunschmann, A., Chavez-Lisambart, L., Reyes, J.C., 2000. Genital diseases in the peruvian dusky dolphin (*Lagenorhynchus obscurus*). Journal of Comparative Pathology 122, 266–277.

Van Bressem, M.F., Van Waerebeek, K., Montes, D., Kennedy, S., Reyes, J.C., Garcia-Godos, I.A., Onton-Silva, K., Alfaro-Shigueto, J., 2006. Diseases, lesions and malformations in the long-beaked common dolphin Delphinus capensis from the Southeast Pacific. Diseases of Aquatic Organisms 68, 149–165.

Browning, H.M., Acevedo-Whitehouse, K., Gulland, F.M.D., Hall, A.J., Finlayson, J., Dagleish, M.P., Billington, K.J., Colegrove, K., Hammond, J.A., 2017. Evidence for a genetic basis of urogenital carcinoma in the wild California sea lion. Proceedings of the Royal Society B 281, 20140240.

Buckles, E.L., Lowenstine, L.J., Funke, C., Vittore, R.K., Wong, H.-N., St. Leger, J.A., Greig, D.J., Duerr, R.S., Gulland, F.M.D., Stott, J.L., 2006. Otarine Herpesvirus-1, not papillomavirus, is associated with endemic tumours in California Sea Lions (*Zalophus californianus*). Journal of Comparative Pathology 135, 183–189.

Bull, J.C., Jepson, P.D., Ssuna, R.K., Deaville, R., Allchin, C.R., Law, R.J., Fenton, A., 2006. The relationship between polychlorinated biphenyls in blubber and levels of nematode infestations in harbour porpoises, *Phocoena phocoena*. Parasitology 132, 565–573.

Caserta, D., Maranghi, L., Mantovani, A., Marci, R., Maranghi, F., Moscarini, M., 2008. Impact of endocrine disruptor chemicals in gynaecology. Human Reproduction Update 14, 59–72. https://doi.org/10.1093/humupd/dmm025.

CLEEN, October 2005, 2005. EuroPCB: Inventory PCB Enforcement in Member States Part 1 Final report of the Chemical Legislation European Enforcement Network (CLEEN) http://www.cleen-europe.eu/file/download/71/EuroPCB_part_I_final.pdf.

Cockcroft, V.G., De Kock, A.C., Lord, D.A., Ross, G.J.B., 1989. Organochlorines in bottlenose dolphins *Tursiops truncatus* from the east coast of South Africa. South African Journal of Marine Science 8, 207–217.

Colegrove, K.M., Gulland, F.M., Naydan, D.K., Lowenstine, L.J., 2009. Tumor morphology and immunohistochemical expression of estrogen receptor, progesterone receptor, p53, and Ki67 in urogenital carcinomas of California sea lions (*Zalophus californianus*). Veterinary Pathology 46, 642–655.

Cramer, K.L., Perryman, W.L., Gerrodette, T., 2008. Declines in reproductive output in two dolphin populations depleted by the yellowfin tunaÂ purse-seine fishery. Marine Ecology Progress Series 369, 273–285. https://doi.org/10.3354/meps07606.

Danil, K., Chivers, S.J., 2007. Growth and reproduction of female short-beaked common dolphins, *Delphinus delphis*, in the eastern tropical Pacific. Canadian Journal of Zoology 85, 108–121.

Deaville, R., Jepson, P.D., 2011. CSIP Final Report for the Period 1st January 2005-31st December 2010. UK Cetacean Strandings Investigation Programme: Report to the UK Department for Food and Rural Affairs and the Devolved Administrations. http://randd.defra.gov.uk/Document.aspx?Document=FinalCSIPReport2005-2010_finalversion061211released[1].pdf.

DeGregori, J., 2012. Challenging the axiom: does the occurrence of oncogenic mutations truly limit cancer development with age? Oncogene. https://doi.org/10.1038/onc.2012.281.

Diamanti-Kandarakis, E., Bourguignon, J.-P., Giudice, L.C., Hauser, R., Prins, G.S., Soto, A.M., Zoeller, R.T., Gore, A.C., 2009. Endocrine-disrupting chemicals: an endocrine society scientific statement. Endocrine Reviews 30, 293–342. https://doi.org/10.1210/er.2009-0002.

