

Endocrine disrupting chemicals and wildlife



Oxford Martin Restatement 6:

A restatement of the natural science evidence base on the effects of endocrine disrupting chemicals on wildlife

Oxford Martin Restatements review the natural science evidence base underlying areas of current policy concern and controversy. Written in policy neutral terms and designed to be read by an informed but not technically specialist audience, restatements are produced by a writing team reflecting the breadth of opinion on the topic in the science community and involve wide consultation with interested stakeholders. The final version of the restatement is peer-reviewed prior to publication.

This paper was published in February 2019 in the Proceedings of the Royal Society B. It deals with the effects of endocrine disrupting chemicals on wildlife.

Endocrine disrupting chemicals (EDCs) are substances that alter the function of the endocrine system and consequently cause adverse effects to humans or wildlife. The release of particular EDCs into the environment has been shown to negatively affect certain wildlife populations and has led to restrictions on the use of some EDCs. Current chemical regulations aim to balance the industrial, agricultural and/or pharmaceutical benefits of using these substances with their demonstrated or potential harm to human health or the environment. A summary is provided of the natural science evidence base informing the regulation of chemicals released into the environment that may have endocrine disrupting effects on wildlife. This summary is in a format intended to be policy neutral and accessible to informed, but not expert, policymakers and stakeholders. Each evidence statement is placed into one of four categories describing the nature of the underlying information.

This pdf contains:

Pages 1–3	A short paper describing the project
Pages 3–11	The restatement itself which is the formal appendix to the paper
Pages 12–56	An annotated bibliography of the evidence underlying the restatement (officially the Electronic Supplementary Material accompanying the paper).

Evidence synthesis



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A restatement of the natural science evidence base on the effects of endocrine disrupting chemicals on wildlife

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Endocrine disrupting chemicals (EDCs) are substances that alter the function of the endocrine system and consequently cause adverse effects to humans or wildlife. The release of particular EDCs into the environment has been shown to negatively affect certain wildlife populations and has led to restrictions on the use of some EDCs. Current chemical regulations aim to balance the industrial, agricultural and/or pharmaceutical benefits of using these substances with their demonstrated or potential harm to human health or the environment. A summary is provided of the natural science evidence base informing the regulation of chemicals released into the environment that may have endocrine disrupting effects on wildlife. This summary is in a format (a 'restatement') intended to be policy-neutral and accessible to informed, but not expert, policy-makers and stakeholders.

1. Introduction

The endocrine system plays a critical role in almost all biological and physiological functions. Endocrine disrupting chemicals (EDCs) are substances (or mixtures of substances) that alter the function of the endocrine system and consequently are capable of causing adverse effects to humans or wildlife [1]. EDCs include compounds with important agricultural, industrial and pharmaceutical uses, which can become pollution problems through inadvertent human or wildlife exposure. Many different types of chemicals can be EDCs and, beyond their effects on the endocrine system, there is no single characteristic or property that they all share. Particular compounds may affect other biological processes in addition to their EDC effects. Some common natural substances may have endocrine effects (for example sugar and caffeine) but concern about EDCs in the environment chiefly focuses on synthetic chemicals that can sometimes be active at low or even very low concentrations. Though not unique to EDCs, the ability of some chemicals to be biologically active at very low concentrations raises particular regulatory issues. Timing of exposure is also critical, because EDCs may only have an effect at particular life-history stages. Many of the first EDCs to attract regulatory attention had long half-lives in the environment and became concentrated in certain species of wildlife, negatively affecting their population viability. More recently, and in addition, there has been concern about widely used substances that are active at relatively low concentrations and,

though short-lived, are commonly found in the environment due, for example, to their continuous release in wastewater.

The aim of the project described here is to provide a 'restatement' of the natural science evidence base relevant to the design and implementation of EDC regulations to protect wildlife. We define wildlife as all non-domesticated animals, including amphibians, fish and invertebrates as well as birds, reptiles and mammals. Humans are also exposed to these chemicals when, for example, they use products containing EDCs or through contamination of food (for an introduction to EDCs and human toxicology see [1] or [2]). Toxicology studies for human health protection may anticipate issues for wildlife and *vice versa*.

Some of the most well-documented examples of wildlife population reductions caused by industrial and agricultural chemicals were due to the endocrine disrupting properties of those chemicals. The widespread use of the organochlorine insecticide DDT from the 1950s onwards was a major driver of declines in birds of prey because of reproductive failure due to eggshell thinning [3,4]. The use of polychlorinated biphenyls (PCBs) in electrical equipment and for other industrial purposes resulted in large quantities of these highly persistent chemicals entering the environment. They have become concentrated in the bodies of species at the top of ecological food webs, particularly in high-latitude regions of the Northern Hemisphere, and are linked to impaired reproduction [5,6]. Use of both types of compounds is now restricted worldwide. Not all the toxic effects of these chemicals are through endocrine disruption, but the association of EDCs with a number of classic cases of pollution affecting wildlife means that they attract particular attention from environmental protection agencies, and raise strong concerns for non-governmental organizations involved in environmental protection.

We have attempted to write this restatement in a succinct manner comprehensible to non-expert but informed readers while providing an entry into the technical literature. We have tried to be policy-neutral, though we realize that this can never be absolute. In a short summary of a very large subject it is impossible to survey all of the literature relevant to the environmental effects of the very many types of EDCs. While our review is inevitably selective, we have tried to emphasize what, in the judgement of the authors, are the generic issues of relevance to multiple EDCs.

2. Methods

This evidence summary was produced using a similar procedure to that used in previous restatements (e.g. [7,8]). The literature on EDCs and wildlife was reviewed and a first draft produced by a subset of the authors. At a workshop, all authors discussed and assessed the different evidence components in the light of the strength and quality of the available literature. Subsequently, using a restricted set of terms (see Appendix A, ¶ 3), each piece of evidence was assigned a code with our assessment of the nature of the evidence base.

A revised evidence summary was produced and further debated electronically to produce a consensus draft. The restatement was then sent to 28 stakeholders or stakeholder groups, including scientists involved in environmental pollution research, representatives of the pharmaceutical, water and chemical industries and non-governmental organizations concerned with environment and conservation, and UK government departments and statutory bodies responsible for environmental chemicals. We asked them to judge whether the literature had been fairly covered

and that we had not inadvertently overlooked key evidence, and to review the evidence codes outlined above. We also asked the stakeholders to comment on whether the restatement achieved its aims of being policy-neutral and not a work of advocacy. The document was revised in the light of much helpful feedback. Though many groups were consulted, the project was conducted completely independently of any stakeholder and was funded by the Oxford Martin School (part of the University of Oxford).

3. Results

The summary of the natural science evidence base relevant to policy-making on EDCs and wildlife is given in Appendix A, with an annotated bibliography (which includes a glossary of technical terms) provided as electronic supplementary material.

4. Discussion

In this restatement, we have used the World Health Organization (WHO) definition (see Appendix A, ¶ 4) of an EDC. This is probably the most commonly employed, though not without issues. For example, as noted above, some substances cause adverse effects but at concentrations that would seldom, if ever, occur in the field. The WHO definition would include them in this category, but the many everyday chemicals involved are not typically considered EDCs.

Even if a chemical is shown to have endocrine disruptive activity on wildlife by the WHO definition, the chief issue for regulators is whether the substance causes harm at the population and ecological community levels. This is often challenging to determine as there are few or no baseline population data available for most species, and typically we have a poor understanding of how different factors affecting mortality and fecundity combine to influence population abundance and resilience.

If an adverse effect is observed in wildlife, determining its cause and identifying any association with a particular chemical compound can be extremely difficult. In almost all cases where an EDC (or mixture of EDCs) has caused adverse effects on wildlife, the connection with exposure to the EDC(s) has been established only after the wildlife population had declined. Improved prediction of which compounds may cause harm when released into the environment would be very helpful. One challenge is to understand how different EDCs combine to affect wildlife. At the moment the potential and actual effects of EDCs (and other chemicals) are generally evaluated on an individual basis, while wildlife populations are exposed to complex cocktails of compounds that can interact with each other [9].

Finally, we note a number of limitations of this study and discuss how it might be extended.

First, we are aware that in attempting to discuss EDCs as a category of chemicals we were unable to provide a detailed evidence summary of all the work relevant to every EDC, due to the numbers and varieties of substances involved. The rationale behind our approach was to discuss common issues relevant to many EDCs, as well as to learn lessons from particular types of chemicals that have been shown to be harmful to wildlife and have thus been banned or their use severely restricted. Restatements for specific EDCs in which the literature is more comprehensively surveyed could be produced if requested by policy-makers. Previous restatements on

neonicotinoid insecticides [7,10] are examples of more targeted studies (involving pollutants that are not EDCs) where a greater coverage of the literature was possible.

The second limitation to our study is that we have focused only on the effects of EDCs on wildlife and not on humans. The reason for this is that the two issues are somewhat different. Society has a very low tolerance of harm done to individual humans, while for wildlife the impacts on populations are typically considered most important. Sources and pathways of exposure to humans and wildlife may also be different. Nevertheless, as we discuss in the restatement, the two topics are related, and bringing them together in the future in the context of the 'One Health' [11] agenda may be valuable.

Finally, the restatement focuses on the natural science evidence base relevant to the regulation of EDCs. Policy-makers seeking to shape regulatory regimes will also require evidence about the economic costs and benefits of different interventions, as well as their political and social acceptability. Performing economic cost-benefit analyses in this area is complicated because of the need to include not only the direct financial impact of regulation (or lack thereof) on industry, consumers and government, but also the direct and indirect economic consequences of the effects of EDCs on human health and the state of the environment. There are also other topics in the social sciences and humanities, including the history and political economy of regulating pollutants in the environment, where research may be valuable to policy-makers in understanding the desirability and acceptability of different modes of chemical regulation to society [12].

Data accessibility. This article has no additional data.

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Appendix A

(A) Introduction and aims

1. Endocrine disrupting chemicals (EDCs) are substances that alter the function of the endocrine (hormone) system of humans and animals, leading to adverse effects on individuals or populations. Some EDCs, singly or as mixtures, can cause negative effects at very low concentrations and

include pollutants that have been shown to severely harm various species of wildlife.

2. The restatement aims to summarize the science evidence base contributing to the development of policy on the impact of EDCs on wildlife. Effects on human health are not covered. It does not attempt to survey comprehensively all evidence relating to every class of EDC, but highlights key generic issues of relevance to policymakers.
3. An assessment by the authors of the nature of the different evidence components is provided. We use the following descriptions, which explicitly are not a ranking, indicated by abbreviated codes.

- [B] Background material, for example describing basic chemistry, legislation etc.
- [S] Strongly supported by a substantial evidence base where further information is unlikely to change the current consensus.
- [L] Less strongly supported by the existing evidence base and where further information might alter the current consensus.
- [E] Expert opinion based on information from related substances or general principles from different fields of science.

(B) What endocrine disrupting chemicals are

This section defines EDCs and gives some examples of better-studied classes, though without providing a comprehensive catalogue.

4. We follow the World Health Organization (WHO), which defines an EDC as 'an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub) populations' [B].
 - a. The endocrine system is made up of the glands and other tissues that secrete hormones: molecules that transmit information within the body [B].
 - b. Hormones can be biologically active at very low concentrations, often in the parts per trillion (ppt, 10^{-12}) to parts per billion (ppb, 10^{-9}) range [B].
 - c. The WHO definition applies to both human and wildlife. It implies that for a substance to be an EDC, it must have an adverse effect on the organism. The demonstration that a chemical alters endocrine function is not enough without harm being demonstrated (other definitions do not have this requirement). Whether harm to the individual affects population viability is a critical question in assessing the ecological effects of EDCs [B].
 - d. The WHO refers to substances that possess properties that might be expected to lead to endocrine disruption in an intact organism, its progeny or (sub)populations as 'potential EDCs' [B]. The European Food Safety Authority (EFSA) refers to substances that interact or interfere with the endocrine system, but do not lead to adverse effects, as 'endocrine active substances' [B].
 - e. Adverse effects are defined as a 'change in the morphology, physiology, growth, development, reproduction or lifespan of an organism that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress or an increase in susceptibility to other influences' [B].

5. There is uncertainty about the fraction of synthetic chemicals entering the environment that are EDCs. Over 140 000 compounds have been registered under the EU regulation Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), of which roughly 30 000 are in common use. Most of these have not been tested for endocrine disrupting effects in the laboratory, and fewer have been investigated *in vivo*. The number of chemicals so far found or suspected to have ED effects is 800–1000 [L].
 - a. High-throughput laboratory screens are available to test large numbers of compounds for evidence of endocrine activity (for example the US Environment Protection Agency's Tox21 programme has assessed over 10 000 compounds *in vitro* for endocrine disrupting and other adverse effects). While valuable as an initial screen, the assays can produce false negatives and false positives and cannot cover all the ways that EDCs may harm wildlife [L].
 - b. The degradation products and metabolites of EDCs may also be EDCs. While their effects will be observed during *in vivo* testing, these metabolic products are less frequently subject to testing *in vitro*. Furthermore, *in vitro* testing systems do not necessarily capture the processes of metabolism that EDCs undergo in an intact organism. Cases are known where secondary products are more potent EDCs, or are present at higher concentrations in the environment, than the parent molecule [S].
6. EDCs in the environment may be (or be derived from) molecules specifically used because of their effects on the endocrine system in humans or wildlife (for example, certain steroid contraceptives, other pharmaceuticals and some pest-control products) or they may be used for completely different purposes with their EDC activity being coincidental (examples include compounds used as plasticizers or flame retardants, and in personal care products) [B].
 - a. While most problematic EDCs are synthetic chemicals, some are natural. For example, the thyroid disrupter perchlorate (¶ 11.e) occurs in natural mineral deposits, while phyto-oestrogens in plants (which may have oestrogenic or anti-oestrogenic effects) can enter the environment from pulp mill effluents (¶ 13.c) [B].
 - b. Some EDCs can also be classified 'persistent organic pollutants' or POPs—highly stable, typically halogenated organic compounds with high lipid solubility. Not all POPs are EDCs [S].
7. The potential threat to wildlife from EDCs became widely accepted in the 1990s, leading to national or international prohibition of some substances, though in a number of cases harm was established and bans enacted before endocrine disruption was identified as the mode of action. Continuing problems result from the persistence of these substances in the environment or their continued use in some countries [B].
 - a. Tributyltin (TBT) was used widely in antifoulant boat paints. Observations of masculinization and sterility of gastropod molluscs in the 1970s, especially in marinas and harbours, led to its identification as a potent mollusc EDC (though initially its mode of action was incorrectly identified) [S]. It persists in anaerobic (low oxygen) marine sediments from which it can re-enter the water body and harm molluscs [S]. National then global bans (2008) have reduced amounts of TBT in the environment to a level that has allowed many marine mollusc populations to recover [S].
 - b. DDT (Dichlorodiphenyltrichloroethane) is an organochlorine insecticide that was used widely in agriculture before bans were introduced in different countries from the 1960s due to its persistence and impacts on both human health and wildlife. Ornithologists observed high incidences of egg shell breakage in nests of birds of prey that were spatio-temporally correlated with DDT use. Experiments (on other bird species) confirmed that the DDT metabolites (DDE and DDD) reduced the reproductive success of birds of prey through egg-shell thinning, probably caused by endocrine disruption in the shell-producing gland, though the precise mechanism is still not clear [S]. A global ban was instituted in 2001, though restricted application in disease vector control is still permitted [B]. This has reduced levels of DDT in the environment and has contributed to the recovery of a number of bird of prey populations in Europe and North America [S]; however, continuing high levels of DDT in Adélie penguins are probably due to its recent release from glacial meltwaters [E].
 - i. Many other organochlorine pesticides (for example dieldrin, endosulfan and dicofol) were also restricted globally or regionally and have subsequently been shown to be EDCs [L, S]. An accidental spill of dicofol into a Florida lake was followed by declines in alligator numbers that have been attributed to its endocrine-mediated effects [L].
 - c. Polychlorinated biphenyls (PCBs) were used widely in industry, particularly in the manufacture of electrical equipment. They impair reproductive and other endocrine functions. From the late 1960s they were found to be present at concentrations high enough to cause toxic effects in many species of wildlife [S]. Concerns for wildlife were raised when farmed mink feeding on Lake Michigan coho salmon suffered reproductive failure due to high levels of PCB in their food [S]. Very high PCB concentrations in Arctic predator and some cetacean and seal populations in European waters have been correlated with long-term population declines and low rates of reproduction [S]. There are numerous types (congeners) of PCBs which differ in their persistence and endocrine properties. Regional and, from 2001, global bans were introduced, subsequent decline of PCBs and other persistent organic pollutants (e.g. DDT ¶ 7b) have been linked to improvements in reproductive success and higher populations of fish-eating vertebrates such as grey seals, otters and fish eagles in northern Europe. However, as they are highly persistent in the environment and continue to pose a threat to some wildlife species.
 - i. For example, no orca calves have been observed in 25 years in a population from north-west Scotland and west Ireland where levels of EDCs (in particular, PCBs) are above the toxic equivalency factor (¶ 19.g.ii) expected to have adverse effects, and higher than those seen elsewhere in the world [S]. A recent modelling study predicts that 40% of global orca populations face extinction in the next 100 years due to PCBs. Populations near sources of pollution and those which feed higher in the food chain are most at risk [L].
8. Natural oestrogens and those used in human contraceptives (which may be the same compounds found in humans and other animals or synthetic molecules with similar actions) raise concern because of the amounts entering the

environment via wastewater, the cumulative effect of multiple substances (see ¶ 19.g) and/or because they have effects on wildlife at very low concentrations.

