Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in
Endocrine and Metabolic Research

Review

The history of endocrine-disrupting chemicals

Philippa D. Darbre

Abstract

This mini-review offers a historical perspective on the emergence of endocrine disruption as a multidisciplinary research area, encompassing studies from ecotoxicology to medicine and from field observations to molecular cell biology. Endocrine-disrupting chemicals (EDCs) are environmental compounds which interfere in the actions of hormones. Some are naturally occurring, but the majority are man-made compounds which have been released without prior knowledge of their impact on animal or human health. Reduction in environmental contamination with EDCs requires regulatory actions at international, national and individual levels. However, the ability of EDCs to act through receptor-mediated mechanisms at low concentrations, often with nonmonotonic dose responses and additively as mixtures, and to act with cell-specific and lifestyle-specific effects poses a considerable challenge to risk assessment.

Addresses

School of Biological Sciences, University of Reading, Reading RG66UB, UK

Corresponding author: Darbre, Philippa D (p.d.darbre@reading.ac.uk)

Current Opinion in Endocrine and Metabolic Research 2019, **7**:26–33

This review comes from a themed issue on **Endocrine Disruptors**

Edited by **Aleksander Giwercman** and **Bernard Jégou**

For a complete overview see the Issue and the Editorial

Available online 5 July 2019

https://doi.org/10.1016/j.coemr.2019.06.007

Keywords

Endocrine disruption, Endocrine-disrupting chemicals, Endocrine disrupters.

Introduction

> 'An endocrine disrupter is an exogenous substance that causes adverse health effects in an intact organism, and/or its progeny, consequent to changes in endocrine function' [1].

A functional endocrine system is needed in all multicellular organisms to ensure the coordinated actions of hormones, which act as chemical messengers for communication between organs and tissues, in the regulation of physiological and behavioural activities. Hormones are secreted by endocrine glands and are then carried to act on target cells where their specificity is determined by binding to cellular receptors. Normal functioning depends on the coordinated actions of a complex network of hormones, all acting in synchrony with one another, at the correct concentrations and at the appropriate times. However, it is now evident that some environmental chemicals have the ability to interfere in the action of hormones, and these have been termed endocrine-disrupting chemicals (EDCs). Some EDCs are present in nature as plant-derived phytoestrogens or fungus-derived mycoestrogens, but the majority are synthetic compounds released into the environment by the activities of man often without previous knowledge of their effects, either alone or in combination, on ecosystems, animal wellbeing or human health (Table 1) [2]. The mechanisms of interference include altering hormone synthesis, altering hormone transport, altering hormone metabolism and/or interfering in actions at the target site by competing for binding to cellular receptors or modifying target cell receptor levels [2]. Alterations may include increasing activity, decreasing activity or stimulating activity at inappropriate times [2].

Early indications of endocrine-disrupting activity in farm animals

Although endocrine disruption has only recently received high profile attention, the phenomenon has been known about for a long time (Figure 1) and almost since the identification of the first hormone in 1902 [3]. The effects of hormones have been known about since ancient times, most notably in the context of the use of castration to change serving males into eunuchs. However, an appreciation of hormones as identifiable chemical messengers began in 1902 after the identification of secretin in the regulation of the digestive system [3]. Early indications of an endocrine-disrupting activity were reported already in the 1920s by pig farmers in the USA concerned by lack of fertility in swine herds fed on mouldy grain [4], which subsequently was shown to result from consumption of mycoestrogens contained in the mould [5]. This was followed by reports in the 1940s from sheep farmers in Western Australia reporting infertility in their sheep after grazing on certain fields of clover [6], again later

Table 1

Environmental chemicals with endocrine-disrupting activity (for detailed references see publication 2).