Diamond, M.L., Melymuk, L., Csiszars, S., Robson, M., 2010. Estimation of PCB stocks, emissions and urban fate: will our policies be effective? Environmental Science and Technology 44, 2777–2783.

EEA Technical Report, 2012. European Environment Agency. The Impacts of Endocrine Disrupters on Wildlife, People and Their Environments. No 2/2012. ISSN: 1725–2237.

Fenton, S.E., 2009. The mammary gland: a tissue sensitive to environmental exposures. Reviews on Environmental Health 24, 319–325.

Folland, W.R., Newsted, J.L., Fitzgerald, S.D., Fuchsman, P.C., Bradley, P.W., Kern, J., Kannan, K., Remington, R.E., Zwiernik, M.J., 2016. Growth and reproductive effects from dietary exposure to Aroclor 1268 in mink (Neovison vison), a surrogate model for marine mammals. Environmental Toxicology and Chemistry 35, 604–618. https://doi.org/10.1002/etc.3201.

Fossi, M.C., Marsili, L., 2003. Effects of endocrine disruptors in aquatic mammals. Pure and Applied Chemistry 75, 2235–2247.

Fukushima, M., Kawai, S., 1981. Variation of organochlorine residue concentration and burden in striped dolphin with growth. In: Fujiyama, T. (Ed.), Studies on the Levels of Organochlorine Compounds and Heavy Metals in the Marine Organisms. University of the Ryukyus, Okinawa, pp. 97–114.

Geraci, J.R., Lounsbury, V.J., 2009. Health. In: William, F.P., et al. (Ed.), Encyclopedia of Marine Mammals, second ed. Academic Press, London, pp. 546–553.

Geraci, J.R., Palmer, N.C., St. Aubin, D.J., 1987. Tumors in cetaceans: analysis and new findings. Canadian Journal of Fisheries and Aquatic Sciences 44, 1289–1300. https://doi.org/10.1139/f87-152.

Geraci, J.R., Harwood, J., Lounsbury, V.J., 1999. Marine mammal die-offs: causes, investigations, and issues. In: Twiss Jr., J.R., Reeves, R.R. (Eds.), Conservation and Management of Marine Mammals. Smithsonian Institution Press, Washington, DC, pp. 367–395.

Gerrodette, T., Forcada, J., 2005. Non-recovery of two spotted and spinner dolphin populations in the eastern tropical Pacific Ocean. Marine Ecology Progress Series 291, 1–21.

De Guise, S., Lagace, A., Beland, P., 1994a. True hermaphroditism in a St. Lawrence beluga whale (*Delphinapterus leucas*). Journal of Wildlife Diseases 30, 287–290.

De Guise, S., Lagacé, A., Béland, P., 1994b. Tumors in St. Lawrence beluga whales (*Delphinapterus leucas*). Veterinary Pathology 31, 444–449.

De Guise, S., Lagacé, A., Béland, P., Girard, C., Higgins, R., 1995. Non-neoplastic lesions in beluga whales (*Delphinapterus leucas*) and other marine mammals from the St lawrence estuary. Journal of Comparative Pathology 112, 257–271. https://doi.org/10.1016/s0021-9975(05)80079-9.

Gulland, F., Trupkiewicz, J., Spraker, T., Lowenstine, L., 1996. Metastatic carcinoma of probable transitional cell origin in 66 free-living California sea lions (*Zalophus californianus*), 1979 to 1994. Journal of Wildlife Diseases 32, 250–258.

Hall, A.J., Hugunin, K., Deaville, R., Law, R.J., Allchin, C.R., Jepson, P.D., 2006a. The risk of infection from polychlorinated biphenyl exposure in the harbor porpoise (*Phocoena phocoena*): a case–control approach. Environmental Health Perspectives 114, 704–711.

Hall, A.J., McConnell, B.J., Rowles, T.K., Aguilar, A., Borrell, A., Schwacke, L., Reijnders, P.J.H., Wells, R.S., 2006b. Individual-based model framework to assess population consequences of polychlorinated biphenyl exposure in bottlenose dolphins. Environmental Health Perspectives 114, 60–64. https://doi.org/10.1289/ehp.8053.