- a. The effects on wildlife of both natural oestrogens (oestrone, E1; oestradiol, E2; and oestriol, E3), and synthetic oestrogens (17 α -ethinyl oestradiol, EE or EE2) used in the contraceptive pill were first noticed in the 1980s when feminized male fish were seen in rivers near municipal wastewater outflows [S]. This observation prompted experiments that demonstrated the presence of oestrogens in the environment were the cause [S] (also see ¶ 24.a).
 - b. Comparison of rivers upstream and downstream of wastewater treatment plants have frequently demonstrated increased feminization (intersex) downstream [S]. The degree to which this affects population densities is not clear, and complicated to determine in species stocked for angling [E]. Studies comparing fish population density in rivers with and without wastewater plants have not found differences, though determining how different environmental factors affect fish abundance is challenging [L].
 - i. There were no differences apparent in the effective population size of roach living in five river catchments with differing levels of wastewater effluent [L].
 - c. Livestock waste is a further source of oestrogens in the environment [S]. The impacts are similar to those caused by human-derived oestrogens from wastewater treatment plants [S].
9. Many pharmaceuticals have endocrine effects. While these have the potential to harm wildlife, their use is relatively unrestricted because of their human health importance [B]. Some examples of high-volume pharmaceuticals include:
- a. Metformin is extensively prescribed, primarily for Type II diabetes; large amounts enter the environment via municipal wastewater. One study has suggested that it may act like a feminizing oestrogen in fish, but this is not proven [L]. Use is expected to increase with the growing incidence of Type II diabetes [E].
 - b. Use of anti-depressants is increasing. Fluoxetine (a selective serotonin reuptake inhibitor [SSRI] marketed as Prozac) is present in municipal wastewater and in the environment. Possible effects on wildlife have been investigated, but it is not yet clear whether typical concentrations are high enough to cause adverse effects [L]. SSRIs mediate a change in neurotransmitter balance with secondary effects on the endocrine system, and there is debate as to whether SSRIs should be considered EDCs [L].
 - c. Bicalutamide and cyproterone acetate are the most commonly prescribed anti-androgens for prostate cancer, and so of potential concern as EDCs in wildlife. Modelling of likely concentrations in UK rivers, and experimental studies on fish, indicated that harm was unlikely to occur at present rates of use [L].
 - d. The progestins are a class of drugs that have similar effects to the hormone progesterone [B]. They are used for contraception, in hormone replacement therapy and as cancer drugs [B]. Individual progestins at concentrations similar to those predicted to occur in UK rivers have been shown in laboratory experiments to have adverse effects on fish and frog reproduction [S], and it is likely that the effects of different types of progestin will combine additively [E] (¶ 19.g).
10. Veterinary pharmaceuticals used in agriculture, in particular those used in relatively large quantities for economic reasons (for example, growth promotion) rather than health reasons, may become environmental EDCs (see also ¶ 12.a) [S].
- a. For example, trenbolone, an anabolic steroid used in the USA and some other countries (banned in the EU) to increase muscle growth in beef cattle, is found in agricultural run-off at concentrations that may affect fish and frog reproductive physiology [S].
11. A number of EDCs with the potential to affect wildlife continue to be used in industry because the extent of their harm is not certain or because of the lack of economically viable, non-EDC substitutes [E].
- a. Bisphenol A (BPA) is found in many plastic products and enters the environment through wastewater and product disposal [B]. There is evidence showing that it can affect reproduction (due to its oestrogenic properties) [S] and that it can also affect neurodevelopment (perhaps through perturbations of thyroid hormones) [L]. BPA may have effects on some wildlife at concentrations regularly observed in the environment [E]. Human health concerns have led to some restrictions (such as use in baby-feed bottles) and to its recent classification as a substance of very high concern (SVHC) under EU REACH (¶ 26) legislation [B].
 - b. Phthalates are plasticizers used to make plastics more pliable and in personal care products. They are among the most abundant man-made chemicals in the aquatic environment, entering through municipal wastewater, sewage sludge application and poor industrial waste disposal [S]. Some phthalates are considered to be risks to human health because of the effects on reproductive and thyroid endocrine systems, and their use in children's toys is restricted in the EU and other jurisdictions [B]. In the laboratory, some phthalates have been shown to have endocrine effects in wildlife, but at above environmentally relevant doses [L].
 - c. Polyfluoroalkyl and perfluoroalkyl substances (PFASs) are used in a variety of industrial processes as well as in fire-fighting foam. Some can affect reproductive and growth endocrine systems, and their presence in humans led to a ban on certain ('long-chain') forms. While they are persistent and bioaccumulate (¶ 17) [S], evidence about whether they cause harm is limited [E]. Other ('short-chain') PFASs continue to be used in industry [B].
 - d. Polybrominated diphenyl ethers (PBDEs) are used as flame retardants in furnishings and electronics, and can have adverse effects on thyroid hormone function [S]. They are persistent and bioaccumulate (¶ 17) and have been found in wildlife throughout the world, and some types (the penta-, octa- and deca- forms) are now banned under international conventions or regional legislations [B].
 - e. Perchlorate is an oxidizing agent used in solid rocket fuels and is also naturally present in some mineral deposits mined as fertilizers [B]. It has been shown to interfere with iodine uptake by the thyroid gland in amphibians, leading to retardation of metamorphosis and reduced growth rates. Thyroid disruption has been demonstrated in some North American wildlife near rocket launching facilities [L].

- f. Nonylphenol is a breakdown product of alkylphenol ethoxylates which are used in manufacturing as surfactants [B]. Nonylphenol and other alkylphenols bind to the oestrogen receptor and have been shown to cause feminization in fish [S]. Nonylphenol ethoxylate has been classified as a 'priority hazardous substance' under the EU Water Framework Directive (¶ 26.b) and its use is restricted in the European Union. However, in other jurisdictions, particularly in industrial areas, concentrations in rivers can be high enough that negative effects on wildlife are very likely [E].
12. There is uncertainty about whether some substances that are known to be harmful to wildlife should be classified as EDCs. This is significant as some jurisdictions have specific regulations governing EDC use.
 - a. Diclofenac is a non-steroidal anti-inflammatory drug (NSAID) used in human and veterinary medicine [B]. It was used to alleviate suffering in cattle in India (where it is now banned). Severe declines (greater than 95%) in vulture populations occurred due to feeding on the carcasses of treated cattle [S]. Initially thought to be an EDC, diclofenac is now known to cause visceral gout and kidney failure through interfering with uric acid transport [S].
 - b. Atrazine is a herbicide used for agricultural weed control in many countries (it is no longer registered in Europe due to concerns about ground water contamination) and enters the environment via spray drift and agricultural run-off [B]. There is some evidence atrazine may lead to feminization of amphibians (and possibly other vertebrates) [L]. Atrazine may also reduce amphibian metamorphosis success, an indication of thyroid hormone disruption [L]. The evidence for the endocrine disruptive effects of atrazine under field conditions is highly contested and politicized, with examples of failure to replicate results and accusations of bias directed at both industry and non-industry researchers [E].
- b. Commercial export of waste, in particular to countries with weak environmental protection, can result in new sources of EDCs entering the environment [S].
- c. Pulp mill effluent contains a range of chemicals, and its composition depends on the processes used and tree species; many plant steroids are endocrine-active substances [B]. Male-biased sex ratios, increases in the expression of male secondary sexual characteristics, changes in fish mating behaviour and decreases in egg production have been found in various species of fish living downstream of pulp mills or experimentally exposed to pulp mill effluent [S].
14. The level of dilution influences the effects of EDCs entering the environment via wastewater discharge. Domestic wastewater can form a high fraction of flow where population densities are high alongside rivers of modest dilution capacity (for example as in much of the UK). Dilution is greater in marine environments, though less so in harbours and shallows seas compared with major oceans [S].
15. Once in the environment, some persistent EDCs (in common with other pollutants) are volatilized and transported over long distances in the atmosphere before redeposition, or are moved long distances by ocean currents [S].
 - a. Persistent EDCs (and some other substances) tend to accumulate at high latitudes because cold oceans hold more dissolved gases, because biodegradation rates are slower at low temperatures and because the probability of re-volatilization into the atmosphere is lower in cold regions [S].
16. EDCs (like other compounds) vary considerably in the rate at which they are broken down in the environment [S]. The half-life of EDCs such as natural oestrogens (¶ 8) is a few days in the aquatic environment while TBT (¶ 7.a) and some forms of PCBs (¶ 7.c) and other organochlorines (¶ 7.b) can persist for decades in soils and sediments [S].
 - a. Concentrations of EDCs in the environment are a dynamic balance between release and breakdown. Persistent compounds break down slowly in the environment but those with rapid turnover (for example BPA [¶ 11.a] or the synthetic oestrogen EE2 [¶ 8]) may still occur at concentrations that may have effects on wildlife if they are continuously released at a sufficiently high rate (termed *pseudopersistence*) [B].
 - b. EDCs can be sequestered in parts of the environment where breakdown or dilution is reduced (for example, in sediments, glacial ice or the deep oceans) and then released at a later time from what become secondary sources of legacy pollutants.
 - c. EDCs used in industry and construction (in particular PCBs [¶ 7.c] and fire retardants [¶ 11.d]) can enter the environment later at the time of disposal or demolition of the buildings into which they are incorporated (¶ 31) [S].
17. EDCs vary in the degree to which they can persist in animal bodies (as do non-EDC contaminants). Lipophilic molecules (which associate with fat) tend not to be excreted and so can increase in concentration (*bioaccumulation* or *bioconcentration*). Predators can acquire EDCs from their prey and their concentrations often increase higher in the food web (*biomagnification*). The two processes of bioaccumulation and biomagnification explain the high concentrations of some EDCs in long-lived apex predators when compared with levels in the environment [S].

(C) How endocrine disrupting chemicals enter and persist in the environment

This section describes how EDCs derived from human activity enter the environment and their subsequent fate. These pathways are largely shared with other non-EDC pollutants.

13. EDCs can enter the environment from point and diffuse sources. The former includes sites where treated and untreated wastewater (via domestic, hospital and industrial sources) is routinely discharged into rivers, waste landfill sites, and incidences of accidental pollutant release. The main diffuse sources are pesticide spray drift and agricultural runoff containing agrichemicals and compounds derived from animal manure. Use of wastewater sludge on agricultural land can be a source of EDCs derived from pharmaceuticals, personal care products and household chemicals such as PBDEs (¶ 11d) used as flame retardants [S].
 - a. Wastewater and landfill leachate contain many different EDCs that vary in time and space [S].

- a. Concentrations of persistent EDCs (e.g. PCBs ¶ 7.c, DDT ¶ 7.b) tend to increase with age in many vertebrate species and so can be particularly high in long-lived individuals [S].
- b. Due to biomagnification, the amount of PCBs (¶ 7.c) in 200–300 g of salmon flesh in Lake Ontario has been estimated to be equivalent to that in ‘several million litres of lake water’ [S].
- c. In mammals, lipophilic EDCs can be transferred to offspring during gestation and lactation. Marine mammals have a very high milk fat percentage leading to substantial lipophilic EDC transfer, particularly in those species that have a relatively long lactation period (for example, cetaceans and polar bears) [S].

(D) How we know if an endocrine disrupting chemical is a problem in wildlife

This section describes how evidence is obtained about the potential endocrine disrupting properties of different chemicals in wildlife. The section begins with studies in the laboratory and moves to information collected in the field.

18. Some substances used in industry and medicine are identified as EDCs when tested for their potential toxicity to human health. As endocrine pathways tend to be highly conserved across different types of organisms such studies are informative in identifying potential threats to wildlife (termed *read across*). Permissible human exposure levels are conservative, and bans and restrictions to protect human health will indirectly benefit wildlife [B].
 - a. Animals distantly related to humans and other vertebrates, and which have very different physiologies, may show unexpected effects not seen in vertebrate toxicity screens. An example is the strong effect of TBT (¶ 7.a) on reproduction in molluscs [S].
 - b. Read across refers to intrinsic risk and can be less informative where wildlife and human exposure are very different. For example, many EDCs occur at relatively high concentrations in aquatic environments where absorption across the epidermis or gills may cause harm not anticipated by laboratory tests with EDCs administered orally to terrestrial animals [B].
19. Laboratory experiments can be carried out to assess the potential endocrine-mediated harm of varying concentrations of a chemical on different animal species (*in vivo*) or in cell culture assays (*in vitro* testing). The experimenter may measure change in hormone levels directly or effects on a *biomarker* (see ¶ 22.a) or an *endpoint* (for example an effect on behaviour, fecundity, growth, disease resistance or survival). The results will be influenced by duration and mode of exposure (for example whether in the animal’s diet or environment), and by the sex and development stage of the animals used. Chronic effects of long-term exposure are more difficult to study compared with acute effects, and are typically estimated using standardized short-term or longer-term assays. Standardized multigenerational assays have been developed for a very limited range of species including species of small fish, rodents and some invertebrates [B].

- a. Only a limited set of species can be maintained in the laboratory (legally and logistically), and work on many species of most concern (for example, endangered species or large vertebrates) is typically impossible. Even for those species that can be maintained in the laboratory it will not be possible to measure all potentially relevant endpoints. Extrapolation of results from laboratory to wildlife species must therefore be made with caution. Logistic and welfare considerations limit the number of animals that can be used in an experiment, reducing the statistical power to detect small effects [B].
- b. Experiments using a range of exposure concentrations are used to calculate ‘no observable adverse effect levels’ (NOAEL) or ‘lowest observable adverse effect levels’ (LOAEL), which are then used to define ‘safe’ thresholds. Non-linearities in the dose–response relation and the difficulties of statistically estimating weak effects may lead to these levels being either over- or under-estimated [B].
- c. Effects observed in the laboratory are often termed ‘environmentally relevant’ if they involve concentrations that have been recorded in the field. In using such a term (or a similar expression), it is desirable to distinguish between peak concentrations (for example near a wastewater effluent site or at a particular time of year) and more typical concentrations in the broader environment and over all seasons [E].
- d. Non-monotonic dose responses (NMDRs) occur where the harmful effect of an EDC increases (or decreases) at both low and high concentrations. There are some laboratory reports of NMDRs from *in vitro* experiments and *in vivo* biomarkers [L]. However, further studies are needed to confirm the reproducibility of these observations, which would have implications for testing strategies and risk assessment [E].
- e. The adverse effects caused by chronic low-level exposure (‘low-dose effects’) may not necessarily be predictable from the effects of higher test doses over shorter exposure times. Current chronic ecotoxicity tests generally include lower concentrations than those used in the past [E].
- f. There is strong evidence for maternal transfer of some EDCs to offspring via eggs in fish, amphibians, reptiles and birds, or via milk or across the placenta in mammals [S]. There is weaker evidence for other transgenerational effects [L].
- g. Wildlife species are exposed to complex mixtures of chemicals. There is evidence that EDCs with similar endocrine action combine additively to affect laboratory model animals [S], and those with opposing effects (for example, masculinizing and feminizing compounds) may counteract each other [E]. Overall, knowledge of how EDCs interact with each other and with other pollutants is limited [E].
 - i. For example, five steroid pharmaceuticals, each at levels below the NOAEL, led to a reduction in the numbers of eggs produced by fish when present together (consistent with a model of independent action).
 - ii. Indices such as oestradiol equivalence for oestrogenic compounds or the toxic equivalency factor for PCBs and related compounds are used to assess the additive effect of defined classes of EDC.

20. Statistical, physiological and population dynamic models can be used to extrapolate laboratory data to estimate individual and population harm [B].
 - a. Understanding how molecular and physiological effects of EDCs observed in the laboratory relate to individual harm in the field can be difficult. For example, a dose that under relatively benign laboratory conditions causes minor harm may have a more major effect in the wild where animals are subject to other biological and non-biological stressors [E]. Conversely, laboratory tests may expose animals to constant concentrations of a substance that they may encounter intermittently in the field [E].
 - b. Wildlife populations may be exposed to highly variable levels of EDCs, possibly restricted to certain life-history stages, factors that complicate extrapolation of laboratory data to the field [E].
 - c. Translating the harm done to individuals to effects on population size and viability is hard as it requires knowledge of the species' ecology. For example, if the size of a population is limited by food then the deaths or reproductive failure of some individuals may not cause significant population decline as the survivors have more food. In contrast, if a population is near a threshold size for viability (possibly because of difficulties in finding mates) relatively few failures to breed could cause extinction [E].
21. Direct measurements of some persistent EDCs can be made in wildlife, and the potential harm they cause inferred from laboratory experiments (typically on different species). [B].
 - a. The presence of the compound *per se* does not necessarily indicate an adverse effect [L]. Some adverse effects may only become apparent long after the compound has dissipated [S] and early life exposure may change sensitivities to other compounds in later life [L].
 - b. High and potentially harmful concentrations of highly persistent EDCs such as PCBs (§ 7.c) occur in the tissue of some predatory birds and sea mammals due to bioaccumulation and biomagnification (§ 17) [S].
 - c. Determining the effect of individual substances in mixtures of EDCs and other substances is difficult (§ 19.g) [E].
22. Observations in wildlife of hormone levels, biomarkers or pathologies associated with endocrine disruption can signal the presence of one or more endocrine-active chemicals in the environment. The signal can suggest the type of EDC involved but may not provide an indication of the specific compound [L].
 - a. In this context, the term 'biomarker' refers to something that can be measured in an organism that covaries with processes influenced by EDCs. While a biomarker change is not an adverse effect, biomarkers are valuable because they can provide an indication of endocrine effects before the effects are strong enough to adversely affect individual health or population viability. However, biomarkers may be affected by other factors in addition to EDCs and it can be difficult to determine the relationship between these changes and individual or population harm [E].
 - i. The most widely used biomarker in wildlife is the egg-laying vertebrate egg protein precursor vitellogenin. The presence of the protein (or transcription of the gene responsible) in males indicates exposure to oestrogenic compounds [S].
 - b. Interference with the hormones involved in sexual development and reproduction can result in a variety of pathologies including feminization of males, masculinization of females, intersexes (individuals showing both male and female characters), changes in mating behaviour, sex ratio biases, poor sperm viability and reproductive failure [S]. Compounds include TBT (§ 7.a), DDT (§ 7.b), PCBs (§ 7.c) and oestrogens (§ 8).
 - c. Thyroid hormones are important in regulating the basal metabolic rate and heart rate, and for growth and development, particularly of the long bones and brain. They are also important in the control of metamorphosis timing in amphibians [B]. Correlations between thyroid hormone levels and different EDCs, particularly some types of PCBs (§ 7.c) and PBDEs (§ 11.d), have been reported in a variety of different wildlife, and there is evidence of a correlation between bone density and PCB exposure in mammals [L].
 - d. Instances of impaired immunity in wildlife have been associated with endocrine active substances including perfluorooctanoic acid (a PFAS) (§ 11.c), TBT (§ 7.a), PCBs (§ 7.c) and trenbolone (§ 10.a), but the extent and type of effects these chemicals have on immunity in wildlife are poorly understood [L].
23. Concern about specific EDCs (e.g. DDT § 7.b, PCBs § 7.c) has arisen because of observations of population declines in wildlife followed by physiological and toxicological studies that have demonstrated endocrine pathologies or high concentrations of that compound. Because the association is correlational rather than experimental, establishing a causal link can be challenging [B].
 - a. EDCs may reduce population viability through negative effects on reproduction [S]. This may not be quickly recognized in long-lived species as there is little immediate effect on population size [B].
24. In principle, field experiments can be used to test the effects of EDCs on wildlife populations, but these are expensive and logistically difficult to carry out with sufficient replication [B].
 - a. Researchers added the artificial oestrogen 17 α -ethinyl oestradiol (EE2), used in contraceptive pills (§ 8) to a lake in Canada. The resulting concentrations of EE2 varied during the year, and at their highest were approximately an order of magnitude greater than the concentrations found in typical effluents (though concentrations of all oestrogenic compounds may reach these levels). Compared with two control lakes and previous population data, one species of fish (fathead minnow) declined drastically in numbers, though the responses of the other species were more variable [S].