Compounds	Use	Source of human exposure
Phytoestrogens	Natural component of plants	Plant materials in food, nutraceuticals, personal care products
Mycoestrogens	Natural component of fungi	Mouldy grain
DDT(and metabolites), dieldrin, lindane, other chlorinated organics	Pesticides	Animal fat (diet), restricted uses allow for inhalation or dermal exposures
Atrazine, glyphosate	Herbicides	Agricultural, urban/domestic gardens
Polychlorinated biphenyls (PCBs)	Electrical industry	Animal fat in diet
Polychlorinated dibenzodioxins (PCDDs)	By-product of incineration	Inhaled, animal fat in diet
Polybrominated diphenyl ethers (PBDEs)	Flame retardant in soft furnishings	Workplace/domestic environment
Perfluorooctanoic acid (PFOA), perfluorooctanesulphonate (PFOS)	Stain resistance of consumer products	Workplace/domestic environment
Bisphenol A (BPA)	Plastics, epoxy resins	Storage of food and beverages (diet), domestic environment
Phthalate esters	Plastics	Domestic consumer products
Alkyl phenols	Detergent	Workplace/domestic environment, personal care products
Alkyl esters of p-hydroxybenzoic acid (parabens)	Preservative	Personal care products, foods, pharmaceuticals
Triclosan	Antiseptic, preservative	Personal care products, domestic consumer products
Benzophenones (also at least 50 other approved organics)	Absorb ultraviolet light	Suncare products, other cosmetics, clothing
Butylphenylmethylpropional, benzyl salicylate, musks	Fragrance	Personal care products, domestic consumer products, air fresheners
Organometals — tributyltin	Molluscicide — antifouling paints	Consumption of contaminated seafood
Metalloestrogen — cadmium	Cigarette smoke	Exposure to cigarette smoke
Metalloestrogen — aluminium	Antiperspirant	Personal care products
Synthetic oestrogen — diethylstilboestrol	Pharmaceutical	Prevention of miscarriage in pregnancy
Synthetic oestrogens — notably ethinylestradiol	Pharmaceuticals, cosmeceuticals	Contraceptive pill, hormone replacement therapy, personal care products
Synthetic progestins	Pharmaceuticals	Contraceptive pill, hormone replacement therapy
Synthetic glucocorticoids	Pharmaceutical— anti-inflammatory	Pharmaceutical taken to reduce inflammation
Paracetamol	Pharmaceutical — analgesic and antipyretic	Pharmaceutical taken for pain relief and fever reduction

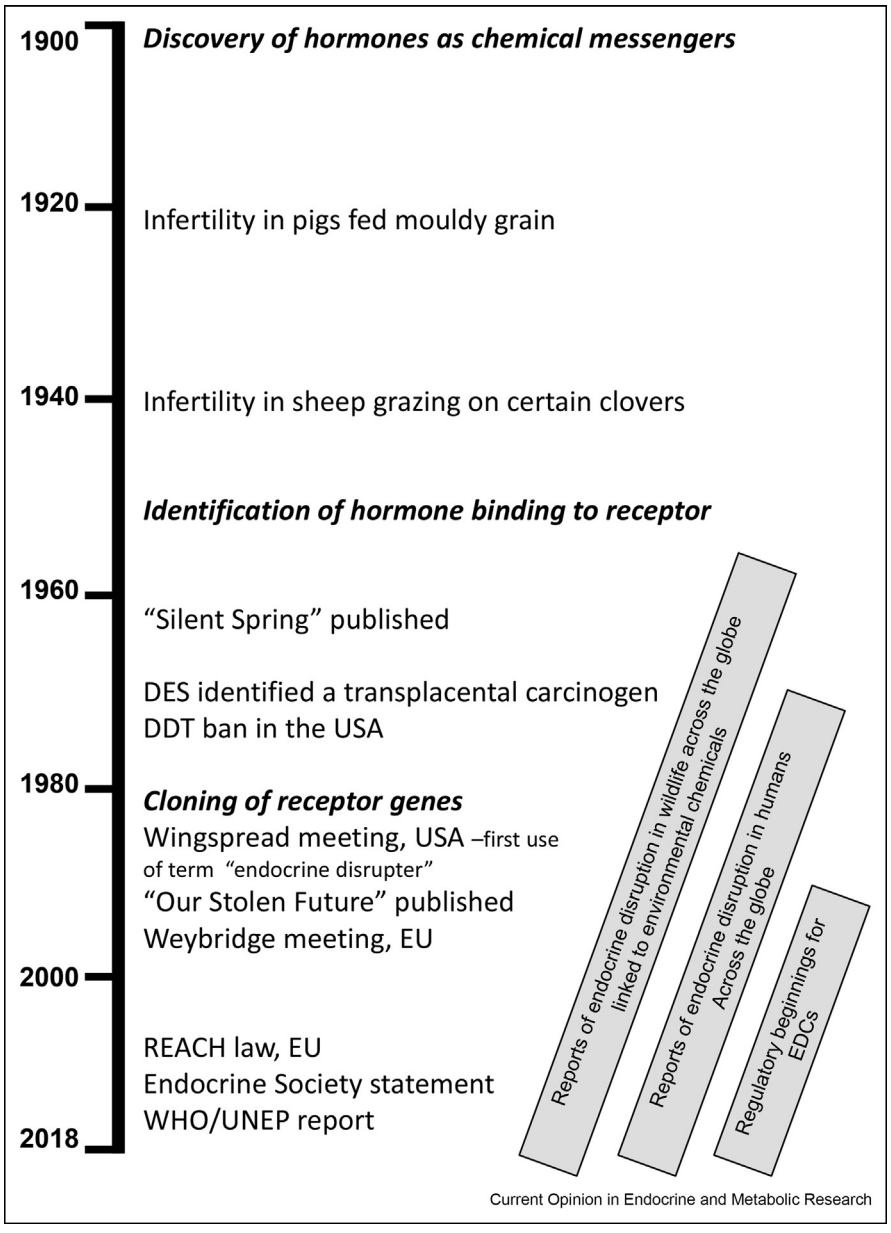
shown to result from consumption of phytoestrogens in the plant material [7].