Hammond, P., Lacey, C., Gilles, A., Viquerat, S., Börjesson, P., Herr, H., Macleod, K., Ridoux, V., Santos, M.B., Scheidat, M., Teilmann, J., Vingada, J., Øien, N., 2017. Estimates of Cetacean Abundance in European Atlantic Waters in Summer 2016 from the SCANS-III Aerial and Shipboard Surveys. Sea Mammal Research Unit, University of St Andrews, UK, pp. 40

Helle, E., Olsson, M., Jensen, S., 1976. PCB levels correlated with pathological changes in seal uteri. Ambio 5, 261–263.

Herbst, A.L., Ulfelder, H., Poskanzer, D.C., 1971. Adenocarcinoma of the vagina. New England Journal of Medicine 284, 878–881. https://doi.org/10.1056/NEJM197104222841604.

Hickie, B.E., Ross, P.S., Macdonald, R.W., Ford, J.K.B., 2007. Killer Whales (*Orcinus orca*) face protracted health risks associated with lifetime exposure to PCBs. Environmental Science and Technology 41, 6613–6619. https://doi.org/10.1021/es0702519.

Hohn, A.A., Ewing, R.Y., Zaias, J., 2007. Reproduction in relation to conservation and commercial exploitation. In: Miller, D.L. (Ed.), Reproductive Biology and Phylogeny of Cetacea. Volume 7 of Series: Reproductive Biology and Phylogeny. Science Publishers, Enfield, pp. 371–389.

Houde, M., Hoekstra, P.F., Solomon, K.R., Muir, D.C., 2005. Organohalogen contaminants in delphinoid cetaceans. Reviews of Environmental Contamination and Toxicology 184, 1–57.

ICES Advice, 2016. Bycatch of small cetaceans and other marine animals – review of national reports under Council Regulation (EC) No. 812/2004 and other information. In: ICES Special Request Advice Northeast Atlantic and Adjacent Seas Ecoregions. ICES Advice 2016, Book 1 6 pp. http://www.ices.dk/sites/pub/Publication%20Reports/Advice/2016/2016/Protected_species_bycatch.pdf.

Ingre-Khans, E., Ågerstrand, M., Rudén, C., 2017. Endocrine Disrupting Chemicals in the Marine Environment. ACES Report Number 16. Department of Environmental Science and Analytical Chemistry, Stockholm University.

Jensen, S., 1996. Report of a new chemical hazard. New Scientist 32, 612.

Jensen, S., Johnels, A.G., Olsson, M., Otterlind, G., 1969. DDT and PCB in marine animals from Swedish waters. Nature 224.

Jepson, P.D. (Ed.), 2005. Cetacean Strandings Investigation and Co-ordination in the UK 2000-2004, Final report to the Department for Environment, Food and Rural Affairs. pp. 1–79. http://www.defra.gov.uk/wildlife-countryside/resprog/findings/index.htm.

Jepson, P.D., Law, R.J., 2016. Persistent pollutants, persistent threats. Science 352, 1388–1389. https://doi.org/10.1126/science.aaf9075.

Jepson, P.D., Bennett, P.M., Deaville, R., Allchin, C.R., Baker, J.R., Law, R.J., 2005. Relationships between polychlorinated biphenyls and health status in harbour porpoises (*Phocoena phocoena*) stranded in the United Kingdom. Environmental Toxicology and Chemistry 24, 238–248.

Jepson, P.D., Deaville, R., Acevedo-Whitehouse, K., Barnett, J., Brownlow, A., Brownell Jr., R.L., Clare, F.C., Davison, N., Law, R.J., Loveridge, J., Macgregor, S.K., Morris, S., Murphy, S., Penrose, R., Perkins, M.W., Pinn, E., Seibel, H., Siebert, U., Sierra, E., Simpson, V., Tasker, M.L., Tregenza, N., Cunningham, A.A., Fernández, A., 2013. What caused the UK's largest common dolphin (*Delphinus delphis*) mass stranding event? PLoS One 8, e60953,. https://doi.org/10.1371/journal.pone.0060953.

Jepson, P.D., Deaville, R., Barber, J.L., Aguilar, À., Borrell, A., Murphy, S., Barry, J., Brownlow, A., Barnett, J., Berrow, S., Cunningham, A.A., Davison, N.J., ten Doeschate, M., Esteban, R., Ferreira, M., Foote, A.D., Genov, T., Giménez, J., Loveridge, J., Llavona, Á., Martin, V., Maxwell, D.L., Papachlimitzou, A., Penrose, R., Perkins, M.W., Smith, B., de Stephanis, R., Tregenza, N., Verborgh, P., Fernandez, A., Law, R.J., 2016. PCB pollution continues to impact populations of orcas and other dolphins in European waters. Scientific Reports 6, 18573. https://doi.org/10.1038/srep18573. http://www.nature.com/articles/srep18573#supplementary-information.