(E) Major European and international chemical legislation concerning endocrine disrupting chemicals

This section briefly indicates some of the major international legislation relevant to EDCs.

25. The Stockholm Convention on Persistent Organic Pollutants (POPs) is a United Nations treaty regulating the

production, use and release of POPs. While many POPs are EDCs, they are covered under the Stockholm Convention due to their persistent and bioaccumulative properties rather than because of endocrine disruption [B].

- a. Chemicals are listed in three categories: Annex A, production and use to be eliminated; Annex B, use restricted; Annex C, production and unintentional release to be reduced with the goal of elimination [B].
26. European Union legislation affecting EDCs differs in the degree to which it takes a hazard-based (emphasizing intrinsic endocrine disrupting properties) or risk-based (emphasizing exposure in addition) approach. Plant Protection Products (such as pesticides) and Biocidal Products legislation emphasize hazard while REACH legislation (which treats EDCs as 'substances of very high concern') emphasizes risk [B]. Under REACH, many substances, including EDCs, may be subject to 'risk mitigation measures', which reduce human exposure and environmental release. While EDCs are assumed to have no safe threshold, plant protection products that are EDCs may be used where human exposure is negligible ('cut-off criteria') [B].
- a. In addition to EU laws, countries in the Union are subject to a number of global and regional conventions that apply to particular types of substance.
 - b. Other European legislation relevant to EDCs includes the Water Framework Directive, which deals with pollution of ground and surface water by substances including, but not limited to, EDCs; the Environmental Quality Standards Directive (which includes a 'watchlist' of chemicals of potential concern) and the Cosmetics Regulation that deals with personal care products containing EDCs [B]. The Marine Strategy Framework Directive deals with pollution of the marine environment; this includes the monitoring of both contaminant concentrations and their biological effects.
 - c. Human pharmaceuticals are regulated separately and are exempt from REACH legislation. An environmental assessment of risks associated with their production and consumption phase is required for products registered post-2004 (EU Directive 2004/27/EC) but authorization cannot be denied on environmental grounds [B].
 - d. The same type of compound can be treated differently by multiple pieces of legislation, for example fungicidal azoles that are used in crop protection and pharmaceuticals [B].
27. Trade in electronic waste and other hazardous materials is governed by the UNEP Basel Convention on the Control of Transboundary Movements of Hazardous Wastes and their Disposal. In addition, the Strategic Approach to International Chemicals Management (SAICM) of the UNEP and the WHO is a policy framework designed to promote chemical safety globally [B].
- restricted (though often the primary motivation for a ban is risk to human health) [B].
- a. Banning (or restrictions on use) leads to a reduction in environmental concentrations, though slowly in the case of more persistent molecules (with PCBs (§ 7.c) being particularly problematic) [S].
 - b. There is evidence of the recovery of wildlife populations in the years (sometimes decades) following chemical bans, e.g. TBT (§ 7.a), DDT (§ 7.b) and PCBs (§ 7.c).
29. Incentivizing replacements for EDCs by chemicals that do not cause endocrine disruption, or are less potent EDCs, can reduce threats to wildlife [E].
- a. There are cases where proposed alternatives have subsequently been shown also to be EDCs. For example, PBDEs (§ 11.d) were developed as a replacement for PCBs (§ 7.c) but were found to be persistent and bioaccumulating EDCs and subsequently some types were banned. Other bromine-containing flame retardants have been developed as replacements, and have also been detected in wildlife, though without harm being demonstrated [S]. Similarly, there is concern that other bisphenol compounds used to replace bisphenol A (§ 11.a) are also EDCs, although effects are only observed at concentrations higher than those currently observed in the environment [L].
30. Wastewater treatment can substantially reduce the amounts of pharmaceutical and other EDCs (as well as other chemicals) entering the environment from this source. Interventions include (but are not limited to) percolation through granular activated carbon, treatment with ozone or wetland construction. Investment in wastewater treatment is determined both by decisions in the private sector and the regulatory environment put in place by government [B].
- a. It has been estimated that upgrading all wastewater plants to granular activated carbon treatment with the specific aim of removing EDCs would cost €30 billion in England and Wales [E]. There are other energy-intensive tertiary treatments and augmented biological treatments that effectively remove EDCs [L]. However, cost, performance and consistency vary, and long-term evaluation is needed [B].
 - b. The more strategic placement of wastewater outlets and management of water levels to reduce periods of low flow could, in theory, reduce the effects of EDCs by ensuring rapid dilution, but the costs and local acceptability of new infrastructure frequently make such changes infeasible [E].
31. Careful handling of waste and of material from industrial and domestic demolition can reduce the volume of EDCs entering the environment. For example, UK regulations require that persistent organic pollutants are either destroyed by incineration or chemical destruction, or are permanently stored underground [B].
- a. Much material containing EDCs, in particular PCBs (§ 7.c), PFASs (§ 11.c), PBDEs (§ 11.d) and other flame retardants, ends up in landfill. Choice of landfill sites and their management can reduce leaching and aerosol transport of EDCs into the environment [S].
 - b. Recycling facilities (e.g. for electronics and plastic waste) can be designed to reduce release of EDCs

(F) What can be done about endocrine disrupting chemicals

This section explores the options open to policy-makers to reduce the effects of EDCs on wildlife.

28. The production and use of some EDCs that pose threats to wildlife have been banned or their use severely

- [S]. The presence of EDCs in many products is unknown as labelling their presence has not been required [B].
- c. Large quantities of waste products enter the environment due to inadequate waste collection and poor waste processing, particularly in developing countries [B]. The EDCs derived from plastics and electronic waste are of particular concern [E].
32. Decontamination of persistent EDCs from heavily polluted sites is possible, although complex and expensive. It is most often carried out where there is a risk to humans. There is a range of decontamination methods suitable for different substances and substrates, including incineration, bioremediation, chemical methods [B].
 - a. The US EPA Superfund Program has supported the remediation of almost 400 sites, many of which were contaminated with EDCs. Clean-up often involves removal of soil or sediment (by dredging in rivers or harbours) then containment of polluted material. Monitoring of remediated sites has shown improvements in indices of ecological health [S].
 33. Specific measures can be taken to reduce the load of EDCs derived from human pharmaceuticals (§ 9) in sewage treatment plants [B].
 - a. Better assessment of possible endocrine-mediated effects on non-human animals, monitoring of sales and prescription data, and a better understanding of their passage through the body and half-life in the environment, can help predict problems to wildlife [E].
 - b. Pharmaceutical EDCs can enter the environment through incorrect disposal which can be reduced by drug take-back schemes (mandated in the European Union) [E]. It has been estimated that 5–10% of prescribed drugs are not used, and of this 12–27% are disposed of in domestic drains [L].
 - c. There is research into 'green' products that have equal therapeutic effectiveness but reduced persistence in the environment or cause less harm to wildlife [B]. Environmental assessments of many products are available and may be used in prescribing [E].
 - d. For hospital and healthcare facilities where pharmaceutical use is high, separating urine from other waste and then treating by continuous electro dialysis followed by ozone decontamination may be justified [E].
 34. There is no feasible way to remove most EDCs completely from the environment, or from the bodies of wildlife. Affected populations may thus benefit from special measures to reduce other stressors (for example, habitat destruction, disease, hunting or persecution) to improve population viability [E].
 35. Monitoring EDC levels in the environment and wildlife, and the population density and reproductive success of affected species, is important in assessing the effectiveness of policy interventions, prioritizing compounds for assessments of persistence, bioaccumulative ability and toxicity (PBT), and providing early warnings of emerging EDC problems. All wildlife populations naturally fluctuate, so extended time series are required to detect trends. Monitoring can be logistically challenging for some of the most at risk environments and species (for example, large Arctic carnivores or cetaceans) [B].
 - a. The UK water industry is carrying out a national programme monitoring 70 different chemicals in effluent and water bodies including some EDCs [B].
 - b. Long-term monitoring programmes have shown persistent organic pollutants in air, water, human tissues (blood and breast milk) and wildlife (raptors and otters) have declined, indicating bans have been effective. However, monitoring programmes do not cover all EDCs of concern (e.g. PFASs § 11.c) [S].
 - c. Historical wildlife population data collected for other purposes, and archived environmental and animal samples, have been valuable in determining baselines and reference values to help interpret future data [S].

(G) Future opportunities and challenges

This section explores factors affecting EDC policy that may change in the future.

36. EDC release into the environment will be affected by demographic and economic trends. Growing populations will lead to greater releases even if per capita use or consumption remains constant. Increasing wealth in developing countries will lead to higher releases associated with greater consumption [S].
37. Recent (and probably future) advances in analytical chemistry will allow the detection of more chemicals at lower concentrations than is possible at the moment, and at a cost that will allow an expansion of chemical monitoring [E].
 - a. Increases in the amount of data on low concentrations of known or suspected EDCs in wildlife and the environment will increase demands for research on the effects of very low-level exposure on individuals and populations [E].
38. Modern molecular biology techniques offer the prospect of high-throughput screening of multiple biomarkers. Interpreting the very large datasets that result, and developing predictors of harm at the individual and especially population level, is a substantial challenge [E].
 - a. There are no *in vivo* tests available for some types of endocrine disruption or in some species [B].
39. Substantial uncertainty exists, and will continue to exist, about possible negative environmental effects of different EDCs, and the degree to which these can be predicted in advance of their introduction. The challenge to policy-makers in designing regulatory regimes is to balance these risks against the economic and other benefits of employing the substance [E].
 - a. Modern environmental economics using concepts such as ecosystem services and natural capital may be helpful in formal cost–benefit analyses, though any regulatory framework will inevitably involve political value judgements [E].
40. Climate change is likely to have both positive and negative influences on the relationship between EDCs and wildlife. Models do not completely agree on how environmental concentrations will change, particularly in the Arctic [E].
 - a. Higher average temperatures will increase the rate of volatilization (evaporation) and degradation of chemical pollutants including EDCs [L].

- b. Reduced annual precipitation may occur in some regions, leading to lower flows and less dilution of wastewater, which will increase concentrations of EDCs [L].
 - c. An increase in extreme rainfall events is expected. This may affect the frequency of point-pollution episodes from farmland and from sewer overflows into river water [L].
 - d. Climate change may cause stress for some wildlife and lessen their ability to withstand further stresses in the form of EDCs [S].
 - e. Climate change may affect the feeding ecology and thus the exposure of wildlife species; for example, earlier break-up of sea-ice has led to polar bears feeding on more heavily contaminated seal species [S].
 - f. EDCs deposited in Arctic and glacial ice may be released upon melting [S].
41. Better healthcare, ageing populations and the rise in obesity and related co-morbidities may increase the

discharge of pharmaceutical EDCs (¶ 9) into the environment (though in an ageing population of constant size, e.g. East Asia, the release of EDCs associated with contraceptives may decline).

- a. Countering this, the introduction and spread of 'green' pharmaceuticals and personalized medicine, nanotechnology and other technologies that enable better drug targeting, and so a reduction in dose, which will reduce EDC discharges [E].
42. Less developed and developing countries tend to have weaker environmental protection mechanisms, and there is typically less information about local EDC concentrations. Volatilization and long-range transport of EDCs from countries with weak regulations can have global consequences. How economic development and environmental protection proceed will determine whether their net effect as sources of EDCs increases or decreases [E].

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Appendix B

A restatement of the natural science evidence base regarding the impacts of endocrine disrupting chemicals on wildlife

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GLOSSARY

Chemicals	
BPA	bisphenol A, a plasticiser, C ₁₅ H ₁₆ O ₂ .
DDT	dichlorodiphenyltrichloroethane, an organochloride insecticide, C ₁₄ H ₉ Cl ₅ .
EDC	endocrine disrupting chemical
E1	oestrone – one of the three major endogenous oestrogens
E2	oestradiol – the primary female sex hormone
EE2 / EE	ethinyl oestradiol – a synthetic derivative of oestradiol
E3	oestriol – one of the three major endogenous oestrogens, only produced in identifiable quantities in mammals during pregnancy
OC	organochloride – an organic (i.e. carbon-based) compound containing at least one covalently bonded atom of chlorine.
PBDE	polybrominated diphenyl ethers, C ₁₂ H _{10-x} Br _x O.
PCB	polychlorinated biphenyl, chemical formula C ₁₂ H _{10-x} Cl _x
PFAS	per (or poly) fluorinated alkylated substances
POP	persistent organic pollutant. Chemicals that bioaccumulate and biomagnify, such as the organochloride pesticides.
PBT	persistent, bioaccumulative, toxic

TBT	tributyltin, contains a (C ₄ H ₉) ₃ Sn group.
vPvBvT	very persistent, very bioaccumulative, very toxic
vtg	vitellogenin
Organisations / Legislation	
CDC	Center for Disease Control (US) https://www.cdc.gov/
DEFRA	Department for Environment, Food & Rural Affairs (UK) https://www.gov.uk/government/organisations/department-for-environment-food-rural-affairs
ECHA	European Chemicals Agency https://echa.europa.eu/
EFSA	European Food Safety Authority http://www.efsa.europa.eu/
FAO	Food and Agriculture Organization of the United Nations http://www.fao.org/home/en
NHS	National Health Service (UK) http://www.nhs.uk/pages/home.aspx
OECD/OCDE	Organisation for Economic Co-operation and Development http://www.oecd.org/
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals http://ec.europa.eu/environment/chemicals/reach/reach_en.htm
UNEP	United Nations Environment Programme http://www.unep.org/
US EPA	US Environmental Protection Agency https://www.epa.gov/

US FDA	US Food and Drug Administration https://www.fda.gov/		exceeds that of its diet – i.e. levels of the compound increase up the food chain, such that highest concentrations occur in top predators.
WHO	World Health Organization http://www.who.int/en/		
Glossary of technical terms		endocrine active	Defined by the EFSA as substances that interact or interfere with the endocrine system, but do not lead to adverse effects.
additive	The effects of two compounds can be predicted from the effects of each individual compound alone.	endocrine disrupting chemical	Defined by the WHO as “an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub) populations”.
androgen	A steroid hormone (natural or synthetic) that regulates the development and maintenance of male characteristics (i.e. masculinising hormones). An anti-androgen blocks the effects of androgens.	epigenetic	A heritable change in the function of genes that does not involve changes to the underlying DNA sequences. Epigenetic changes can switch genes on or off and determine which proteins are transcribed.
adverse effect	Defined by the WHO and FAO as a “change in the morphology, physiology, growth, development, reproduction or lifespan of an organism that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress or an increase in susceptibility to other influences”.	exposure	The measurement of both the amount of, and the frequency with which, a substance comes into contact with a person or the environment.
bioaccumulation	The process in which a chemical substance is absorbed by all routes of exposure (dietary as well as dermal and respiratory paths) and thus includes food chain transfer. As the chemical is not expelled, the amount increases in the animal’s body over time, as a result the internal concentration of the chemical is greater than in the external environment.	hazard	Anything that may cause harm, such as chemicals, electricity, adverse weather etc.
bioconcentration	The process by which a chemical is absorbed by an organism only through its respiratory and dermal surfaces. As the chemical is not expelled, the amount increases in the animal’s body over time, as a result the internal concentration of the chemical is greater than in the external environment.	oestradiol	The most important of the three major natural oestrogens. Also called estradiol or E2.
biomagnification	When the concentration of the chemical in an organism	oestriol	One of the three major natural oestrogens, also called estriol or E3.
		oestrogens	The primary female sex hormones. These are steroid hormones that develop, regulate and maintain the female reproductive system (i.e. feminising hormones). There are three main oestrogens produced naturally, oestrone, oestradiol and oestriol. Oestrogens are also essential for male fertility. Synthetic oestrogens include steroidal oestrogens such as ethinyl oestradiol and non-steroidal ones such as diethylstilbestrol.

	An anti-oestrogenic compound blocks the effects of the oestrogens.		constantly present at concentrations that may have effects on wildlife because they are continuously released at a sufficiently high rate (typically in wastewater).
oestrone	One of the three major natural oestrogens, also called estrone or E1.		
organic	In chemistry, organic refers to compounds containing carbon. All known life is based on organic compounds. An organic compound will also contain hydrogen and may contain a number of other atoms.	risk	The probability that something (person, animal, environment) will be harmed (e.g. experience an adverse health effect) if exposed to a hazard, together with an indication of how serious the harm could be.
persistent organic pollutant	Organic chemical substances that possess a particular combination of physical and chemical properties such that, once released into the environment, they remain intact for exceptionally long periods of time (many years); become widely distributed throughout the environment as a result of natural processes involving soil, water and, most notably, air; accumulate in the fatty tissue of living organisms including humans, and are found at higher concentrations at higher levels in the food chain; and are toxic to both humans and wildlife. Source: Stockholm Convention (2008a).	vitellogenin	The protein from which the egg yolk is derived. Found in all egg-laying vertebrates.
progesterone	The primary progestogen synthesised by humans, it is involved in the menstrual cycle, pregnancy and embryogenesis. Often abbreviated as 'P4'.	wildlife	All non-domesticated animals, including amphibians, fish and invertebrates as well as birds, reptiles and mammals.
progestins	Synthetic progestogens with similar effects to those of the natural hormone progesterone. They have important effects on the female reproductive system and are used in hormonal birth control and menopausal hormonal therapy.		
progestogens	Alternatively called progestagens or gestagens, a class of steroid hormone (natural or synthetic) that activate the progesterone receptor.		
pseudopersistent	Compounds that breakdown rapidly in the environment (i.e. non-persistent) but are		

INTRODUCTION AND AIMS

AB1. Definition given here is consistent with that of the WHO (Bergman *et al.*, 2012).