Endocrine disruption in wildlife populations

A significant landmark in awareness of endocrine disruption as a widespread phenomenon resulting from man-made chemicals was the publication in 1962 of the book 'Silent Spring' by Rachel Carlson (Figure 1) [8]. This book warned of the long-term consequences for loss of wildlife populations after the liberal agricultural use of pesticides and herbicides. In the following years, endocrine-disrupting properties were reported widely in wildlife living in water, in air and on land after exposure to industrial chemicals such as the pesticide dichlorodiphenyltrichloroethane, its metabolites and other organochlorine compounds [9–12]. International environmental organisations were established to champion awareness, but a follow-on book 'Our Stolen Future' published by Colborn et al [13] in 1996 describes even more serious environmental warnings which demonstrate the inadequacy of measures taken in the interim period to counter the problem.

Endocrine disruption has been reported widely in aquatic wildlife where links have been established between reproductive abnormalities/population declines and specific chemical exposures in the water. Early work showed extensive loss of bivalves and gastropods in harbour waters after exposure to tributyltin. Tributyltin is a biocide which was introduced in the 1970s into antifouling paints for treating the underside of ships, but the release of this compound into harbour waters led to widescale masculinisation (imposex) of bivalves and gastropods and consequent population declines [14].

Figure 1



Cartoon outlining historical landmarks in the recognition of endocrine disruption. Bold italics indicate landmarks in endocrinology research; normal text indicate landmarks in endocrine disruption research. EDC, endocrine-disrupting chemical; DES, diethylstilbestrol; DDT, dichlorodiphenyltrichloroethane; WHO, World Health Organization; UNEP, United Nations Environment Programme.

An accidental spill of the pesticide dicofol into a tributary of Lake Apopka in Florida, USA, in 1980 resulted in serious loss of the alligator population. Genital abnormalities were reported in both male and female alligators, and Apopka female alligators were reported with abnormal ovarian morphology, large numbers of polyovular follicles, and raised plasma oestradiol levels [15]. In the UK, there was an early warning of feminisation of male fish in rivers downstream of sewage effluent works, associated in particular with the induction of vitellogenin (an exclusively female protein) and appearance of ovarian tissue in the testes [16]. A gradient of effect was reported with fish at closest proximity to the sewage outflow giving the most severe responses [16]. Further studies using caged fish confirmed the sewage effluent to be responsible for the responses, and chemical fractionation showed the presence of natural and synthetic oestrogens at biologically relevant concentrations [16].

Synthetic hormones and pharmaceuticals

In the 1930s, chemists in London led by Sir Charles Dodds were synthesising a range of chemicals with oestrogenic properties [17]. Initiated with the intentions of studying the mechanisms of oestrogen action, a potential pharmaceutical value of such compounds was realised and a new industry of synthetic hormones was born. The developing culture of sexual freedom in the 1960s embraced the use of oral contraceptives containing synthetic oestrogens and progestins [18]. As this same generation grew older, hormone replacement therapy became a normal expectation for control of menopausal symptoms [19]. The long-term consequences of the desire to control reproductive hormone exposures have yet to be fully understood, not only in terms of effects on the individual person but also in terms of the consequences of releasing so many synthetic hormones and their metabolites into the environment.