Johnson, S., Lowenstine, L., Gulland, F.M.D., Jang, S., Imai, D., Almy, F., Delong, R., Gardner, I., 2006. Aerobic bacterial flora of the vagina and prepuce of California sea lions (*Zalophus californianus*) and investigation of associations with urogenital carcinoma. Veterinary Microbiology 114, 94–103.

Jonsson, B., Gustafsson, O., Axelman, J., Sundberg, H., 2003. Global accounting of PCBs in the continental shelf sediments. Environmental Science and Technology 37, 245–255.

Kannan, K., Blankenship, A., Jones, P., Giesy, J., 2000. Toxicity reference values for the toxic effects of polychlorinated biphenyls to aquatic mammals. Human and Ecological Risk Assessment 6, 181–201.

Kennedy, P.C., Miller, R.B., 1993. The female genital system. In: Jubb, K.V.F., et al. (Ed.), Pathology of Domestic Animals, vol. 3, fourth ed. pp. 349–470.

King, D.P., Hure, M.C., Goldstein, T., Aldridge, B.M., Gulland, F.M.D., Saliki, J.T., Buckles, E.L., Lowenstine, L.J., Stott, J.L., 2002. Otarine herpesvirus-1: a novel gammaherpesvirus associated with urogenital carcinoma in California sea lions (*Zalophus californianus*). Veterinary Microbiology 86, 131–137. https://doi.org/10.1016/s0378-1135(01)00497-7.

Law, R.J., 1994. Collaborative UK Marine Mammal Project: Summary of Data Produced 1988–1992. Fisheries Research Technical. Report 97. Directorate of Fisheries Research, Ministry of Agriculture, Fisheries and Food, Lowestoft, UK.

Law, R.J., Jepson, P.D., 2017. Europe's insufficient pollution remediation. Science 356. https://doi.org/10.1126/science.aam6274.

Law, R., Jepson, P., Deaville, R., Reid, R., Patterson, I., 2006. Collaborative UK marine mammals strandings project: summary of contaminant data for the period 1993-2001. In: Sci. Ser. Tech. Rep., 131. Cefas Lowestoft. 72 pp http://www.cefas.co.uk/publications/techrep/tech131.pdf.

Law, R.J., Barry, J., Barber, J.L., Bersuder, P., Deaville, R., Reid, R.J., Brownlow, A., Penrose, R., Barnett, J., Loveridge, J., Smith, B., Jepson, P.D., 2012. Contaminants in cetaceans from UK waters: status as assessed within the cetacean strandings investigation programme from 1990 to 2008. Marine Pollution Bulletin. 64, 1485–1494. https://doi.org/10.1016/j.marpolbul.2012.05.024.

Letcher, R., Bustnes, J., Dietz, R., Jenssen, B., Jorgensen, E., Sonne, C., Verreault, J., Vijayan, M., Gabrielsen, G., 2010. Exposure and effects assessment of persistent organohalogen contaminants in arctic wildlife and fish. Science of The Total Environment 408, 2995–3043.

Lipscomb, T.P., Scott, D.P., Garber, R.L., Krafft, A.E., Tsai, M.M., Lichy, J.H., Taubenberger, J.K., Schulman, F.Y., Gulland, F.M., 2000. Common metastatic carcinoma of California Sea Lions (*Zalophus californianus*): evidence of genital origin and association with novel gammaherpesvirus. Veterinary Pathology Online 37, 609–617. https://doi.org/10.1354/vp.37-6-609.

Lockyer, C.H., 1987. Observations on the Ovary of the Southern Minke Whale, 38. Scientific Reports of the Whales Research Institute, Tokyo, pp. 75–89.

Lundin, J.I., Ylitalo, G.M., Booth, R.K., Anulacion, B., Hempelmann, J.A., Parsons, K.M., Giles, D.A., Seely, E.A., Hanson, M.B., Emmons, C.K., Wasser, S.K., 2016. Modulation in persistent organic pollutant concentration and profile by prey availability and reproductive status in southern resident killer whale scat samples. Environmental Science and Technology 50, 6506–6516. https://doi.org/10.1021/acs.est.6b00825.