AB2. No references cited.

AB3. Categories developed by authors based on schemes used in previous Restatements (Godfray *et al.*, 2013; Godfray *et al.*, 2014; Godfray *et al.*, 2015; Dadson *et al.*, 2017; McLean *et al.*, 2017).

WHAT ARE EDCS?

AB4. The WHO definition (Bergman *et al.*, 2012) is the most commonly used definition (Futran Fuhrman *et al.*, 2015). Vandenberg *et al.* (2016) discuss techniques to determine if a chemical meets the above definition. Solecki *et al.* (2016) discusses some of the complexities arising from the WHO definition and provides a consensus statement from a range of scientists as to how it should be interpreted. The WHO has produced two highly detailed reviews on the effects of EDCs on both humans and wildlife (Damstra *et al.*, 2002; Bergman *et al.*, 2012), as has the European Environment Agency (Weybridge Report, 1996; Weybridge+15, 2012). Matthiessen *et al.* (2018) have also recently reviewed the evidence for impacts of EDCs on wildlife populations.

- a. For an overview of the function of the different endocrine glands, see Bergman *et al.* (2012), or, for a medical focus, see Gurnell *et al.* (2010) and Weetman (2010).
- b. Vandenberg *et al.* (2012), Table 2, reports levels of different hormones in the human body. EDCs can also act at very low concentrations, e.g. TBT (Matthiessen & Gibbs, 1998).
- c. See Vandenberg (2014), Futran Fuhrman *et al.* (2015) and Zoeller *et al.* (2014) for discussion of adverse effects of EDCs. The US Environment Protection Agency (EPA) defines endocrine disrupting chemicals as “an exogenous agent that interferes with the production, release, transport, metabolism, binding, action or elimination of natural hormones in the body responsible for the maintenance of homeostasis, and the regulation of developmental processes” (Kavlock *et al.*, 1996). The EPA’s definition includes certain heavy metals not normally considered EDCs (Georgescu *et al.*, 2011; Scognamiglio *et al.*, 2016). The Endocrine Society defines EDCs as “exogenous chemical(s), or mixtures of chemicals, that interfere with any aspect of hormone action” (Gore *et al.*, 2015). Zoeller *et al.* (2014), Table 1, provides alternative definitions for endocrine disruptors; the main difference being whether “adverse effects” must be shown for the chemical to be considered an EDC. Table 2 of Zoeller *et al.* (2014) gives a range of definitions of “adverse effects”.
- d. Definition of endocrine active substances from European Food Safety Authority (2016). Definition of potential endocrine disruptor from Bergman *et al.* (2012) and Weybridge Report (1996). An example of an endocrine active substance that is not a disruptor might be sugar or caffeine at higher than usual doses (Zoeller *et al.*, 2014). All

endocrine active substances have the potential to be disruptors (European Food Safety Authority, 2016).

- e. International Programme on Chemical Safety (2009).

AB5. Hartung (2009) and Judson *et al.* (2009) report on the numbers of chemicals in use and the numbers that have undergone safety testing. The World Health Organization (Bergman *et al.*, 2012) estimates 800 chemicals are known or suspected EDCs while the US Food and Drug Administration (FDA) estimates 1000 are (Vandenberg, 2014). Futran Fuhrman *et al.* (2015) lists databases of potential or actual EDCs. For a summary of EDCs and suspected EDCs see United Nations Environment Programme and The International Panel on Chemical Pollution (2016). The OECD ranks chemicals (including many EDCs) by global production volume (OECD/OCDE, 2009). The US endocrine disruptor screening program is a tiered testing programme for EDCs, where Tier 1 identifies endocrine active substances and Tier 2 tests those for adversity and determines the dose response (US EPA, 2017c).

- a. The Tox21 screening test (US EPA, 2017a) involves 30 different cell-based *in vitro* assays of approximately 10,000 chemical tested at 15 concentrations (Huang *et al.*, 2016; Richard *et al.*, 2016). Hartung (2009) discusses the problem of false positives and negatives.
- b. Boxall *et al.* (2004) and Sumpter and Johnson (2005) review the presence and toxicity of degradation products. Manibusan and Touart (2017) reviews *in vitro* and *in vivo* tests. *In vitro* tests provide data on mechanism of action. For example, MBP, produced by metabolic activation of BPA, is more oestrogenic than BPA (Moreman *et al.*, 2018).

AB6. Actual or potential EDCs include, but are not limited to, the following: Plasticisers such as phthalates (Harris *et al.*, 1997; Oehlmann *et al.*, 2009), bisphenols (Oehlmann *et al.*, 2009; Bhandari *et al.*, 2015b), parabens (Routledge *et al.*, 1998; Boberg *et al.*, 2010); various industrial compounds: tri-butyl tin (TBT) (Sousa *et al.*, 2014), PCBs (Koppe & Keys, 2002), PBDEs (Law *et al.*, 2014; Jinhui *et al.*, 2017), PFASs (Post *et al.*, 2012), alkyl-phenols (Routledge & Sumpter, 1997; Sumpter, 2009), perchlorate (Trumpolt *et al.*, 2005), dioxins and furans (Custer *et al.*, 2005), effluent from pulp and paper mills (van den Heuvel, 2010); pharmaceuticals (Runnalls *et al.*, 2010); personal care products such as triclocarban (Chung *et al.*, 2011), triclosan (Veldhoen *et al.*, 2006); plant protection products (i.e. pesticides) such as TBT and triphenyl tin (Hu *et al.*, 2009; Sousa *et al.*, 2014), atrazine (Rohr & McCoy, 2010), organochloride (OC) pesticides (Newton, 2013; Rosner & Markowitz, 2013), glyphosate (Lancôt *et al.*, 2013; Lancôt *et al.*, 2014), vinclozolin (Gazo *et al.*, 2013), azoles (Matthiessen & Weltje, 2015). OC pesticides include DDT, aldrin, chlordane, chlordane, dieldrin, endrin, heptachlor, hexachlorobenzene, lindane, mirex, pentachlorophenol and its salts and esters, technical endosulfan and its related isomers, toxaphene (Stockholm Convention, 2008a).

- a. For details on perchlorate, see AB11.e and for pulp mills effluent see AB13.c. The impacts of phyto-oestrogens on human health are reviewed by Zaheer and Humayoun Akhtar (2017).

- b. Definition of persistent organic pollutants from Stockholm Convention (2008b). Almost all (98%) of POPs are halogenated – i.e. some of the hydrogen atoms have been replaced by fluorine, chlorine, bromine or iodine (Scheringer *et al.*, 2012). Chlorine is the most common replacement.

AB7. Vandenberg *et al.* (2009) briefly review the history of the field. The Wingspread Conference in 1991 was pivotal in determining that disparate pathologies observed in a variety of organisms were endocrine-mediated (WingSpread Consensus Statement, 1995; Colborn *et al.*, 1996).

- a. For an overview of organotin chemistry and use, see Hoch (2001), Antizar-Ladislao (2008) and Sousa *et al.* (2014), and for legislation, the International Maritime Organisation (2002). (Matthiessen, 2013), Sousa *et al.* (2013), Alzieu (2000) and Santillo *et al.* (2002) provide a comprehensive overview of the history of the discovery of the effects of TBT. The mechanism of action was eventually determined to involve interactions with the nuclear retinoid-X receptor (RXR), the peroxisome proliferator-activated receptor γ (γ PPAR) and their heterodimers (Sousa *et al.*, 2010; Matthiessen, 2013; Pascoal *et al.*, 2013; Sousa *et al.*, 2014; Lagadic *et al.*, 2017). The evidence associating TBT with gastropod declines is reviewed in Matthiessen and Gibbs (1998) and Sousa *et al.* (2013). Gastropod declines and/or masculinisation (imposex) has been reported from harbours and marinas globally (Matthiessen, 2013): e.g. in England (Gibbs & Bryan, 1986), France (Oehlmann *et al.*, 1996), North Sea (Hallers-Tjabbes *et al.*, 1994), Japan (Horiguchi *et al.*, 2000; Azuma *et al.*, 2014), New Zealand (Smith & Mcveagh, 1991), New South Wales, Australia (Roach & Wilson, 2009), South Africa (Marshall & Rajkumar, 2003), Morocco (Lemghich & Benajiba, 2007), British Columbia, Canada (Horiguchi *et al.*, 2004), Greenland (Strand *et al.*, 2006).

Harbour sediments as secondary sources of TBT is discussed in Antizar-Ladislao (2008).

Marine gastropod and bivalve populations have increased following the TBT ban (Smith, 1996; Colson & Hughes, 2004; Galante-Oliveira *et al.*, 2009; Morton, 2009; Birch *et al.*, 2013; Langston *et al.*, 2015).

- b. An overview can be found in Damstra *et al.* (2002) Chapter 4. For histories for the discovery of the effects of DDT in the UK and USA, see Newton (2013) and Rosner and Markowitz (2013) respectively.

The presence of broken eggs in nests of UK raptors was first observed in the late 1940's (Ratcliffe, 1958, 1960).

Attribution of this phenomena to DDT is reported in Ratcliffe (1967) with details in Ratcliffe (1970). Ratcliffe (1970) reported that declines in eggshell thickness also occurred in a range of other species; also see Olsen *et al.* (1993). Early experiments confirming DDT as the cause of egg shell thinning are reviewed by Cooke (1973).

Populations of peregrine falcons, the world's most widespread raptor, declined wherever DDT-induced egg-shell thinning was >17% (Newton, 2013). A reduction in productivity and/or nesting success of many other species has been spatially and/or temporally associated with DDT (often in conjunction with PCBs) including (but not limited

to) bald eagles (Grier, 1982; Bowerman *et al.*, 2000; Bowerman *et al.*, 2003), sea eagles (Jensen, 1972; Roos *et al.*, 2012), osprey (Henny *et al.*, 2010), brown pelicans (Anderson *et al.*, 1975), double-crested cormorants (Weseloh *et al.*, 1983; Weseloh *et al.*, 1995), merlins (Newton, 1973; Newton & Haas, 1988), various Australian raptors (Olsen *et al.*, 1992; Olsen *et al.*, 1993). DDT and other organochloride pesticides have been found in various bird species at concentrations similar to those linked with population declines in Africa (Frank *et al.*, 1977; Yohannes *et al.*, 2014), India (Senthilkumar *et al.*, 2001) and China (Chen *et al.*, 2009).

DDT and its metabolites (DDD, dichlorodiphenyldichloroethane and DDE, dichlorodiphenyldichloroethylene) can be found in wildlife; their endocrine disrupting actions have been extensively reviewed (Lundholm, 1987; Kelce *et al.*, 1995; Lundholm, 1997; Berg *et al.*, 2004; Holm *et al.*, 2006; Felton *et al.*, 2015). One metabolite (*o,p'*-DDT) causes malformations in the shell-producing gland while a different metabolite (*p-p'*-DDE) causes egg shell thinning by inhibiting prostaglandins, decreasing calcium uptake.

DDT bans in individual countries have been in place since the 1970's (Bouwman *et al.*, 2013) and it was globally banned under the Stockholm Convention in 2004. Its use in vector control programmes is reviewed by van den Berg (2009).

Banning DDT lead to the population recovery of adversely affected birds of prey, for example, osprey (Henny *et al.*, 2010), bald eagles (Grier, 1982), peregrine falcon and sparrowhawks (Newton, 2013) and some populations of Californian condor (Felton *et al.*, 2015). Roos *et al.* (2012) reported on improvements in reproductive success that occurred concurrent with declines of DDT and PCBs in European otters, grey seals and sea eagles in Sweden.

Glaciers as a source of DDT in Adélie penguin eggs and subcutaneous fat is discussed by Geisz *et al.* (2008).

For an overview on the work on alligators at Lake Apopka, see Guillette *et al.* (2000) and Woodward *et al.* (2011). A wide-range of adverse effects have been observed in Lake Apopka alligators (Guillette *et al.*, 2000; Toft *et al.*, 2003; Gunderson *et al.*, 2004; Milnes *et al.*, 2005; Milnes *et al.*, 2008; Milnes & Guillette, 2008).

- c. Koppe and Keys (2002) discusses the history of discovery of effects and the regulatory history of polychlorinated biphenyls (PCBs); they were banned under the Stockholm Convention in 2002. Harrad *et al.* (1994) outlined the use and fate of PCBs in the UK.

PCBs have been found in wildlife since the late 1960's (Risebrough *et al.*, 1968; Jensen, 1972). Examples of taxa in which PCBs have been found are listed in AB21.

Different types (congeners) of PCBs may have either oestrogenic or anti-oestrogenic properties (Zhang *et al.*, 2014). Boas *et al.* (2006) reviewed the impact of PCBs on thyroid function; for mechanisms also see Das *et al.* (2006). PCBs also affect the stress hormone (corticosterone) system (e.g. Glennemeier and Denver (2001), Nordstad *et al.* (2012), Sonne (2010), Tartu *et al.* (2015b)).

PCBs are the major POP detected in wildlife in industrial regions (Huber *et al.*, 2015; Tartu *et al.*, 2015b) and are still

having severe effects because of their toxicity, lipophilic nature and long environmental half-lives (Jepson *et al.*, 2016; Jepson & Law, 2016).

The replacement of PCBs as flame retardants with PBDEs is discussed by Vandenberg *et al.* (2015), Alaei *et al.* (2003) and Boas *et al.* (2006).

Reproductive failure in farmed mink fed contaminated salmon from the Great Lakes was observed in the late 1960's; experiments confirmed PCBs to be the causal agent (Aulerich *et al.*, 1971; Aulerich & Ringer, 1977; Brunström *et al.*, 2001). Some mink populations are in decline (Wren, 1991; Basu *et al.*, 2007), show adverse health effects linked to PCBs (Harding *et al.*, 1999; Beckett *et al.*, 2005) and/or have body burdens high enough to have reproductive effects (Bursian *et al.*, 2006; Bursian *et al.*, 2013). Potential population level effects have also been observed in the related European mink (Lopezmartin *et al.*, 1994).

Cetaceans may be particularly susceptible to the effects of POPs (McKinney *et al.*, 2011a; Sonne *et al.*, 2018). Jepson *et al.* (2016) reported on the high concentrations of PCBs in orca (killer whales, *Orcinus orca*), striped dolphins (*Stenella coeruleoalba*) and harbour porpoises (*Phocoena phocoena*) in European waters. They suggest that these concentrations may be responsible for the continued decline of these populations; alternative causes of decline (including other pollutants) were ruled out. Other cetacean populations for which EDCs are of notable concern include beluga whales from the St Lawrence estuary (Québec, Canada) (Martineau *et al.*, 1987; Béland *et al.*, 1993) and orca on the coasts of British Columbia, Canada and Washington, USA (Ross *et al.*, 2000). Toxicity threshold is calculated from the toxic equivalency factors that allow for mixture of dioxins, furans and/or PCBs to be expressed as a single number, for details of their calculation, see Van den Berg *et al.* (1998).

Desforges *et al.* (2018) created an individual-based model for orca populations globally and collated data on PCB concentrations of the different populations. They calculated the effect of PCBs on reproduction and immune function for each of the 19 population and determined that the populations were predicted to decline for eight of these populations were predicted to decline ($\lambda < 1$). Stability was predicted for two populations; some model simulations suggest that these may be at risk of decline. Population increase was predicted for a further nine populations ($\lambda > 1$).

AB8. Johnson *et al.* (2013) described levels of oestrogens in European rivers; their potency is discussed by Sumpter and Johnson (2005). Khan and Nicell (2014) model how changes to contraceptive use might alter the level of oestrogens entering the environment.

- a. The American English names for these compounds are also commonly used – estrone, estradiol, estriol and ethinylestradiol. Sumpter and Johnson (2008), Tyler and Filby (2011), Jobling and Owen (2013) and Jobling (2014) provide historic accounts. The first surveys of oestrogenic effects of sewage effluent were conducted by Purdom *et al.* (1994), further UK surveys include Harries *et al.* (1997), Jobling *et al.* (1998); Jobling *et al.* (2002a); Jobling *et al.* (2002b); Jobling *et al.* (2006) and van Aerle *et al.* (2001).

- b. The phenomenon of feminisation in wild fish is reviewed by Bahamonde *et al.* (2013). Jobling and colleagues have conducted surveys that correlated wastewater treatment plants, in particular the levels of oestrogens released, with levels of intersex in roach throughout the United Kingdom (Jobling *et al.*, 1998; Jobling *et al.*, 2002a; Jobling *et al.*, 2002b; Jobling *et al.*, 2006). Jobling *et al.* (2002b) and Harris *et al.* (2011) demonstrated that higher levels of intersex are associated with a reduction in fertility and reproductive success in the roach. Fish populations have been found to be self-sustaining (Hamilton *et al.*, 2014; Johnson & Chen, 2017). Johnson and Chen (2017) did not find consistent correlations between predicted oestrogen concentrations and the abundance of four species of UK river fish (roach, perch, dace and bleak) in four river basins (38 sites) over six – 17 years. There were no differences in effective population size of roach in rivers with and without wastewater (Hamilton *et al.*, 2014). The effective population size is the number of reproducing individuals in a population.
- c. Oestrogens from livestock in the UK are discussed by Johnson *et al.* (2006); Matthiessen *et al.* (2006). Alvarez *et al.* (2013), Schoenborn *et al.* (2015) and Tremblay *et al.* (2018) outline the amounts entering the environment in the US, Switzerland and New Zealand respectively.

AB9. Runnalls *et al.* (2010) reports use of some endocrine-active pharmaceuticals (steroids) in the UK and discusses potential environmental impact. der Beek *et al.* (2016) reviews global presence of pharmaceuticals in the environment.