The use of synthetic hormones, however, now extends beyond control of reproduction in humans to control of reproduction in cattle for the meat and dairy industry [20]. Synthetic glucocorticoids are prescribed widely as anti-inflammatory agents [21]. Antiestrogens, aromatase inhibitors [22], and antiandrogens are prescribed for cancer therapy. *N*-acetyl-*p*-aminophenol (paracetamol) is a widely used non-prescription analgesic (pain relief) and antipyretic (reduce fever) drug and possesses endocrine-disrupting activities [23]. Phytoestrogens are organic compounds produced naturally by plants which have the ability to mimic or interfere in the action of oestrogens and are found in over 300 different plant species [7]. On the basis that compounds of 'natural' origin are assumed to be less harmful than man-made compounds, marketing of plant material or plant extracts containing phytoestrogens has been widely adopted for self-medication, most notably in relief of postmenopausal symptoms.

The legacy of diethylstilbestrol

Diethylstilbestrol (DES) is a synthetic nonsteroidal oestrogen that was first synthesised in 1938 [17] and then prescribed to several million women between 1940 and 1971 to prevent threatened miscarriage in the first trimester of pregnancy [24]. In 1971, it was reported to have caused a rare vaginal cancer in daughters born to women who had taken DES during pregnancy [25], and as a result, further prescription ceased. Long-term follow-on studies have revealed that *in utero* exposure to DES is associated with an increased lifetime risk of a range of adverse reproductive health outcomes and not only for daughters but also for sons [26]. These effects of DES have demonstrated not only that there can be adverse health effects in the human population after exposure to a potent synthetic oestrogen but also that exposure *in utero* can have effects which are lifelong even without any further exposure after birth.

Development of assays for detecting endocrine-disrupting activity

An understanding of the molecular actions of hormones was facilitated after the identification of cellular receptor proteins in the 1960s and then cloning of the receptor genes in the 1980s. This enabled further research to unravel the range of different receptor proteins, their cellular distribution across tissues and the mechanisms by which they relayed signals into the target cells by genomic and nongenomic mechanisms [2]. However, these studies also generated a range of *in vitro* assays for hormone action and consequently enabled testing of individual environmental chemicals for agonist or antagonist activity through these receptors [2]. The effects most widely reported are of oestrogen-disrupting, androgen-disrupting and thyroid hormone–disrupting activities, but disruption to other receptor systems has also been noted including progesterone receptor, glucocorticoid receptor, peroxisome-proliferator activated receptors and pregnane X receptor [2]. The binding of environmental chemicals to the aryl hydrocarbon receptor can influence expression of cytochrome P450 genes; some of which act in the synthesis and/or metabolism of hormones [27].

Using such assays, some of the early studies were aimed at investigating whether pollutant organochlorine compounds possessed oestrogenic activity which might explain their observed reproductive effects in wildlife. Accordingly, dichlorodiphenyltrichloroethane and its metabolites [28], polychlorinated biphenyls (PCBs) [28] and polychlorinated dibenzodioxins [29] were investigated, and some were found to have oestrogen-disrupting properties in the molecular assays. With the passage of time, other industrial chemicals were also investigated, and hence, the alkyl phenols [30] and phthalates [31] also came under the spotlight as enlarging the portfolio of known environmental chemicals with oestrogenic activity. The report of the leaching out of the oestrogenic compound bisphenol A from laboratory plasticware [32] stimulated a new focus of research into the wider implications of the use of oestrogenic compounds in plastics [33]. The reports that parabens (alkyl esters of *p*-hydroxybenzoic acid) also possess oestrogenic activity in these *in vitro* assays [34] generated questions as to their ability to enter the human body from use as preservatives in consumer products. At the time, it was assumed that metabolism after oral consumption in food or pharmaceuticals would result in removal of the ester grouping with rapid excretion and that dermal application in personal care products would not result in any uptake into the human body [34]. For these reasons, the demonstration in 2004 of parabens in human breast tissue [35] sparked heated

debate but, in time, led to the confirmation that parabens are indeed widely present in the human population, not only in human breast tissue (which is an oestrogen-sensitive tissue and the site of the main female cancer) but also in over 95% of human urine samples [34]. In time, this has led to the realisation that personal care products contain many oestrogenic chemicals which are not only adversely affecting aquatic wildlife populations but also entering the human body [2].