Marsh, H., Kasuya, T., 1984. Changes in the Ovaries of the Short-finned Pilot Whale, *Globicephala Macrorhynchus*, with Age and Reproductive Activity Report of the International Whaling Commission. pp. 331–335.

Martineau, D., 2012. Chapter 17 Contaminants and health of beluga (*D. leucus*) in St Lawrence estuary. In: Levengood, J.M. (Ed.), Ecology and Animal Health. The Baltic University Programme. Uppsala University, Uppsala, Sweden, pp. 139–148.

Martineau, D., Béland, P., Desjardins, C., Lagacé, A., 1987. Levels of organochlorine chemicals in tissues of beluga whales (*Delphinapterus leucas*) from the St. Lawrence Estuary, Quebec Canada. Archives of Environmental Contamination and Toxicology 16, 137–147.

Martineau, D., Lagacé, A., Béland, P., Higgins, R., Armstrong, D., Shugart, L.R., 1988. Pathology of stranded beluga whales (*Delphinapterus leucas*) from the St. Lawrence Estuary, Québec, Canada. Journal of Comparative Pathology 98, 287–310. https://doi.org/10.1016/0021-9975(88)90038-2.

Martineau, D., De Guise, S., Fournier, M., Shugart, L., Girard, C., Lagacé, A., Béland, P., 1994. Pathology and toxicology of beluga whales from the St. Lawrence Estuary, Quebec, Canada. Past, present and future. Science of The Total Environment 154, 201–215. https://doi.org/10.1016/0048-9697(94)90088-4.

Martineau, D., Lemberger, K., Dallaire, A., Labelle, P., Lipscomb, T.P., Michel, P., Mikaelian, I., 2002. Cancer in wildlife, a case study: beluga from the St. Lawrence Estuary, Québec, Canada. Environmental Health Perspectives 110, 1–7.

McAloose, D., Newton, A.L., 2009. Wildlife cancer: a conservation perspective. Nature Reviews Cancer 9, 517–526.

McEntee, K., 1990. Cysts in and around the ovary. In: McEntee, K. (Ed.), Reproductive Pathology of Domestic Mammals. Academic Press, London, pp. 52–68.

McFee, W.E., Osborne, C.A., 2004. Struvite calculus in the vagina of a bottlenose dolphin (*Tursiops truncatus*). Journal of Wildlife Diseases 40, 125–128.

Mendolia, C., 1989. Reproductive Biology of Common Dolphins (*Delphinus delphis* Linnaeus) off the South East Coast of Southern Africa. University of Port Elizabeth, Port Elizabeth, p. 111.

Mirimin, L., Viricel, A., Amaral, A.R., Murphy, S., Ridoux, V., Rogan, E., 2009a. Population Genetic Structure of Common Dolphins in the North-east Atlantic Using Microsatellite Loci and mtDNA Control Region Markers Report to the International Whaling Commission, SC/61/SM27.

Mirimin, L., Westgate, A.J., Rogan, E., Rosel, P., Read, A.J., Coughlan, J., Cross, T., 2009b. Population structure of short-beaked common dolphins (*Delphinus delphis*) in the North Atlantic Ocean as revealed by mitochondrial and nuclear genetic markers. Marine Biology 156, 821–834.

Mongillo, T.M., Ylitalo, G.M., Rhodes, L.D., O'Neill, S.M., Noren, D.P., Hanson, M.B., 2016. Exposure to a Mixture of Toxic Chemicals: Implications for the Health of Endangered Southern Resident Killer Whales. U.S. Dept. Commer., NOAA Tech. Memo. NMFS-NWFSC-135, p. 107. https://doi.org/10.7289/V5/TM-NWFSC-135.

Moon, H.J., Han, S.Y., Shin, J.-H., Kang, I.L.H., Kim, T.S., Hong, J.H., Kim, S.-H., Fenton, S.E., 2007. Gestational exposure to nonylphenol causes precocious mammary gland development in female rat offspring. Journal of Reproduction and Development 53, 333–344. https://doi.org/10.1262/jrd.18055.

Muir, D.C.G., Ford, C.A., Rosenberg, B., Norstrom, R.J., Simon, M., Béland, P., 1996. Persistent organochlorines in beluga whales (*Delphinapterus leucas*) from the St. Lawrence River estuary. I. Concentrations and patterns of specific PCBs, chlorinated pesticides and polychlorinated dibenzo-p-dioxins and dibenzofurans. Environmental Pollution 93, 219–234.