- a. Metformin is commonly prescribed for diabetes (World Health Organization, 2016; NHS choices). It can be found at high concentrations in the environment due to the large number of users (Anderson *et al.*, 2004; Scheurer *et al.*, 2012; Al-Odaini *et al.*, 2013; Oosterhuis *et al.*, 2013), high daily dose (Scheurer *et al.*, 2012; Oosterhuis *et al.*, 2013; British National Formulary, 2016) and because it is mainly excreted unchanged rather than metabolised (Scheurer *et al.*, 2012). Studies on its environmental presence include Blair *et al.* (2013), Trautwein *et al.* (2014), also see Al-Odaini *et al.* (2013), Ghoshdastidar *et al.* (2015), Kosma *et al.* (2015) and ter Laak *et al.* (2014). Mechanisms of action of metformin are described by Overturf *et al.* (2015) and Huang *et al.* (2016). As metformin does not structurally resemble oestrogens, it should not cause oestrogenic activity (Crago *et al.*, 2016); however, Niemuth and Klaper (2015) found it to have feminising effects on fathead minnow. For discussion of the need for validation of this result, see Sumpter *et al.* (2016) and reply (Klaper & Niemuth, 2016).
- b. Use of fluoxetine (commonly known as Prozac) and other antidepressants is increasing (Mars *et al.*, 2017); Gardner *et al.* (2012) surveyed levels in wastewater effluent from throughout the UK. As it acts on the neuroendocrine system, adverse effects in wildlife are likely to be behavioural (Sumpter *et al.*, 2014). Mennigen *et al.* (2011) reviews experiments on small fish that have been conducted both at and above concentrations observed in the

environment; while adverse effects have been observed at environmental levels (e.g. Margiotta-Casaluci *et al.* (2014), the evidence is insufficient to determine whether current levels of fluoxetine in rivers is of concern (Sumpter *et al.*, 2014). High levels of fluoxetine have been reported to alter *Daphnia magna* reproductive investment (Campos *et al.*, 2016), reduce feeding (and thus size) of amphibians (Connors *et al.*, 2009; S  fholm *et al.*, 2014) and alter diurnal rhythms of birds (Bean *et al.*, 2014).

- c. The anti-androgens, bicalutamide and cyproterone acetate, are the most commonly prescribed anti-androgens in the UK (Runnalls *et al.*, 2010). Modelling of concentrations in UK rivers by Green *et al.* (2015). Green *et al.* (2015) showed that there was no effect of mixtures of bicalutamide and cyproterone acetate on small fish (minnow & medaka) at the maximum concentrations predicted to occur in the UK in untreated effluent.
- d. For use, prescription rates and occurrence in the environment of progestins see Runnalls *et al.* (2010), Kumar *et al.* (2015) and Fent (2015). Kumar *et al.* (2015) and Orlando and Ellestad (2014) review effects of progestins on fish; different progestins vary greatly in potency. For studies on fish see Kumar *et al.* (2015), Paulos *et al.* (2010), Zeilinger *et al.* (2009), Runnalls *et al.* (2013), Fent (2015), and for amphibians, see Kumar *et al.* (2015) and S  fholm *et al.* (2014).

AB10. See reviews by Biswas *et al.* (2013) and Renner (2002). Low doses of antibiotics are also used as growth promoters in some countries (banned in the EU) and enter the environment (Page & Gautier, 2012) but as they do not act via the endocrine system, they are not EDCs.

- a. For uses of trenbolone in agriculture, see Reinhardt and Wagner (2014). It is banned in the EU (European Commission, 2017b) but is used illegally in bodybuilding e.g. Friedman *et al.* (2016). It enters freshwaters through livestock urine and manure (Saaristo *et al.*, 2013). Experimental studies in the laboratory (both at current environmental and higher than environmental levels) have demonstrated adverse effects on fish mating behaviour (e.g. Bertram *et al.* (2015), Heintz *et al.* (2015), Tomkins *et al.* (2016)) and sexual development both in frogs (Li *et al.*, 2015; Haselman *et al.*, 2016) and fish (Baumann *et al.*, 2014; Forsgren *et al.*, 2014; Leet *et al.*, 2015; Massart *et al.*, 2015).

AB11. See individual chemicals below for discussion about uncertainty surrounding harm and Vandenberg *et al.* (2015), Section 6 for a discussion about substitute chemicals.

- a. The uses of bisphenol A are described by Plastics Europe (2016) and Vandenberg *et al.* (2009) describes some of the biochemical properties of BPA. The movement of BPA into the environment is reported by Im and Loffler (2016) and Flint *et al.* (2012) while studies on the levels of BPA in freshwater include Fromme *et al.* (2002), Campbell *et al.* (2006), Flint *et al.* (2012), Scott *et al.* (2014) and Bhandari *et al.* (2015b).

The mechanisms of BPA are described in Vandenberg *et al.* (2012) and potency is discussed by Rubin (2011) (Section 6); Richter *et al.* (2007) and Segner *et al.* (2003) compare

potencies in different tests. Moreman *et al.* (2018) demonstrates that the degradation product of BPA, MBP, is more oestrogenic than the parent compound.

Studies reviewing the effects of BPA on wildlife include Bhandari *et al.* (2015b), Oehlmann *et al.* (2009), Flint *et al.* (2012) and Mills and Chichester (2005). Intergenerational effects were observed at higher than environmental levels by Bhandari *et al.* (2015a); earlier studies are reviewed by Flint *et al.* (2012). Human health effects of BPA are controversial (Vandenberg *et al.*, 2009; Gies & Soto, 2013; Ranciere *et al.*, 2015). The details of BPA regulations can be found in Plastics Europe (2016), EFSA (2015) and Flint *et al.* (2012).

- b. For uses of phthalates, see CDC (2016). The quantity of phthalates in the aquatic environment is reviewed by Tyler *et al.* (1998), Bhatia *et al.* (2015) and Gao and Wen (2016). Details on legislation can be found in European Council for Plasticisers and Intermediates (2014) and European Chemicals Agency (2015). Bioaccumulation and bioconcentration of phthalates tends to be low although it varies between compounds (Oehlmann *et al.*, 2009) and with species (Rhind *et al.*, 2005; Lenoir *et al.*, 2014; Adeogun *et al.*, 2015). Oehlmann *et al.* (2009) reviewed impact of phthalates on wildlife. More recent experiments conducted at levels higher than observed in the environment have found both feminisation and masculinisation of fish (Aoki *et al.*, 2011; Xu *et al.*, 2014; Bhatia *et al.*, 2015) and adverse effects on amphibian thyroid function (Shen *et al.*, 2011; Mathieu-Denoncourt *et al.*, 2015). Hauser and Calafat (2005) gives evidence for effects in humans.

- c. For details of polyfluoroalkyl and perfluoroalkyl substances (PFASs) chemistry, see Buck *et al.* (2011). There are a range of industrial uses of PFASs (Prevedouros *et al.*, 2006; Lindstrom *et al.*, 2011; Land *et al.*, 2015); airport use of PFAS-containing aqueous fire-fighting foams has severely contaminated waterways near airports (Awad *et al.*, 2011; Ahrens *et al.*, 2015).

One PFAS, perfluorooctanoic acid (PFOA, a surfactant) has been found in human serum (Hansen *et al.*, 2001; Lindstrom *et al.*, 2011; Land *et al.*, 2015) and later in wildlife where it bioaccumulates (Giesy & Kannan, 2001; Houde *et al.*, 2006; Lau *et al.*, 2007; Fair *et al.*, 2010); Houde *et al.* (2011); Tartu *et al.*, 2018) PFASs are highly persistent due to the presence of the C-F bond.

For reviews of toxic and endocrine effects of PFASs in humans and other animals, see Lau *et al.* (2007), Jensen and Leffers (2008) and Post *et al.* (2012). Experimental findings of effects on the thyroid hormone system have been inconsistent (Chang *et al.*, 2008; Cheng *et al.*, 2011). While PFASs may alter sex hormone function (Du *et al.*, 2009; Shi *et al.*, 2009; Mommaerts *et al.*, 2011), many of these experiments were conducted at levels higher than those observed in the environment. Exposure to PFASs may be correlated with adverse reproductive effects in European eels (Couderc *et al.*, 2016), black-legged kittiwakes (Tartu *et al.*, 2014a) and tree swallows (Custer *et al.*, 2012). Part of the reason for the lack of evidence for harm is because there are technical challenges to working with PFASs

(authors' opinion). They are highly hydrophobic (i.e. repel water), as such, achieving and maintaining a given exposure level is difficult.

- d. PBDE chemistry and use reviewed in Alaee *et al.* (2003) and Jinhui *et al.* (2017) respectively. It should be noted that levels of PBDEs reported from different studies may not be directly comparable as analytical methods and types assessed will differ in different laboratories (Frouin *et al.*, 2011).
Anti-androgenic and/or oestrogenic effects of PBDEs have been found in experiments conducted at levels similar to or higher than those observed in the environment (Fernie *et al.*, 2008; Eng *et al.*, 2012; Van Schmidt *et al.*, 2012; Neuman-Lee *et al.*, 2015; Yu *et al.*, 2015).
There are structural similarities between PBDEs and the thyroid hormone, thyroxine (T4) (Hale *et al.*, 2008); effects on thyroid function are reviewed by Yu *et al.* (2015). Studies have found correlations between levels of PBDEs and thyroid hormone levels in a range of wildlife species and populations (Hall *et al.*, 2003; Das *et al.*, 2006; Hall & Thomas, 2007; Villanger *et al.*, 2011a; Morrissey *et al.*, 2014). In experiments conducted at higher than environmental levels, PBDEs inhibited amphibian metamorphosis (Balch *et al.*, 2006) and altered expression of genes related to thyroid hormone production (Yost *et al.*, 2016). Human health effects are described by Law *et al.* (2014).
PBDEs are widely present in the environment (Allchin *et al.*, 1999; Hale *et al.*, 2008; Bartrons *et al.*, 2012; Lee & Kim, 2015) and in wildlife, reviewed by Law *et al.* (2014) and Lee and Kim (2015). Allchin *et al.* (1999) documented release into UK rivers.
PBDEs bioaccumulate/bioconcentrate (Quinete *et al.*, 2011; Gaylor *et al.*, 2012; Mo *et al.*, 2012; Lee & Kim, 2015) and are maternally transferred (Wu *et al.*, 2009; Alava *et al.*, 2012; Law *et al.*, 2014).
For details of PBDE legislation see Jinhui *et al.* (2017) and Section MAJOR LEGISLATION CONCERNING EDCs.
- e. For a review of the chemistry, sources and uses of perchlorate see Trumpolt *et al.* (2005). There are multiple forms of perchlorate, most commercial use involves one of ammonium perchlorate (NH₄ClO₄), perchloric acid (HClO₄), potassium perchlorate (KClO₄) or sodium perchlorate (NaClO₄). Urbansky *et al.* (2001) reviews occurrence in mineral deposits used as fertiliser. Perchlorate is highly soluble in water and is a major groundwater contaminant in the USA (Hatzinger, 2005) causing human health concerns (Blount *et al.*, 2006). Levels of perchlorate in freshwater and drinking waters in the USA are reviewed by Dean *et al.* (2004) and Brandhuber *et al.* (2009).
The impact of perchlorate on thyroid hormone production is well understood (Wolff, 1998; Clewell *et al.*, 2004). Retardation of amphibian metamorphosis, thyroid gland abnormalities and reduced growth rates in amphibians have been observed in experiments at levels similar those observed at contaminated sites (Goleman *et al.*, 2002; Tietge *et al.*, 2005; Bulaeva *et al.*, 2015). Adverse effects on thyroid function have also been experimentally found in birds (McNabb *et al.*, 2004; Rainwater *et al.*, 2008), fish

(Park *et al.*, 2006; Mukhi & Patino, 2007; Furin *et al.*, 2015), turtles (Eisenreich *et al.*, 2012). Thyroid disruption of fish and frogs has been correlated with environmental levels of perchlorate (Theodorakis *et al.*, 2006).

- f. Chemistry, use and legislation of the alkylphenols, see Soares *et al.* (2008). Sumpster (2009) discusses the range of nonylphenol isomers. Nonylphenol binds to the oestrogen receptor (White *et al.*, 1994). For feminisation of fish in UK rivers, see Sheahan *et al.* (2002b); Sheahan *et al.* (2002a), for lab studies see Watanabe *et al.* (2017) and Pickford *et al.* (2003). Soares *et al.* (2008) and Berge *et al.* (2012) review presence in the environment globally. After the EU ban, its presence in imported textiles was still a major source (Månsson *et al.*, 2008); the importation of textiles containing alkylphenols has now been banned (Government Chemist and Environment Agency, 2015). The US EPA states that nonylphenol should not exceed 6.6 µg L⁻¹ in freshwater and 1.7 µg L⁻¹ in saltwater (David *et al.*, 2009).
- AB12.** If a chemical is identified as an EDC, the policy options open are different to if it is classed as a different type of pollutant (Thornton, 2007). Hill's criteria (Fedak *et al.*, 2015) is one method that may be used to determine whether a chemical might be considered an EDC, but see Bergman *et al.* (2015).
- a. Diclofenac is a popular non-steroidal anti-inflammatory drug used to treat mild to moderate pain (McGettigan & Henry, 2013). The decline of Gyps vultures in India, Pakistan and Nepal and link with diclofenac has been well documented, reviewed by Pain *et al.* (2008), Cuthbert *et al.* (2014). Some other species have also suffered less-severe population declines as a result of diclofenac use (Cuthbert *et al.*, 2006; Galligan *et al.*, 2014; Sharma *et al.*, 2014). Mechanisms of action are primarily non-EDC and are described by Swan *et al.* (2006b) and Naidoo and Swan (2009).
Diclofenac has been banned for veterinary use (Pain *et al.*, 2008; Cuthbert *et al.*, 2014), while an alternative (meloxicam) is available (Swan *et al.*, 2006a; Naidoo *et al.*, 2010; Cuthbert *et al.*, 2014), illegal use occurs (Cuthbert *et al.* 2016).
 - b. Solomon *et al.* (1996) detailed use of atrazine in corn production, its movement and persistence in the environment. For status in Europe and history of atrazine regulation see Lewis *et al.* (2015), European Commission (2003) and Ackerman (2007). Sass and Colangelo (2006) and Ackerman (2007) compare the US and EU approach to pesticide registration policy (in particular, how scientific evidence is used in decision-making) and how that has led to the different status for atrazine.
The mechanism behind (potentially) feminising effects is poorly understood (Papoulias *et al.*, 2014). Studies have found negative effects at (high) environmentally relevant levels using both the frog species *Xenopus laevis* (Hayes *et al.*, 2002b; Tavera-Mendoza *et al.*, 2002; Hayes *et al.*, 2006; Hayes *et al.*, 2010) and *Rana pipiens* (Hayes *et al.*, 2002a, 2003; Langlois *et al.*, 2010). Other studies have found no change to the measured endpoints in *Xenopus laevis* (Jooste *et al.*, 2005b; Oka *et al.*, 2008; Kloas *et al.*, 2009). The experimental methods used are frequently contested, for example, the study of Jooste *et al.* (2005b) was heavily

criticised by Hayes (2005) and response (Jooste *et al.*, 2005a). Systematic reviews have also reached opposing conclusions (Rohr & McCoy, 2010; Van Der Kraak *et al.*, 2014). Langlois *et al.* (2010) also found some effects on metamorphosis.

Hayes (2004) criticised studies that have found no ED effects of atrazine on methodological grounds, while Van Der Kraak *et al.* (2014) has done the same for studies that found effects. A discussion of the association between funding source and findings is presented by Hayes (2004) and Reeves (2015). The debate over atrazine and its effects on amphibians has become highly politicised; see Dalton (2010), Howard (2013), Aviv (2014) and Reeves (2015).

HOW EDCS ENTER AND PERSIST IN THE ENVIRONMENT

AB13. Point source pollution is defined as “pollution arising from specific identifiable points, such as the end of pipes discharging waste water” (Defra, 2012). The major point source is wastewater effluent (Keller *et al.*, 2014). Other sources include effluent from hospitals (Langford & Thomas, 2009; Verlicchi *et al.*, 2012) and industry (Allchin *et al.*, 1999; Pothitou & Voutsas, 2008). Industrial and military sites are often point sources of pollutants due to accidental or inappropriate waste disposal (Ormerod *et al.*, 2000; Henning *et al.*, 2003; Neigh *et al.*, 2006; Johnson *et al.*, 2009b; Fu *et al.*, 2011). Teuten *et al.* (2009) reviewed movement of plasticisers and other EDCs from waste disposal sites into surface waters. Diffuse pollution is defined as “pollution not arising from a specific, identifiable point”, such as from agricultural land and brownfield sites (Defra, 2012). Oestrogens produced by livestock runoff farmland and enter water courses exposing aquatic species (Johnson *et al.*, 2006; Matthiessen *et al.*, 2006). Terrestrial species may be affected by feeding on contaminated aquatic prey (Dods *et al.*, 2005; Markman *et al.*, 2008; Markman *et al.*, 2011) or by feeding on pastures fertilised with sewage sludge (e.g. (Rhind *et al.*, 2005; Rhind, 2009). Smith (2009) and Verlicchi and Zambello (2015) review the presence and implications of contaminants including EDCs in sewage sludge used as fertiliser. Approximately 80% of the UK’s sewage sludge is reused as a soil enhancer and fertiliser (this is the environmentally preferred option), up from 44% in 1992 (Defra, 2012). Sludge can contain household chemicals such as flame retardant PBDEs (Davis *et al.*, 2012).

- a. Reviews and examples of EDCs in wastewater include Campbell *et al.* (2006), Kasprzyk-Hordern *et al.* (2008), Miegé *et al.* (2009), Arukwe *et al.* (2012), Stuart *et al.* (2012), Scott *et al.* (2014), Bhandari *et al.* (2015b), Sorensen *et al.* (2015).
- b. Import of hazardous material including waste of electrical and electronic equipment (e-waste) and release into the environment in Nigeria and China is described by Sindiku *et al.* (2015) and Wong *et al.* (2007) respectively. Reports of the presence of EDCs in wildlife at e-waste sites in China include Wu *et al.* (2009) and Fu *et al.* (2011). Routes of exposure and human health impacts of electronic waste are described by Frazzoli *et al.* (2010).
- c. The presence of androgenic and oestrogenic compounds in wood is reviewed by van den Heuvel (2010), dioxins were often present in pulp mill effluents (Kovacs *et al.*, 1995).