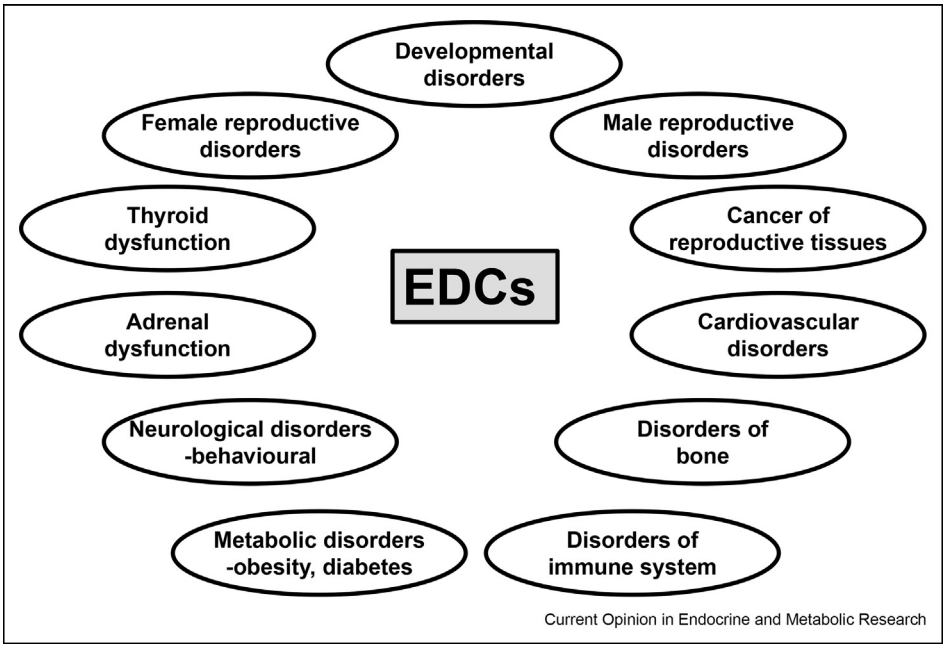
In parallel with these studies, other research was directed at effects on thyroid function. The toxicity of PCBs had been highlighted by an incident in Japan in 1968 where many people had been poisoned by consumption of rice oil contaminated with PCBs from a heat exchanger liquid [36], and research into the mechanisms of action revealed effects on the thyroid and, in particular, on thyroid hormone synthesis [2]. In the following years, other industrial chemicals including most notably the polybrominated diphenyl ethers used as flame retardants and perfluoro compounds (perfluorooctanoic acid, perfluorooctanesulphonate) used as stain resistance agents also revealed thyroid-disrupting activities [2].

Environmental exposures and human endocrine health

In turning to questions of relevance for human health, the long-debated questions remain as to the extent to which effects in wildlife or in animal models might also occur in the human population in response to the same chemicals, and the extent to which effects observed in human cells *in vitro* might be predictive of consequences for human health *in vivo*. The effects of human exposure to DES made clear that humans could also be vulnerable to endocrine disruption [26]. However, a new focus on human health evolved in the early 1990s following reports of declining sperm quality in men living in Denmark compared with those in its less industrial neighbour Finland [37]. The decline in sperm quality appeared linked also to incidence of hypospadias, cryptorchidism and testicular cancer, defining a new testicular dysgenesis syndrome hypothesised to result from exposure to pollutant chemicals [38]. This opened the door to discussion concerning a role for environmental chemicals more widely in increasingly reported female and male reproductive problems, increasing incidence of cancers in reproductive tissues and disorders of thyroid and adrenal function (Figure 2) [2].

Another new aspect to considerations of human health was uncovered when, in 1990s, David Barker [39] proposed a link between foetal development and adult disease. With the unfolding legacy of DES, it was becoming apparent that exposure to untoward endocrine agents *in utero* could have long-term effects into adult life without the need for any further exposure [26] and animal models began to reveal that exposure to a variety of endocrine-disrupting chemicals could also

Figure 2



Human endocrine disorders reported to result from exposure to endocrine-disrupting chemicals. EDC, endocrine-disrupting chemical.