Munson, L., Calzada, N., Kennedy, S., Sorensen, T.B., 1998. Luteinized ovarian cysts in Mediterranean striped dolphins. Journal of Wildlife Diseases 34, 656–660.

Murphy, S., 2004. The Biology and Ecology of the Common Dolphin *Delphinus delphis* in the North-east Atlantic. University College Cork.

Murphy, S., Winship, A., Dabin, W., Jepson, P.D., Deaville, R., Reid, R.J., Spurrier, C., Rogan, E., López, A., González, A.F., Read, F.L., Addink, M., Silva, M., Ridoux, V., Learmonth, J.A., Pierce, G.J., Northridge, S.P., 2009. Importance of biological parameters in assessing the status of *Delphinus delphis*. Marine Ecology Progress Series 388, 273–291. https://doi.org/10.3354/meps08129.

Murphy, S., Pierce, G.J., Law, R.J., Bersuder, P., Jepson, P.D., Learmonth, J.A., Addink, M., Dabin, W., Santos, M.B., Deaville, R., Zegers, B.N., Mets, A., Rogan, E., Ridoux, V., Reid, R.J., Smeenk, C., Jauniaux, T., López, A., Farré, J.M.A., González, A.F., Guerra, A., García-Hartmann, M., Lockyer, C., Boon, J.P., 2010. Assessing the effect of persistent organic pollutants on reproductive activity in common dolphins and harbour porpoises. NAFO/ICES/NAMMCO symposium "The Role of Marine Mammals in the Ecosystem in the 21st Century". Journal of Northwest Atlantic Fishery Science 42, 153–173.

Murphy, S., Deaville, R., Monies, R.J., Davison, N., Jepson, P.D., 2011. True hermaphroditism: first evidence of an ovotestis in a cetacean species. Journal of Comparative Pathology 144, 195–199.

Murphy, S., Pinn, E.H., Jepson, P.D., 2013. The short-beaked common dolphin (*Delphinus delphis*) in the North-eastern Atlantic: distribution, ecology, management and conservation status. In: Hughes, R.N., et al. (Ed.), Oceanography and Marine Biology: An Annual Review, vol. 51. CRC Press, pp. 193–280.

Murphy, S., Perrott, M., McVee, J., Read, F., Stockin, K.A., 2014. Deposition of growth layer groups in dentine tissue of captive common dolphins *Delphinus delphis*. In: NAMMCO Scientific Publication Volume 10: Age Estimation of Marine Mammals with a Focus on Monodontids. https://doi.org/10.7557/3.3017.

Murphy, S., Barber, J.L., Learmonth, J.A., Read, F.L., Deaville, R., Perkins, M.W., Brownlow, A., Davison, N., Penrose, R., Pierce, G.J., Law, R.J., Jepson, P.D., 2015. Reproductive failure in UK harbour porpoises *Phocoena phocoena*: legacy of pollutant exposure? PLoS One 10, e0131085. https://doi.org/10.1371/journal.pone.0131085.

Murphy, S., Evans, P.G.H., Pinn, E., Simmonds, M., Pierce, G.J., 2018a. Conservation and management of common dolphins; lessons learned from the North-east Atlantic. Aquatic Conservation: Marine and Freshwater Ecosystems (in preparation).

Murphy, S., Pocknell, A., Bailey, J., Deaville, R., Perkins, M., Jepson, P.D., 2018b. Rare cetacean ovarian neoplasms. Diseases of Aquatic Organisms (in preparation).

Natoli, A., Cañadas, A., Vaquero, C., Politi, E., Fernandez-Navarro, P., Hoelzel, A., 2008. Conservation genetics of the short-beaked common dolphin (*Delphinus delphis*) in the Mediterranean Sea and in the eastern North Atlantic Ocean. Conservation Genetics 9, 1479–1487.

Newman, S.J., Smith, S.A., 2006. Marine mammal neoplasia: a review. Veterinary Pathology Online 43, 865–880. https://doi.org/10.1354/vp.43-6-865.

Norman, S., Garner, M., Berta, S., Dubpernell, S., Klope, M., 2011. Vaginal calculi in a juvenile harbor porpoise (*Phocoena phocoena*). Journal of Zoo and Wildlife Medicine 42, 335–337.