Observational and experimental studies on the masculinisation of fish living downstream of pulp mill effluent include Larsson and Forlin (2002), Kovacs *et al.* (1995), Jones and Reynolds (1997) and are reviewed by van den Heuvel (2010). Human health effects of phyto-oestrogens are reviewed by Rietjens *et al.* (2017).

AB14. Jobling and Tyler (2003), Sumpter and Johnson (2005), Walsh *et al.* (2016) and Williams *et al.* (2009) review dilution in UK rivers. Johnson *et al.* (2013) and Keller *et al.* (2014) review dilution factors for Europe and internationally respectively. Comparisons between the UK, Europe and North America can be found in Tyler and Jobling (2008). Keller *et al.* (2014) discuss spatial and temporal variability of dilution factors within countries – reasons for differences are both due to seasonal flow variations and population patterns. Hall and Thomas (2007) compare PCB load in seals from different sites across the UK. Trautwein *et al.* (2014) showed how metformin and its transformation product, guanylurea, dilute as they travel downstream and enter the ocean. Dilution in the ocean was not sufficient to prevent adverse effects of TBT (Hallers-Tjabbes *et al.*, 1994).

AB15. Gusev *et al.* (2012) reviews intercontinental transport of persistent organic pollutants. Using knowledge of long-range atmospheric transport and properties of the compounds of interest, models have been constructed to determine the rate and mechanism by which chemicals might move through the environment (Prevedouros *et al.*, 2004; Fenner *et al.*, 2005; Guglielmo *et al.*, 2009). Studies describing movement of particular EDCs include work on DDT (Wania & Mackay, 1996), PCBs (Beyer & Biziuk, 2009) and PFASs (Prevedouros *et al.*, 2006; Kwok *et al.*, 2013).

- a. Reviewed by Nadal *et al.* (2015). Atmospheric transport is believed to be the dominant pathway of persistent organic pollutants to Antarctica (Noel *et al.*, 2009); much of the PCBs released in the UK is believed to have been transported to the Arctic (Harrad *et al.*, 1994).

AB16. Oestrogens and some pharmaceuticals may be broken down by photodegradation and/or microbial degradation (Lin & Reinhard, 2005; Zuo *et al.*, 2006; Cajthaml *et al.*, 2009; Yu *et al.*, 2013; Zuo *et al.*, 2013). For details of degradation in English rivers, see Jürgens *et al.* (2002).

Half-lives of persistent organic pollutants depend on both the compound (and for PCBs, type) and substrate in which the chemical occurs (de Mora *et al.*, 1995; Sarradin *et al.*, 1995; Sinkkonen & Paasivirta, 2000; Ritter *et al.*, 2011). Estimates of half-lives may be derived from laboratory experiments (Watanabe *et al.*, 1995; Dowson *et al.*, 1996).

- a. Sumpter and Johnson (2008) discuss “pseudopersistence”. Examples of pseudopersistent EDCs in wastewater include BPA and high-use pharmaceuticals such as EE2, metformin or the antiandrogens (Daughton & Ternes, 1999; Zhang & Li, 2011; Hampel *et al.*, 2015).
- b. Pollutants may be contained within substrates such as harbour sediments, soils and glaciers. When these substrates are disturbed (or melt) the pollutant is released into the environment. These contaminated substrates are referred to as secondary sources. They will become

relatively more important for persistent organic pollutants as primary sources (e.g. PCB-containing electrical capacitors) are eliminated (Nizzetto *et al.*, 2010; Stuart-Smith & Jepson, 2017); for example, sediments in harbours are a source of TBT (Antizar-Ladislao, 2008) and soil is likely to become a relatively more important source of PCBs in the UK (Lu *et al.*, 2015). Glaciers as a secondary source of POPs is reported by Weinhold (2009), Geisz *et al.* (2008), Cheng *et al.* (2014) and Kwok *et al.* (2013). PCBs have been reported from the deep ocean (Mariana and Kermadec trenches) by Jamieson *et al.* (2017).

- c. For example, PCBs are present in many buildings constructed between 1950-1970, in particular in caulk or sealant (Harrad *et al.*, 2009; Frederiksen *et al.*, 2012; Herrick *et al.*, 2016). PBDE flame retardants are present in a wide range of consumer products (Jinhui *et al.*, 2017).

AB17. Bioconcentration is the process by which a chemical is absorbed by an organism only through its respiratory and dermal surfaces, while bioaccumulation is the process in which a chemical substance is absorbed by all routes of exposure (dietary as well as dermal and respiratory paths) and thus includes food chain transfer. Chemicals that bioaccumulate or bioconcentrate are not expelled, as such, the amount increases in the animal's body over time and therefore the internal concentration of the chemical will become greater than in the external environment. Biomagnification is when the concentration of the chemical in an organism exceeds that of its diet – i.e. levels of the compound increase up the food chain. These terms are defined in the **Error! Reference source not found.** and are reviewed and discussed by Arnot and Gobas (2006) and Yarsan and Yipe (2013). For example, the PFOA (a PFAS) concentration in the liver of beluga whales was 889 times that of cod (Houde *et al.*, 2006). Pollutants that biomagnify include PBDEs (Quinete *et al.*, 2011; Mo *et al.*, 2012; Lee & Kim, 2015), PCBs (Dietz *et al.*, 2000; Mackintosh *et al.*, 2004; Quinete *et al.*, 2011), DDT and other OC pesticides (Dietz *et al.*, 2000; Skarphedinsdottir *et al.*, 2010; Gui *et al.*, 2014), PFASs (Houde *et al.*, 2006; Haukas *et al.*, 2007; Kelly *et al.*, 2009).

- a. There was a positive correlation between age and PCB load in Svalbard ringed seals (Wolkers *et al.*, 1998) and Norwegian male coastal otters (Christensen *et al.*, 2010), male beluga whales (Wade *et al.*, 1997), male mink (Persson *et al.*, 2013) and in male and post-reproductive female northern resident orca (Ross *et al.*, 2000). Positive correlations have been found in some studies of polar bears (Smithwick *et al.*, 2005) but fasting may lead to negative correlations as fats containing EDCs are metabolised (Henriksen *et al.*, 2001) – when an animal is fasting (during times of stress or post-weaning) and living off their fat reserves, persistent organic pollutants will be mobilised along with lipids and concentrations of persistent organic pollutants in the serum will increase (Louis *et al.*, 2014; Jenssen *et al.*, 2015). Other reasons for an absence of a relationship can include maternal transfer (Wade *et al.*, 1997; Ross *et al.*, 2000; Bytingsvik *et al.*, 2012a), changes in elimination ability with age (Smithwick *et al.*, 2005) or “growth dilution” (Wang *et al.*, 2013), which is where the concentration of the chemical reduces as the animal

increases in size (Arnot & Gobas, 2006); the absolute amount of chemical in the animal's body may not change.

- b. Leatherland (1997).
- c. Maternal transfer of PCBs in polar bears is discussed by Bytingsvik *et al.* (2012a) and Beckmen *et al.* (2003). Other compounds found in very young mammals includes PBDEs (Alava *et al.*, 2012), PFASs (Bytingsvik *et al.*, 2012b), phthalates have also been found in human breast milk (Adeogun *et al.*, 2015). By transferring POPs to their offspring, females lower their body burden of POPs. As a result, levels of POPs can be higher in males than females (e.g. Verreault *et al.* (2006), Bustnes *et al.* (2007), Wu *et al.* (2009), Christensen *et al.* (2010), Villanger *et al.* (2011b), Gui *et al.* (2014)).

HOW WE KNOW IF AN EDC IS A PROBLEM IN WILDLIFE

AB18. There is an extensive literature on the human health effects of EDCs, see Bergman *et al.* (2012) and Damstra *et al.* (2002) for an overview. Most fish, amphibians, reptiles, birds and mammals respond the same way to most hormones, but invertebrates may not (Sumpter & Johnson, 2005; Vandenberg *et al.*, 2012). Sumpter and Johnson (2005) and Lyons (2003) discuss cross-species extrapolation of endocrine disrupting effects – termed the “read across” hypothesis. The read-across hypothesis is reviewed by Rand-Weaver *et al.* (2013), and Ankley and Gray (2013) explore the significance of it for toxicological testing. Brown *et al.* (2014) review the effects of human drugs on fish, for example, metformin alters glucose metabolism in fish (Hertz *et al.*, 1989; Polakof *et al.*, 2011; Capiotti *et al.*, 2014). Jobling and Tyler (2003) report on the sensitivity of fish to EDCs in comparison to other vertebrates.

- a. There may be differences in sensitivity both between species (e.g. Kidd *et al.* (2014), van Aerle *et al.* (2001)) and within species (e.g. Spearow (1999)). Hartung (2009) discusses some issues with the use of *read across* principles for establishing human health impacts. Sousa *et al.* (2014) and Sousa *et al.* (2013) reviewed the effects of TBT on a variety of taxa (bacteria, phytoplankton, plants, crustaceans, molluscs, fish and mammals).
- b. For example, humans are exposed to BPA through ingestion of food stored in BPA-containing plastics, and via thermal print paper and household plastic items (Rubin, 2011; Healy *et al.*, 2015), while exposure to fish and other aquatic wildlife is via wastewater and landfill leachate (Oehlmann *et al.*, 2009; Flint *et al.*, 2012).

AB19. Experiments can be technically challenging because of the very low concentrations of chemicals in wildlife. Examples of studies measuring changes in thyroid and sex hormone levels may be found in the sections describing individual compounds. The Organisation for Economic Co-operation and Development (OECD) provides experimental guidelines for *in vitro* and *in vivo* tests (Manibusan & Touart, 2017; OECD/OCDE, 2017) for various species of invertebrates (earthworms, insects and molluscs), fish, amphibians, birds and rodents. These guidelines are reviewed by Coady *et al.* (2017) and Manibusan and Touart (2017). A number of outcomes or endpoints may be assessed in these tests, reviewed by Ankley and Gray (2013). Endpoints may be referred to as *mechanistic* or *apical*. Mechanistic endpoints indicate how

a chemical works, for example, an increase in vitellogenin production indicates that a feminising substance is oestrogenic rather than anti-androgenic. Changes in hormone levels are mechanistic endpoints. Apical endpoints are those associated with survival and reproduction (Marty *et al.*, 2017), these can be incorporated into models to assess effects on populations (Ankley & Gray, 2013). Dang *et al.* (2011) compares mechanistic (biomarker) and apical endpoints. The most commonly measured biomarker is vitellogenin, production in males indicates a chemical is oestrogenic (Sumpter & Jobling, 1995; Tyler *et al.*, 1996). Other *in vitro* assays commonly used include: Chemical Activated Luciferase gene expression (CALUX) used to detect specific chemicals, particularly dioxins (Windal *et al.*, 2005), yeast-based screens for detecting oestrogenic and androgenic substances (Sohoni & Sumpter, 1998; Bovee *et al.*, 2007), and the E-screen which is used to detect oestrogenic substances (Soto *et al.*, 1995).

Studies have explored the effects of development stage (Foran *et al.*, 2002; Liney *et al.*, 2005; Ciocan *et al.*, 2010; Crago *et al.*, 2016); sex (Villanger *et al.*, 2011b; Tartu *et al.*, 2014a); route or pathway of exposure (Pickford *et al.*, 2003) and duration of exposure (Vandenberg *et al.*, 2014) on responses to EDCs.

- a. Rats and mice are often used to assess the human health impacts e.g. Chang *et al.* (2008), Jasarevic *et al.* (2011). Five species of small fish are frequently used to determine the effects of water-borne pollutants (fathead minnows *Pimephales promelas*, Japanese medaka *Oryzias latipes*, zebrafish *Danio rerio*, three-spined stickleback *Gasterosteus aculeatus* and rainbow trout *Oncorhynchus mykiss*), and the use of these species is often specified in OECD test protocols (OECD/OCDE, 2011; Manibusan & Touart, 2017). There may be differences in sensitivity both between species (e.g. Kidd *et al.* (2014), van Aerle *et al.* (2001)) and within species, e.g. Spearow (1999). Jaspers (2015) discusses some of the issues surrounding selecting an appropriate model species for experiments of ED effects, with particular reference to birds. For discussion of sample sizes needed, see Coady *et al.* (2017). Work on the development of a multi-generational avian test was abandoned in part due to the large number of animals that would be required to achieve statistical power (OECD/OCDE, 2018a). Multi-generational effects are reviewed by Parrott *et al.* (2017).
- b. Lewis *et al.* (2002) describes how the NOAEL and related measures are determined. NOEL (no observable effect level) may also be used.
- c. Chen *et al.* (2010) and Johnson (2010) investigated how river oestrogen concentrations changed both downstream of point-sources and between seasons in Taiwan and the UK respectively. Assessments of concentrations of oestrogens in rivers have been conducted for the UK (Williams *et al.*, 2009; Williams *et al.*, 2012) and Europe (Johnson *et al.*, 2013). Weltje and Sumpter (2017) provides a comment on literature reports of “environmentally relevant concentrations”.
- d. For overviews of non-monotonic effects see Lagarde *et al.* (2015), Zoeller and Vandenberg (2015), Futran Fuhrman *et al.* (2015) and Parrott *et al.* (2017). Vandenberg *et al.* (2012) provides tables (Table 6 & 7) listing cases of non-monotonic doses responses (NMDR); a wide variety of EDCs are implicated (but see Rhomberg and Goodman (2012) and reply by Vandenberg (2015)). Vandenberg (2015) and Vandenberg *et al.* (2012) describe potential mechanisms of non-monotonic effects, it is likely they occur due to multiple simultaneous modes of action producing counter-acting effects. Parrott *et al.* (2017) discusses what NMDR might mean for risk assessment. NMDRs are often considered in conjunction with low-dose effects because often the change in directionality occurs at low doses (e.g. Futran Fuhrman *et al.* (2015)). However, it should be considered a separate issue as the change in directionality of the response can, in theory, occur at any concentration (Beausoleil *et al.*, 2013; Vandenberg, 2014).
- e. Standardised ecotoxicity tests have been developed by the OECD (OECD/OCDE, 2017). For definitions of low dose effects, see Kortenkamp (2007) and Vandenberg (2014), and Zoeller *et al.* (2014) discusses issues surrounding these definitions. For a detailed discussion about how low dose effects can occur, the difficulty in extrapolating to or from the effects at higher doses and a table listing studies in which low dose effects have been found, see Vandenberg *et al.* (2012) and Vandenberg (2014). Kortenkamp (2008) reviews experimental studies of mixtures of EDCs at low-doses. Kaiser (2000) reports on the acceptance by the US EPA that low dose effects occur and need to be incorporated into testing, also see Beausoleil *et al.* (2013).
- f. For evidence of maternal transfer of EDCs in the eggs of birds or reptiles and in very young mammals where transfer occurs mostly via milk see Beckmen *et al.* (2003) and Stockin *et al.* (2010). EDCs found in eggs of fish, amphibians, birds and reptiles include PCBs (French Jr *et al.*, 2001; Henning *et al.*, 2003; Alava *et al.*, 2011a; Basile *et al.*, 2011; Erikstad *et al.*, 2013); DDT and other OC pesticides (Woodward *et al.*, 2011; Stoker *et al.*, 2013; Colabruzzo *et al.*, 2015); phthalates (Huber *et al.*, 2015); PBDEs (Wu *et al.*, 2009; Law *et al.*, 2014); PFASs (Yoo *et al.*, 2008; Leat *et al.*, 2013; Routti *et al.*, 2015), butyl tins (Hu *et al.*, 2009). For details of maternal transfer via milk, see AB17.c. Schwindt (2015) reviewed evidence for transgenerational effects following either maternal or paternal exposure to EDCs in aquatic wildlife (fish, amphibians and invertebrates). Koppe and Keys (2002) discusses how transgenerational effects may occur in relation to PCBs. The best documented example of transgenerational effects is that of diethylstilbestrol (DES), a non-steroidal oestrogen used as a human pharmaceutical. Observational studies in humans and experiments in rats have found similar adverse effects in children/rat pups exposed *in utero* and in their offspring (Fenichel *et al.*, 2015). Laboratory studies that have noted greater effects of EE2 on the offspring of exposed fish (or later generations) than in the exposed fish themselves include Nash *et al.* (2004) and Bhandari *et al.* (2015a). However, mechanisms for these effects are unclear. Hamilton *et al.* (2015) did not find inter-generational effects in the roach.
- g. Wastewater contains a mix of pharmaceuticals (Daughton & Ternes, 1999; Overturf *et al.*, 2015) and various other compounds (Kasprzyk-Hordern *et al.*, 2008; Stuart *et al.*,

2012; Sorensen *et al.*, 2015), notably phthalates (Bhatia *et al.*, 2015) and BPA and other phenolic compounds (Berge *et al.*, 2012; Zheng *et al.*, 2015). Animals living in the high Arctic generally contain a wide range of persistent organic pollutants (Bustnes *et al.*, 2007; Villanger *et al.*, 2011b; Villanger *et al.*, 2011a; Erikstad *et al.*, 2013; Routti *et al.*, 2014; Andersen *et al.*, 2015; Routti *et al.*, 2015). Kapraun *et al.* (2017) describes a technique for identifying common mixtures of chemicals for studies of human exposure. Relatively new non-target screening methods can determine which mixtures are commonly found in wildlife e.g. Norman Network (2012-2018).

Effects of mixtures of EDCs that have the same mode of action (e.g. mixtures of oestrogenic compounds) are reviewed by Kortenkamp (2007) and Kortenkamp (2008). Studies providing examples of additive effects include Brian *et al.* (2005), Miller *et al.* (2012), Rajapakse *et al.* (2002) and Thorpe *et al.* (2003). Where departures from additivity have been observed e.g. Crofton *et al.* (2005), the effects have been small (Kortenkamp, 2007).

The combined impact of EDCs that function differently (e.g. androgens with oestrogens) is poorly understood, however, their action cannot be assumed to be additive (Kortenkamp, 2007; Futran Fuhrman *et al.*, 2015). We also have little understandings how EDCs may interact with other non-EDC pollutants.