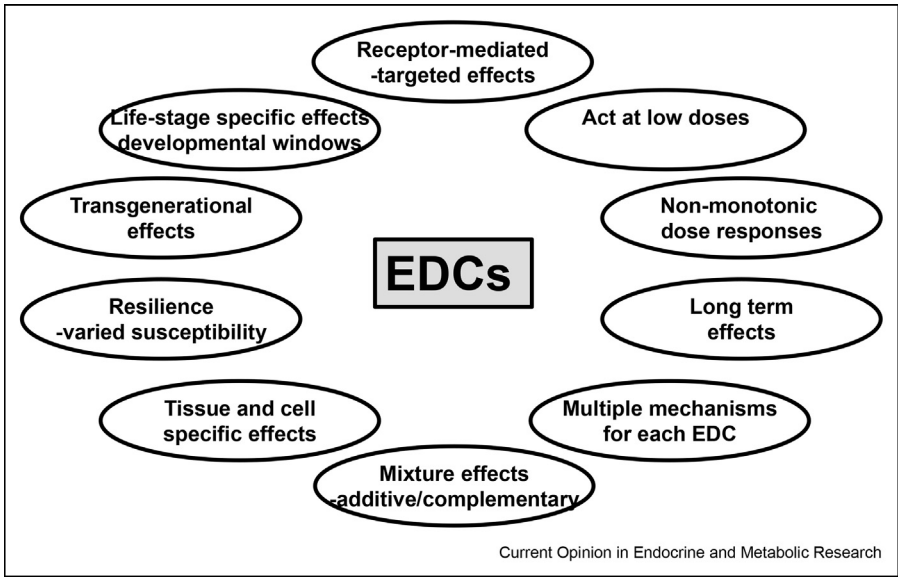
have that effect [2]. Most notably, the unfolding epidemic of obesity was suggested to be linked to aberrant endocrine exposures *in utero* and, in particular, to exposure to environmental chemicals with obesogenic properties [40].

Regulatory beginnings

This review has described the historical emergence of endocrine disruption as a new multidisciplinary research area encompassing studies from ecotoxicology to medicine and encompassing broad range field observations to detailed molecular cell biology studies. One of the most significant early scientific meetings on endocrine disruption was the World Wildlife Fund Wingspread Conference in Wisconsin in the USA in 1991, which was where the term 'endocrine disrupter' was first proposed [41] and which was followed up 15 years later [9]. In Europe, the Weybridge meeting in 1996 [1] and Weybridge 15 years on meeting [11] report complementary findings to those in the USA. Other countries including Australia, Korea and Japan have held similar meetings. In 2009, after 18 years of research after the Wingspread meeting, a scientific statement was published by the Endocrine Society of the USA outlining mechanisms and effects of endocrine disrupters and showing how experimental and epidemiological studies converge with human clinical observations 'to implicate EDCs as a significant concern to public health' [10]. In 2013, the World Health Organization and the United Nations Environment Programme released a comprehensive report on EDCs, calling for more research to fully understand the associations between EDCs and the risks to human and animal health [12].

Scientific consensus statements from these and other meetings have led to discussions as to how regulatory measures might be taken to reduce exposure to suspect chemicals. However, regulatory action by governments is dependent on risk assessment, and the actions of endocrine disrupters pose considerable challenges to current toxicological risk assessment strategies (Figure 3). Because EDCs act through receptor-mediated mechanisms, their actions are more specific than classical nonspecific toxicants, allowing EDCs to act at much lower concentrations and through targeted cellular actions [2]. Their actions are tissue-specific and effects in one tissue may not predict for effects in another tissue because effects are dependent on the presence/quantity of receptors in the target cells/tissues. Effects may also differ at different life stages, often with a susceptibility window during *in utero* development or early postnatal life. Furthermore, consequences of exposure during early life may take until into adult life to be realised without the need for any further exposure and may even persist into the following generation (transgenerational) [2]. Dose responses can be nonmonotonic [42], and just as for hormones, EDCs may have different effects to low and high concentrations which challenges classical toxicology assumptions of a linear response allowing for prediction of a safe low dose. Because many different EDCs may act through similar or complementary

Figure 3



Mechanisms of action of endocrine-disrupting chemicals which set them apart from other toxic compounds. EDC, endocrine-disrupting chemical.