O'Shea, T.J., Reeves, R.R., Long, A.K., 1999. Marine mammals and persistent ocean contaminants. In: Proceedings of the Marine Mammal Commission Workshop, Keystone, Colorado, 12–15 October 1988, pp. 1–150.

Padmanabhan, V., Sarma, H.N., Savabieasfahani, M., Steckler, T.L., Veiga-Lopez, A., 2010. Developmental reprogramming of reproductive and metabolic dysfunction in sheep: native steroids vs. environmental steroid receptor modulators. International Journal of Andrology 33, 394–404. https://doi.org/10.1111/j.1365-2605.2009.01024.x.

Pierce, G.J., Santos, M.B., Murphy, S., Learmonth, J.A., Zuur, A.F., Rogan, E., Bustamante, P., Caurant, F., Lahaye, V., Ridoux, V., Zegers, B.N., Mets, A., Addink, M., Smeenk, C., Jauniaux, T., Law, R.J., Dabin, W., López, A., A. Farré, J.M., González, A.F., Guerra, A., García-Hartmann, M., Reid, R.J., Moffat, C.F., Lockyer, C., Boon, J.P., 2008. Bioaccumulation of persistent organic pollutants in female common dolphins (*Delphinus delphis*) and harbour porpoises (*Phocoena phocoena*) from western European seas: geographical trends, causal factors and effects on reproduction and mortality. Environmental Pollution 153, 401–415.

Reeves, R.R., Rolland, R., Clapham, P.J., 2001. Causes of reproductive failure in North Atlantic right whales: new avenues of research. Report of a workshop held 26–28 April 2000. In: Northeast Fisheries Science Centre Reference Document 01-16, Falmouth, Massachussetts, p. 46.

Reijnders, P.J.H., 1980. Organochlorine and heavy metal residues in harbour seals from the Wadden sea and their possible effects on reproduction. Netherlands Journal of Sea Research 14, 30–65.

Reijnders, P.J.H., 1986. Reproductive failure in common seals feeding on fish from polluted coastal waters. Nature 324, 456–457.

Reijnders, P., 2003. Reproductive and developmental effects of environmental organochlorines on marine mammals. In: Vos, J.G., et al. (Ed.), Toxicology of Marine Mammals. Taylor and Francis, London, pp. 55–66.

Reijnders, P.J.H., Aguilar, A., Donovan, G.P., 1999. Chemical pollutants and cetaceans. Journal of Cetacean Research and Management (Special Issue 1) (International Whaling Commission, Cambridge).

Rewell, R.E., Willis, R.A., 1950. Some tumours of wild animals. Journal of Pathology and Bacteriology 62, 450–452. https://doi.org/10.1002/path.1700620321.

Robeck, T.R., Atkinson, S.K., Brook, F., 2001. Reproduction. In: Leslie Dierauf and Frances M.D., Gulland (Ed.), CRC Handbook of Marine Mammal Medicine, second ed. 193–236.

Robeck, T.R., Steinman, K.J., Greenwell, M., Ramirez, K., Van Bonn, W., Yoshioka, M., Katsumata, E., Dalton, L., Osborn, S., O'Brien, J.K., 2009. Seasonality, estrous cycle characterization, estrus synchronization, semen cryopreservation, and artificial insemination in the Pacific white-sided dolphin (*Lagenorhynchus obliquidens*). Reproduction 138, 391–405. https://doi.org/10.1530/rep-08-0528.

Russell, P., Robboy, S.J., Prat, J., 2009. Ovarian sex cord-stromal and steroid cell tumors. In: Robboy, S.J., et al. (Ed.), Robboy's Pathology of the Female Reproductive Tract, second ed. Churchill Livingstone Elsevier.

Schwacke, L.H., Voit, E.O., Hansen, L.J., Wells, R.S., Mitchum, G.B., Hohn, A.A., Fair, P.A., 2002. Probabilistic risk assessment of reproductive effects of polychlorinated biphenyls on bottlenose dolphins (*Tursiops truncatus*) from the Southeast United States coast. Environmental Toxicological Chemistry 21, 2752–2764.