- i. Thrupp *et al.* (2018).
- ii. Toxic equivalency factors (TEF) outlined by Van den Berg *et al.* (1998) and oestradiol equivalency factors by Williams *et al.* (2009). To calculate the EEQ, the potency of each compound is evaluated as a fraction of oestradiol; the final EEQ concentration is the sum of the quantities of different oestrogens corrected for their different potencies. The TEF uses a similar approach with 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) used as a standard.

AB20. Models that attempt to assess the impacts of EDCs on populations include Hanson *et al.* (2005), Hall *et al.* (2006), (Goutte *et al.*, 2014).

- a. For example, a minor change in timing of metamorphosis in amphibians due to thyroid disruption causes changes in adult body size (earlier metamorphosis leads to smaller adults). Timing of metamorphosis can also be affected by other stressors (Wilbur & Collins, 1973; Rohr *et al.*, 2004), and these effects are likely to be additive (Darling & Côte, 2008). Size then affects prey availability, predation risk and mating success (Rohr *et al.*, 2004; Rohr & McCoy, 2010).
- b. For example, UK river fish may spawn once in spring or multiple times from April to October (Nunn *et al.*, 2007). As concentrations of oestrogens in UK river water are typically highest in late summer (Johnson, 2010), exposure of the early life-history stages of river fish will vary depending on spawning date.
- c. Population-level processes are those processes whose magnitude depends on population size (density-dependent factors; a typical example would be starvation due to competition for food). The reduction in a species population size caused by EDCs (a density-independent factor) may be

less if they result in reduced density-dependent mortality through factors acting subsequently. A reduction in birth rate might increase survivorship due to less competition for food. Such effects are likely to be common in wildlife population dynamics though very difficult to predict in the absence of detailed study. "Allee effects" are density-dependent factors that increase in severity at low densities (a typical example would be reduced fecundity due to failure to find a mate at low population densities). For further discussion, see Mace *et al.* (2008). An example of population modelling incorporating Allee effects is Molnar *et al.* (2014)'s model of the polar bears of Viscount Melville Sound, Canada.

AB21. Thousands of studies have measured the presence of persistent organic pollutants in wildlife. Evidence of endocrine disrupting chemicals have been found in wildlife far from pollution sources, for example, in the high Arctic (Routti *et al.*, 2014; Andersen *et al.*, 2015; Tartu *et al.*, 2018), Antarctica (George & Frear, 1966; Bustnes *et al.*, 2007; Routti *et al.*, 2015), in high alpine lakes (Bartrons *et al.*, 2012), in the deep ocean (Takahashi *et al.*, 2000), on isolated islands (Alava *et al.*, 2011b; Bachman *et al.*, 2014; Wang *et al.*, 2015).

POPs that are EDCs have been found in a biologically diverse range of taxa at all trophic levels. However, in many populations, concentrations will be low enough that they do not present harm to the organism. The results from experiments outlined in AB7.c on mink have been used to determine toxic concentrations for other species such as otter (Brunström *et al.*, 2001) and various marine mammals (Folland *et al.*, 2016). The toxic equivalent threshold calculated for harbour seals was used to determine whether PCB levels in orca could be having adverse effects (Ross *et al.*, 2000). Some representative examples of POPs that are EDCs in wildlife include:

Invertebrates: apple snails (Fu *et al.*, 2011); crustaceans and bivalves (Lee & Kim, 2015) .

Freshwater fish: lake sturgeon (Jacobs *et al.*, 2014), white sturgeon (Feist *et al.*, 2005), fish in the Salton Sea, California (Moreau *et al.*, 2007), large-scale suckers (Jenkins *et al.*, 2014); mummichogs (Matta *et al.*, 2001), Elbe river fish (Cervený *et al.*, 2016), largemouth bass (Colli-Dula *et al.*, 2016), European eels (Couderc *et al.*, 2016).

Marine fish: deep-sea lantern fish (Takahashi *et al.*, 2000), cod (Powley *et al.*, 2008), commercial fish species (Taylor & Johnson, 2016).

Amphibians and Reptiles: diamond backed terrapins (Basile *et al.*, 2011), cricket frogs (Reeder *et al.*, 1998); loggerhead turtles (Alava *et al.*, 2011a); alligators (Woodward *et al.*, 2011).

Birds: dippers (Ormerod *et al.*, 2000), American robins (Henning *et al.*, 2003), high Arctic eiders and shags (Huber *et al.*, 2015), Cooper's hawks (Elliott *et al.*, 2015), chinstrap penguins (Jara-Carrasco *et al.*, 2015); albatrosses (Tartu *et al.*, 2015a; Wang *et al.*, 2015), common eider ducks (Tartu *et al.*, 2015a), south polar skua (Bustnes *et al.*, 2006), herring gulls (Fox *et al.*, 2008; Huber *et al.*, 2015; Letcher *et al.*, 2015), tree swallows (Custer *et al.*, 2014), lesser black-backed gulls (Bustnes *et al.*, 2008).

Land mammals: deer mice (Johnson *et al.*, 2009b), humans (Sousa *et al.*, 2013), otters (Basu & Head, 2010; Christensen *et al.*, 2010; Roos *et al.*, 2012), Arctic foxes (Aas *et al.*, 2014;

Andersen *et al.*, 2015), mink (Hornshaw *et al.*, 1983), grizzly bears (Christensen *et al.*, 2005), badgers, raccoon dogs, wild boar and deer (Tomza-Marciniak *et al.*, 2014).

Sea mammals: polar bears (Tartu *et al.*, 2018); blue whale (Trumble *et al.*, 2013); harbour seals (Hall & Thomas, 2007); Californian sea lions (Le Boeuf *et al.*, 2002), various cetacean species (Law *et al.*, 2005; Bachman *et al.*, 2014; Ryan *et al.*, 2014), Hector's and Maui's dolphins (Stockin *et al.*, 2010); harbour porpoises (Beineke *et al.*, 2005); sea otters (Murata *et al.*, 2008), bottlenose dolphins (Lahvis *et al.*, 1995; Schwacke *et al.*, 2012; Adams *et al.*, 2014); ringed seals (Routti *et al.*, 2015; Gebbink *et al.*, 2016).

- a. Darbre (2015) states that the presence of EDCs in the body is not an adverse effect and does not mean that adverse effects have occurred. However, if the EDCs were not present, there would be no concern. Diethylstilbestrol (DES) in humans is an example where adverse effects were observed long after the chemical had dissipated, exposure *in utero* caused vaginal cancer later in life (Fenichel *et al.*, 2015). Green *et al.* (2018) found that early life exposure of zebrafish to EE2 increased sensitivity to different oestrogens (EE2, BPA and phyto-oestrogens) later in life.
- b. Sonne (2010) gives reasons why Arctic species are so affected by PCBs. Examples of predatory birds and high Arctic sea mammals containing high concentrations of persistent organic pollutants include:
Predatory birds: herring gulls (Huber *et al.*, 2015; Letcher *et al.*, 2015), glaucous gulls (Sagerup *et al.*, 2009; Erikstad *et al.*, 2013; Tartu *et al.*, 2015a); black legged kittiwake (Tartu *et al.*, 2014a), peregrine falcon (Holmstrom *et al.*, 2010; Elliott *et al.*, 2015); marsh harrier (Pain *et al.*, 1999); bald eagles (Grier, 1982; Bowerman *et al.*, 2003; Pittman *et al.*, 2015); northern fulmar (Verreault *et al.*, 2013); common kestrel (Eriksson *et al.*, 2016), tawny owl (Eriksson *et al.*, 2016), osprey (Eriksson *et al.*, 2016), barn owls (Jaspers *et al.*, 2013), great skua (Leat *et al.*, 2013), ivory gull (Lucia *et al.*, 2015).
High Arctic sea mammals: polar bears (Villanger *et al.*, 2011b), various seal species (Hall & Thomas, 2007; Routti *et al.*, 2008; Gabrielsen *et al.*, 2011; Routti *et al.*, 2015; Gebbink *et al.*, 2016), polar bears (Derocher *et al.*, 2003; Smithwick *et al.*, 2006; McKinney *et al.*, 2011b; Dietz *et al.*, 2013), beluga whales (McKinney *et al.*, 2006; Raach *et al.*, 2011), orca (Ross, 2006; Noel *et al.*, 2009; Jepson *et al.*, 2016). Orca are the most highly PCB-contaminated mammal both in Europe and globally (Wolkers *et al.*, 2007).
- c. Examples of studies that have found high degrees of correlation between the different persistent organic pollutants, many of which are EDCs, include Alava *et al.* (2012), Bustnes *et al.* (2007), Das *et al.* (2006), Elliott *et al.* (2015), Pain *et al.* (1999). For example, Erikstad *et al.* (2013) found that the correlation between the different types of PCBs and organochloride pesticides measured in glaucous gulls on Bear Island, Svalbard, Norway ranged from 66-98%.

AB22. Individual level effects are changes that alter the health of an individual animal. Lyons (2003) and Vandenberg (2015) highlight some of the difficulties with commonly measured

endpoints. Hirabayashi and Inoue (2011) explain that an observed change to hormone levels may not always be considered an adverse effect due to homeostasis. There are a range of biomarkers available for various endocrine systems, see reviews by Scholz and Mayer (2008), Hutchinson *et al.* (2005). Other stressors (natural and anthropogenic) can also cause pathologies that appear similar to the effects of EDCs (e.g. Sonne *et al.* (2005)). Epidemiological criteria can be used to link stressors including EDCs with observed pathologies (Fox, 1991); for example, McMaster *et al.* (1996) used these criteria to link pulp mill effluent with fish reproductive abnormalities.

- a. The World Health Organization (1993) defines a biomarker as "any measurement that reflects an interaction between a biological system and an environmental agent, which may be chemical, physical or biological". There are a range of biomarkers available for various endocrine systems, see reviews by Scholz and Mayer (2008), Hutchinson *et al.* (2005). Using meta-analysis, Bosker *et al.* (2010) determined that there was a significant relationship between biomarkers (sex hormones, VTG and relative gonad size) and reproductive output (egg production) in small fish but there was high uncertainty when predicting population-level effects from these biomarkers. They suggest that multiple biomarkers should be used due to the incidence of false negatives, however this may increase the rate of false positives.
 - i. Vitellogenin (*vtg*) is an indicator of oestrogen exposure in egg-laying vertebrates (Robinson, 2008) but not invertebrates (Short *et al.*, 2014). Vitellogenin is often used as an indication of feminisation of fish (i.e. intersex) however the relationship between the two has not been well-characterised (Bahamonde *et al.*, 2013).
- b. Mills and Chichester (2005) review reproductive effects on small fish and Sonne (2010) reviews the reproductive impacts of EDCs on polar bears, sledge dogs and Arctic foxes. Compounds with adverse effects on reproduction include (but are not limited to) DDT, TBT, PCBs, trenbolone, steroid oestrogens, BPA, phthalates, nonyl-phenol. EDCs that can override effects of temperature on sex determination in turtles and/or crocodilians causing altered sex ratios include dicofol, DDT, E2, BPA, chlordane, dioxins and PCBs (Crews *et al.*, 1995; Guillette *et al.*, 2000; Vos *et al.*, 2000; Milnes & Guillette, 2008; Bhandari *et al.*, 2015b; Jandegian *et al.*, 2015). Behavioural effects (reviewed by Basu and Head (2010)) are likely to be underreported (Lyons, 2006).
- c. Thyroid hormones are essential for normal development and for the control of many aspects of adult physiology in vertebrates (Weetman, 2010; Gore *et al.*, 2015). The major thyroid hormones are thyroxine (T4) and triiodothyronine (T3); both increases and decreases in levels of thyroid hormones are problematic. Compounds with adverse effects on thyroid hormone production include phthalates, PCBs, PBDE, perchlorate. Rohr and McCoy (2010) in the section entitled "Background on metamorphosis" discuss how thyroid hormone disruptors can affect the timing of amphibian metamorphosis and the consequences of this. Changes in timing of metamorphosis

can be responsible for changes to adult body size (Mathieu-Denoncourt *et al.*, 2015).

Bone density is influenced by both thyroid (Gorka *et al.*, 2013) and sex hormones (Cauley, 2015). Effects of EDCs on bone density are reviewed by Agas *et al.* (2013).

- d. While EDCs can have effects on immune function, the effects are mostly weak and the mechanisms are poorly understood (Weybridge+15, 2012), reviewed by Milla *et al.* (2011). Derocher *et al.* (2003) has suggested that impaired immune system in Svalbard polar bears due to POPs might be limiting polar bear population growth. Links between the sex hormone system and immune system in rodents are reported by Grossman (1985). Adverse effects on the immune system have been observed with TBT in harbour seals (Frouin *et al.*, 2008) and reviewed by Fent (1996), PCBs in bottlenose dolphins (Schwacke *et al.*, 2012) and seals (Hammond *et al.*, 2005), trenbolone in rainbow trout (Massart *et al.*, 2015), PFOA in humans (Post *et al.*, 2012). EDCs can also affect the stress hormones (glucocorticoids) which regulate the immune system e.g. Tartu *et al.* (2014b).

AB23. Some of the difficulties in linking population declines with pollutants are highlighted by Safford and Jones' (1997) investigation into the causes of Mauritius kestrel and cuckoo-strike declines, which they determine were caused by DDT. Roos *et al.* (2012) is an example of a correlative study linking improvements in reproductive success in European otters, grey seals and sea eagles in Sweden with declining concentrations of persistent organic pollutants. Other environmental changes may obscure the association between population changes and pollutant concentrations. For example, Henny *et al.* (2010) discusses conservation measures and other factors that occurred contemporaneously with DDT decline that may have independently caused an increase in osprey numbers. Sumpter and Johnson (2008) discuss improvements in overall water quality (decreases in gross pollution) that could be obscuring any relationship between oestrogen concentrations and fish population size.

AB24. Authors' opinion.

- a. Kidd *et al.* (2007) added ethinyl oestradiol (EE2) to a lake in the Canadian Experimental Lakes Area in Ontario and monitored changes in the densities of different species compared to both reference lakes and the treated lake prior to the EE2 additions. Fathead minnow (*Pimephales promelas*) nearly became extinct (Kidd *et al.*, 2007) but the population recovered after the treatment ended (Blanchfield *et al.*, 2015). There were differences in the population responses of other fish and invertebrates (Palace *et al.*, 2006; Kidd *et al.*, 2014).

MAJOR LEGISLATION CONCERNING EDCs

AB25. An overview and history of the Convention can be found at Stockholm Convention (2008b) and Stockholm Convention (2008c), respectively.

- a. Most of the POPs are listed under Annex A. PBDEs have a specific exemption for use in recycled products. DDT and PFOS are listed under Annex B that states: "Parties must

take measures to restrict the production and use of the chemicals listed under Annex B in light of any applicable acceptable purposes and/or specific exemptions listed in the Annex". There are a number of accepted purposes for use of PFOS including for photoimaging, use in firefighting foam, in medical devices and in baits for leafcutter ants. The sole accepted purpose of DDT is "disease vector control" – i.e. control of malarial mosquitoes (Stockholm Convention, 2008d). The World Health Organization (2011) recommends that DDT should only be used for indoor spraying and use must be carefully monitored.

AB26. The selection of risk vs. hazard-based approaches to EDC regulation is discussed by Matthiessen *et al.* (2017). Details on the REACH legislation is provided by the European Chemicals Agency (2017) and how it relates to EDCs by the European Commission (2016c). Criteria under which chemicals are considered EDCs for regulatory purposes by the EU are outlined in European Commission (2016b), European Commission (2017a) and Bourguignon *et al.* (2016). For comment and response see Bourguignon *et al.* (2016), Watson (2016) and Kortenkamp *et al.* (2016). For details of the hazard-based approach in the Plant Protection Products Regulation and Biocidal Products Regulation see Slama *et al.* (2016). Restrictions on use of EDCs may be applied under REACH legislation in the form of "risk management measures" (Bruinen de Bruin *et al.*, 2007). Silbergeld *et al.* (2015) compare REACH legislation with legislation in other countries, particularly the USA and China. Also see European Chemicals Agency (2018). EDCs registered in the EU as plant protection products and associated "cut-off criteria" are reviewed by Marx-Stoelting *et al.* (2014) and consequences discussed at Chandler *et al.* (2008) and Theodoris (2008). "Cut-off criteria" would allow the use of EDCs in plant protection products where the risk of human exposure is negligible (Marx-Stoelting *et al.*, 2014).

- a. EU chemical and environmental legislation is supplemented by global and regional conventions to which the EU, Member States and other European countries are party, such as the Helsinki Convention on the Baltic Sea (1992), OSPAR Convention on the NE Atlantic (1992), Stockholm Convention on Persistent Organic Pollutants (2001) and Minamata Convention on Mercury (2013) (although it is not clear whether mercury is an EDC).
- b. Details of the EU Water Directives Framework described at European Commission (2016a). The oestrogens and diclofenac have been included on the First Watchlist of the Environmental Quality Standards Directive for the "specific purpose of better informing suitable risk reduction measures". For further details and discussion on the Watchlist, see Negrão de Carvalho *et al.* (2015) and Owen and Jobling (2012). Potential of cosmetics to act as endocrine disruptors is reviewed by Nicolopoulou-Stamati *et al.* (2015). For information about the Marine Strategy Framework Directive of the EU aimed at achieving or maintaining "Good Environmental Status" in European seas, see Berg *et al.* (2015) and Lyons *et al.* (2017). "Good Environmental Status" is determined by 11 Descriptors; Descriptor 8 states "Concentrations of contaminants are at

levels not giving rise to pollution effects”, for discussion of this Descriptor, see Lyons *et al.* (2017).

- c. Kampa *et al.* (2010) and Keil (2010) review regulation relating to pharmaceuticals.
- d. Azoles are reviewed by Matthiessen and Weltje (2015). They can be EDCs but adverse effects only occur at levels higher than observed in the environment, e.g. Brown *et al.* (2015).

AB27. Details of the Basel Convention described in Basel Convention (2011) and SAICM at SAICM (2017). Breivik *et al.* (2011) discusses export of waste (some of which is illegal) from developed to developing countries.

WHAT CAN BE DONE ABOUT EDCS?

AB28. Many POPs have been banned under the Stockholm Convention and/or EU Legislation. Severe restrictions may be placed on the use of particular substances under the Stockholm Convention or under REACH legislation in the form of risk management measures (Bruinen de Bruin *et al.*, 2007). The Stockholm Convention allows for malarial spraying for vector control purposes, i.e. control of mosquitoes that vector malaria. The WHO recommends indoor residual spraying of DDT in epidemic areas and in areas with high and constant malaria transmission; the benefits to human health of preventing malaria are thought to outweigh the adverse effects of DDT (Mandavilli, 2006; World Health Organization, 2011). Wildlife effects may not have been adequately studied (Bouwman *et al.*, 2011).

- a. While persistent organic pollutants are widely present in the environment even after banning, overall levels of banned chemicals have declined in the environment e.g. Koschorreck *et al.* (2015) and in wildlife, e.g. Dietz *et al.* (2013). There will be time lags between bans and declines (Holmstrom *et al.*, 2010).
- b. Examples of population recovery after bans are described above (TBT AB7.a; DDT **Error! Reference source not found.**; PCBs AB7.c)

AB29. Vandenberg *et al.* (2015) discusses “regrettable replacements”. Examples of replacements with non-EDC compounds include the replacement of DDT by other pesticides, primarily organophosphates and carbamates (Oberemok *et al.*, 2015) and replacements of TBT with copper-based biocides (Ciriminna *et al.*, 2015). However these compounds may have non-EDC adverse effects (Evans, 1999).

- a. PBDEs were used to replace flame-retardant PCBs (Alaee *et al.*, 2003; Boas *et al.*, 2006) and are released when PBDE-containing items are discarded or recycled (Wu *et al.*, 2009; Gaylor *et al.*, 2012). PBDEs have been replaced with various novel brominated flame retardants (Alaee *et al.*, 2003; Ali *et al.*, 2011; Dodson *et al.*, 2012) that may also have ED effects (Patisaul *et al.*, 2013) and have been found in Antarctic wildlife (Wolschke *et al.*, 2015).

Various bisphenol compounds (bisphenols AF, B, F and S) are popular replacements for BPA (Kinch *et al.*, 2015) and have similar or greater endocrine-disrupting (oestrogenic) effects (Yang *et al.*, 2011; Eladak *et al.*, 2015; Rochester & Bolden, 2015; Chen *et al.*, 2016; Usman & Ahmad, 2016),

including in laboratory fish (Ji *et al.*, 2013; Naderi *et al.*, 2014; Qiu *et al.*, 2016; Le Fol *et al.*, 2017; Moreman *et al.*, 2017). Their potency compared to BPA is reviewed by Chen *et al.* (2016), Table 3. Moreman *et al.* (2017) states that the rank order of oestrogenicity in a range of zebrafish tissues was BPAF > BPA = BPF > BPS. Seltenrich (2015) discusses some of the issues surrounding finding replacement products for BPA and other plasticisers. Glass baby bottles are the fastest growing segment of the baby bottle market due to concern over EDCs in plasticisers, discussed in (Business Wire, 2016).

AB30. An overview of wastewater treatment in the UK can be found at Defra (2012). The size (number of people served), type and flow of the sewage treatment works has a major bearing on the amount of oestrogenic chemicals in the environment (Sumpter & Johnson, 2005). Different drugs are removed to different extents by sewage treatment plants (Wennmalm & Gunnarsson, 2009) and different types of sewage treatment have differing abilities to remove oestrogenic chemicals (Baynes *et al.*, 2012). Gardner *et al.* (2013) and (Comber *et al.*, 2018) review the effectiveness of UK wastewater treatment plants on their ability to remove pharmaceuticals (and other chemicals) from wastewater. Oller *et al.* (2011) and Ruhl *et al.* (2014) review the ability of advanced oxidation processes (i.e. ozonation and other technologies) and activated carbon to remove various compounds respectively. A disadvantage of granulated activated carbon is that it moves the compound from the wastewater into the carbon (reviewed by Zanella *et al.* (2014)). Ternes *et al.* (2004) discusses the chemistry of different compounds (not all EDCs) and how that affects how they move through different types of sewage treatment works, also see Miege *et al.* (2009). The ability of constructed wetlands to remove pharmaceuticals is reviewed by Li *et al.* (2014) and Morvannou *et al.* (2015). Johnson *et al.* (2007) models how different wastewater treatments could alter the concentrations of oestrogens in river water. A reduction in oestrogenicity should reduce levels of intersex. In Kitchener, ON, Canada, the wastewater treatment plant was upgraded from carbonaceous activated sludge to nitrifying activated sludge (Hicks *et al.*, 2017). This was associated with a decrease in intersex in male rainbow darter. Prior to the upgrade 70-100% of male fish were intersex, this decreased to <10% subsequently and the severity of intersex was also reduced.

- a. Costs calculated by Owen and Jobling (2012). Other options discussed by Baynes *et al.* (2012) and (Margot *et al.*, 2013).
- b. Authors’ opinion.

AB31. UNEP Chemicals and Waste Branch (2016) states that less than 20% of the total PCBs produced have been eliminated. The largest environmental source is leakage from electrical equipment (transformers and capacitors) ((Creaser *et al.*, 2007; UNEP Chemicals and Waste Branch, 2016)), they are also present in caulk or sealant of many buildings built 1950-1970, reviewed by (Harrad *et al.*, 2009; Frederiksen *et al.*, 2012; Herrick *et al.*, 2016). See discussion by Stuart-Smith and Jepson (2017) and Law and Jepson (2017).

PBDEs enter the environment when household products containing them are discarded (Rahman *et al.*, 2001; Balch *et al.*, 2006; Gaylor *et al.*, 2012; Neuman-Lee *et al.*, 2015).

UK regulations require that persistent organic pollutants are either destroyed by incineration or chemical destruction or are permanently stored underground (UK Government, 2015). For a review of techniques for persistent organic pollutant destruction, see Amend and Lederman (1992) and Magr (2003). New dechlorination (destruction of the molecule through removal of the chlorine atoms) technologies are being developed e.g. Celtic Recycling (2009).

- a. Challenges of dealing with persistent organic pollutants at waste management sites is reviewed by Weber *et al.* (2011) and Die *et al.* (2015). Examples of EDCs presence in landfills and recycling facilities can be found in Allchin *et al.* (1999); Wu *et al.* (2009); Fu *et al.* (2011)
- b. See above. The presence of PBDEs affects the recycling of this e-waste (Li *et al.*, 2013).
- c. Guerrero *et al.* (2013) reviews issues around solid waste management in developing countries. Significant amounts of plastics are found in the environment globally (Cozar *et al.*, 2014). BPA and phthalates are often found in plastics while electronic waste (e-waste) contains PCBs, PBDEs, dioxins and plasticisers. The issue of e-waste is reviewed by Perkins *et al.* (2014), Needhidasan *et al.* (2014) and Grant *et al.* (2013).

AB32. Contaminated sites can be cleaned up, methods for decontamination depend on both the compound and substrate. Techniques and case studies are reviewed by Gomes *et al.* (2013). Methods of removing pesticides from soils are reviewed by Morillo and Villaverde (2017); Sudharshan *et al.* (2012) focuses on DDT. Bioremediation involves using bacteria and fungi to break the compounds down, reviewed by Shannon and Unterman (1993), Aislabie *et al.* (2010) and Passatore *et al.* (2014). Using high temperatures to remove PCBs from soil is discussed by Qi *et al.* (2014). Other emerging technologies discussed by Wang *et al.* (2017) and Rybnikova *et al.* (2016).

- a. The United States Environment Protection Agency Superfund program is described at US EPA (2017b). New Bedford Harbor is an example of a remediated site (Nelson & Bergen, 2012).

AB33. Strategies for preventing pharmaceuticals from entering the environment are reviewed by Blair (2016) and Straub (2016). Authorisation of veterinary medicines in the EU considers risks and benefits, including the risk of environmental harm (Chapman *et al.*, 2017). Guidelines regarding the use and disposal of veterinary medicines are described by Price and Tait (2012) for vets, and for farmers by the Veterinary Medicines Directorate (2014).

- a. Assessments of EDC effects in wildlife can be predicted from the “read across” hypothesis (Rand-Weaver *et al.*, 2013; Brown *et al.*, 2014). A database that connects drugs to their target proteins in unrelated species can be used to predict which species may be affected (Verbruggen *et al.*, 2018). Examples of correlates between pharmaceutical sales/prescription data and levels in freshwater systems include ter Laak *et al.* (2014) and van Nuijs *et al.* (2015). Daughton (2014) discusses some limitations of this

approach. Excretion rates of pharmaceuticals vary from 80–100% for metformin to 2–5% for paracetamol (Corcoran *et al.*, 2010; Scheurer *et al.*, 2012; Al-Odaini *et al.*, 2013). Bu *et al.* (2016) and Walters *et al.* (2010) review degradation rates in the freshwater and soils respectively.

- b. Pharmaceuticals enter the environment via disposal of drugs, reviewed by Daughton and Ruhoy (2011). Drug takeback schemes discussed by Kampa *et al.* (2010). Castensson and Ekedahl (2010) review disposal of unused medication – 12–27% are figures for the UK,
- c. Clark *et al.* (2010) and Kümmerer (2010) review some of the issues and chemistry involved in developing “greener” pharmaceuticals. The Swedish Environmental Classification of Pharmaceuticals classifies drugs on their environmental hazard properties and the risk to the aquatic environment (Stockholm County Council, 2014–2015).
- d. For details on urine separating toilets, see Blair (2016) and Lamichhane and Babcock (2012). A life cycle assessment that used the University of Florida campus as a case study (Landry & Boyer, 2016), suggested that urine separating toilets would have a 90% lower environmental impact due to saving 6.6 million gallons of water. However, decreasing pharmaceutical load using ozonation was more ecotoxic and cost 30% more.

AB34. As the CDC reports that no methods exist to remove PCBs from badly affected humans (CDC Agency for Toxic Substances and Disease Registry, 2014), we can conclude that some EDCs cannot be removed from wildlife under any circumstances. However, other EDCs such as BPA are readily eliminated from the body (Genuis *et al.*, 2012). For removal from the environment see AB32.

AB35. Sumpter and Johnson (2005) discuss that for most fish species we do not have a good indication of what the rates of intersex in the absence of environmental pollutants would be i.e. what baseline rates are.

- a. For details of the UK Water Industry Research Limited’s monitoring programme, see UK WIR (2017) and Gardner *et al.* (2012), some of the findings are detailed in Gardner *et al.* (2012), Gardner *et al.* (2013) and (Comber *et al.*, 2018).
- b. Global monitoring of POPs in air water and human blood and breast milk under Stockholm Convention described by Hung *et al.* (2016), Magulova and Priceputu (2016) and Stockholm Convention (2008e). The HBM4EU project monitors a range of chemicals including some EDCs in humans across Europe (HBM4EU, 2017). EU raptor populations are monitored by European Cooperation in Science and Technology (2018) and described by Espin *et al.* (2016), while the Predatory Bird Monitoring Scheme in the UK (Centre for Hydrology & Ecology, 2018) is reviewed by Walker *et al.* (2008) and the otter project of Cardiff University (2018) is a long term surveillance scheme using otters found dead to measure contaminants. Levels of POPs can be correlated with other measures of health e.g. Kean *et al.* (2013).
- c. Examples of studies using museum specimens to determine effects of pollutants includes Reeder *et al.* (2005) who

determined that intersex in Illinois cricket frogs only occurred following introduction of PCBs; Lind *et al.* (2003) and Sonne *et al.* (2004) showed that bone mineral density of Baltic grey seals and polar bears respectively was higher prior to the introduction of organochlorines; and Ratcliffe (1970) used museum collections to demonstrate that egg shells of various UK birds had thinned since about 1950 when DDT was introduced.

FUTURE OPPORTUNITIES AND CHALLENGES

AB36. Global population growth statistics by

United Nations Population Fund (2018). For example, plastic production and use is expected to increase globally (Andrady & Neal, 2009; Thompson *et al.*, 2009). In India consumption of virgin plastic increased from 0.8kg per capita in 1990/91 to 3.2 kg in 2000/2001 in line with increases in GDP, and is predicted to increase six-fold between 2000 and 2030 (Mutha *et al.*, 2006). By 2050 an estimated 12,000 Mt of plastic waste is predicted to occur in landfills or the natural environment assuming current waste management practices (Geyer *et al.*, 2017). Modelling has suggested that population increases and demographic shifts will have a greater impact on steroid oestrogen concentrations in the Thames Basin than climate change, which is predicted to decrease water flow (Keller *et al.*, 2015).

AB37. Buchberger (2011) and Concha-Graña *et al.* (2013) review techniques to measure environmental levels of pharmaceuticals and organochloride pesticides respectively. der Beek *et al.* (2016) observed that the smaller spectrum of pharmaceuticals detected in samples from developing countries was most likely due to the lack of adequately equipped environmental laboratories. An example of a non-target screening programme is Norman Network (2012-2018), also see Dulio *et al.* (2018).

- a. Authors' view, for discussion on issues with undertaking laboratory research on ED effects see AB19.

AB38. One example is Toxcast (AB5.a). Messerlian *et al.* (2017) review how "omics" technologies can be used in EDC research. Difficulties in applying *in vitro* tests to individual effects is discussed by Futran Fuhrman *et al.* (2015). Adverse outcome pathways (AOPs) are described by OECD/OCDE (2018b) with application to EDCs by Ankley *et al.* (2010), Kramer *et al.* (2011) and Manibusan and Touart (2017).

- a. Gaps in endocrine testing methods discussed by Coady *et al.* (2017) and Manibusan and Touart (2017).

AB39. Gee (2013) discusses the balancing of risks for policy making. As an example, Sass and Colangelo (2006) and Ackerman (2007) both use atrazine to compare the US and EU approach to pesticide registration policy. Changing contraceptive use to non-hormonal methods (condoms) would decrease levels of EE2 in the environment, however the increased failure rate also needs consideration (Khan & Nicell, 2014), as the highest rates of oestrogen excretion are from pregnant women.

- a. Some attempts have been made to calculate the financial costs of EDC exposure on human health. Calculated estimates of the human health costs caused by EDCs in the European Union ranged from €714 million to €251 billion with a median of €1.63 billion or 1.28% of GDP (Trasande *et al.*, 2016). In the USA costs are estimated to be 2% of GDP

(Attina *et al.*, 2016). Jaacks and Prasad (2017) comment that if costs to aquaculture and agriculture were included, human health costs would be higher.

Markandya *et al.* (2008) review the implications of the loss of the ecosystem service of cattle carcass removal services by vultures due to diclofenac. Without vultures, the cattle corpses were eaten by dogs, leading to an increase in the dog population and thus human cases of rabies, which are estimated to have cost US\$34 billion 1993-2006.

There is a discussion of the economic benefits of TBT as an antifoulant boat paint in Evans (1999).

AB40. Reviews on the interaction between EDCs (particularly the POPs) and climate change include Alava *et al.* (2017), Nadal *et al.* (2015), Lamon *et al.* (2009), Noyes *et al.* (2009) and Schiedek *et al.* (2007). Jenssen (2006) review potential effects on Arctic fauna and Alava *et al.* (2017) reviews effects of climate change and pollutants on marine systems. The redistribution of some chemicals (e.g. PCBs) is projected to be greater than others such as PBDEs (Paul *et al.* (2012), differences in model findings discussed by Hansen *et al.* (2015). Keller *et al.* (2015) and Lu *et al.* (2015) review how climate change will affect the UK distribution of oestrogens and PCBs respectively.

- a. Noyes *et al.* (2009).
- b. Johnson *et al.* (2009a). Walsh *et al.* (2016) reviews present and future water resources in the Thames Basin.
- c. Westra *et al.* (2014). For discussion surrounding changes in rainfall in the UK, see Dadson *et al.* (2017).
- d. Schiedek *et al.* (2007) discusses stress generated by climate change and by EDCs and how they might interact. Studies investigating the interaction between EDCs and temperature include Little and Seebacher (2015), Brown *et al.* (2015), Patra *et al.* (2007) and Rohr *et al.* (2011).
- e. Shifts of polar bears diets in Hudson Bay (McKinney *et al.*, 2009) and East Greenland (McKinney *et al.*, 2013).
- f. Ma *et al.* (2011) modelled the remobilisation of POPs due melting sea ice in the Arctic. The melting of the Oberaar glacier in the Swiss Alps has caused POP levels in Lake Oberaar to increase from the late-1990's (Weinhold, 2009; Bogdal *et al.*, 2010).

AB41. Changing burden of disease globally profiled in the Global Burden of Disease Study 2013 Collaborators (2015). Bech *et al.* (2011) review how aging population will alter health care expenditure. Increases in obesity and related co-morbidities (particularly diabetes) are covered by World Health Organization (2014) and World Health Organization (2016). The use of anti-depressants is expected to increase (Kantor *et al.*, 2015). Globally, contraceptive use is expected to increase (2015-2030) but declines are expected in some regions (United Nations Department of Economic and Social Affairs, 2015). Post-menopausal hormone replacement therapy has declined due to concerns surrounding side-effects (Sprague *et al.*, 2012).

- a. Personalised medicine is reviewed in Schork (2015) and by NHS England (2017). The use of nanotechnology in medicine is reviewed by Etheridge *et al.* (2013) and D'Mello *et al.* (2017). For details of "green pharmaceuticals" see AB33.c.

AB42. For an overview of the EDC situation in Africa, see Bornman *et al.* (2017). Reviews of organochloride pesticide use in developing countries/regions include South Asia (Ali *et al.*, 2014), China (Li *et al.*, 2016), the Philippines (Mackintosh *et al.*, 2015) and Nigeria (Sindiku *et al.*, 2015). Use of EDCs may differ between regions, examples include phthalates (Berge *et al.*, 2013), alkylphenols (Berge *et al.*, 2012) and PBDEs (Li *et al.*, 2016). DDT is used for control of malaria mosquitoes in some countries (van den Berg, 2009). Pesticides banned under the Stockholm Convention are illegally used in some developing countries (Jan *et al.*, 2009; Ali *et al.*, 2014).

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