Seibel, H., Siebert, U., Schöpper, H., Wohlsein, P., 2012. Granulosa cell tumour in a harbour porpoise (*Phocoena phocoena*) from German waters. Diseases of Aquatic Organisms 99, 79–83. https://doi.org/10.3354/dao02449 PMID: 22585304.

Siebert, U., Wunschmann, A., Weiss, R., Frank, H., Benke, H., Frese, K., 2001. Post-mortem findings in harbour porpoises (*Phocoena phocoena*) from the German North and Baltic Seas. Journal of Comparative Pathology 124, 102–114.

Sinkkonen, S.P.J., 2000. Degradation half-life times for PCDDs, PCDFs and PCBs for environmental fate modelling. Chemosphere 40, 943–949.

Steinberg, R.M., Walker, D.M., Juenger, T.E., Woller, M.J., Gore, A.C., 2008. Effects of perinatal polychlorinated biphenyls on adult female rat reproduction: development, reproductive physiology, and second generational effects. Biology of Reproduction 78, 1091–1101.

Stolk, A., 1950. Tumours in whales. Amsterdam Naturalist 1, 28–33.

Subramanian, A.N., Tanabe, S., Tatsukawa, R., Saito, S.N.M., 1987. Reduction in the testosterone levels by PCBs and DDE in Dall's porpoises of Northwestern North Pacific. Marine Pollution Bulletin 18, 643–646.

Tornero, V., Hanke, G., 2016. Chemical contaminants entering the marine environment from sea-based sources: a review with a focus on European seas. Marine Pollution Bulletin 112, 17–38. https://doi.org/10.1016/j.marpolbul.2016.06.091.

United Nations Environment Programme, 2001. The Stockholm Convention on Persistent Organic Pollutants (UNEP, Nairobi, 2001). http://chm.pops.int/default.aspx.

Viricel, A., Strand, A., Rosel, P., Ridoux, V., Garcia, P., 2008. Insights on common dolphin (*Delphinus delphis*) social organization from genetic analysis of a mass-stranded pod. Behavioral Ecology and Sociobiology 63, 173–185.

Vos, J.G., Bossart, G.D., Fournier, D.A., O'Shea, T.J., 2003. Toxicology of Marine Mammals. New Perspectives: Toxicology and the Environment. Taylor & Francis.

Wells, R.S., Tornero, V., Borrell, A., Aguilar, A., Rowles, T.K., Rhinehart, H.L., Hofmann, S., Jarman, W.M., Hohn, A.A., Sweeney, J.C., 2005. Integrating life-history and reproductive success data to examine potential relationships with organochlorine compounds for bottlenose dolphins (*Tursiops truncatus*) in Sarasota Bay, Florida. Science of the Total Environment 349, 106–119.

Woodhouse, C.D., Reinne, C.J., 1991. Observations of vaginal calculi in dolphins. Journal of Wildlife Diseases 27, 421–427.

Ylitalo, G.M., Stein, J.E., Hom, T., Johnson, L.L., Tilbury, K.L., Hall, A.J., Rowles, T., Greig, D., Lowenstine, L.J., Gulland, F.M.D., 2005. The role of organochlorines in cancer-associated mortality in California sea lions (*Zalophus californianus*). Marine Pollution Bulletin 50, 30–39. https://doi.org/10.1016/j.marpolbul.2004.08.005.

Yordy, J.E., Wells, R.S., Balmer, B.C., Schwacke, L.H., Rowles, T.K., Kucklick, J.R., 2010. Life history as a source of variation for persistent organic pollutant (POP) patterns in a community of common bottlenose dolphins (*Tursiops truncatus*) resident to Sarasota Bay, FL. Science of the Total Environment 408, 2163–2172.

Zoeller, R.T., Brown, T.R., Doan, L.L., Gore, A.C., Skakkebaek, N.E., Soto, A.M., Woodruff, T.J., Vom Saal, F.S., 2012. Endocrine-disrupting chemicals and public health protection: a statement of principles from the endocrine society. Endocrinology 153, 4097–4110.

Zoeller, R.T., Bergman, Å., Becher, G., Bjerregaard, P., Bornman, R., Brandt, I., Iguchi, T., Jobling, S., Kidd, K.A., Kortenkamp, A., Skakkebaek, N.E., Toppari, J., Vandenberg, L.N., 2014. A path forward in the debate over health impacts of endocrine disrupting chemicals. Environmental Health 13, 118. https://doi.org/10.1186/1476-069x-13-118.