mechanisms, there can be additive effects from mixtures [43], which also challenge the classical toxicology approach of assessing each chemical in isolation. Another challenge arising from the development of *in vitro* testing methods is the ease/speed with which *in vitro* data can be generated compared with *in vivo* data, and it is on the *in vivo* data that classical toxicological risk assessment has relied. One approach to resolving the data generation issue has been to construct adverse outcome pathways. Adverse outcome pathways provide a conceptual framework by which exposure to an EDC may be causally linked to an adverse health outcome through a sequential or branching chain of events at different levels of biological organisation from molecular and cellular to whole body and population responses. This provides a useful model based on mechanistic reasoning where measurements cannot be made at every step, where a single EDC does not act at every step or where multiple EDCs act by complementary mechanisms. Furthermore, it helps the environmental reality of the need to identify culprit chemical sources where only a population phenomenon is known or vice versa of the need to investigate whether environmental chemicals with endocrine-disrupting properties could be causing adverse health outcomes.

In response to the scientific consensus, government regulatory procedures are being established at both national and international levels. In the USA, the Environment Protection Agency has set up screening programmes for chemicals for endocrine disrupter activity and now incorporated into the ToxCast programme [44]. In the European Union, EDCs are now managed under the legislation of REACH (registration, evaluation and authorisation of chemicals). International initiatives include agreements under the Rotterdam Convention of the United Nations Environment Programme (www.pic.int) and the Stockholm Convention (www.pops.int) and from the Organisation for Economic Cooperation and Development (OECD). Nongovernmental organisations and the mass media continue to play a major role in championing awareness of the implications of endocrine disruption, often emphasising more strongly adoption of the precautionary principle compared with government regulatory bodies. Finally, there remains not only a collective but also an individual responsibility to change habits for the greater good. Many challenges remain ahead, especially in social and political aspects, but only the future can decide whether the final outcome could run counter to that predicted so often by Haile Selassie:

> "Throughout history it has been the inaction of those who could have acted; the indifference of those who should have known better; the silence of the voice of justice when it mattered most; that has made it possible for evil to triumph." (Haile Selassie)

Conflict of interest statement

Nothing declared.

References

Papers of particular interest, published within the period of review, have been highlighted as:

* of special interest

1. *Report of the proceedings of the european workshop on the impact of endocrine disrupters on human health and wildlife. Weybridge, UK. Report EUR17549 of the environment and climate change research programme of DGXII of the european commission*. 1996.

2. * Darbre PD. *Endocrine disruption and human health*. New York: Elsevier/Academic Press; 2015.
Overview of EDCs: sources, mechanisms and implications for human health.

3. Bayliss WM, Starling EH: **The mechanism of pancreatic secretion**. *J Physiol* 1902, **28**:325–353.

4. McNutt SH, Purwin P, Murray C: **Vulvo-vaginitis in swine: preliminary report**. *J Am Vet Med Assoc* 1928, **73**:484.

5. Bennett JW, Klich M, Mycotoxins: *Clin Microbiol Rev* 2003, **16**: 497–516.

6. Bennets H, Underwood EJ, Shier FL: **A specific breeding problem of sheep on subterranean clover pasture in Western Australia**. *Aust Vet J* 1946, **22**:2–12.

7. * Woods HF: *(chairman), Phytoestrogens and health*. Crown copyright UK; 2003.
Comprehensive review on phytoestrogens.

8. Carson R: *Silent spring*. USA: Houghton Mifflin; 1962.
Prophetic book detailing observed losses of wildlife populations from environmental chemicals.

9. Hotchkiss AK, Rider CV, Blystone CR, Wilson VS, Hartig PC, Ankley GT, Foster PM, Gray CL, Gray LE: **Fifteen years after "Wingspread" - environmental endocrine disrupters and human and wildlife health: where we are today and where we need to go**. *Toxicol Sci* 2008, **105**:235–259.

10. Diamanti-Kandarakis E, Bourgignon JP, Giudice LC, Hauser R, Prins GS, Soto AM, Zoeller T, Gore AC: **Endocrine-disrupting chemicals: an endocrine society scientific statement**. *Endocr Rev* 2009, **30**:293–342.

11. European Environment Agency (EEA): *The impacts of endocrine disrupters on wildlife, people and their environments*. Luxemburg: Publications Office of the European Union; 2012. The Weybridge+15 (1996-2011) report, ISBN 978-92-9213-307-B.

12. Bergman A, Heindel JJ, Jobling S, Kidd KA, Zoeller RT. *The state of the science of endocrine disrupting chemicals -2012*. United Nations Environment Programme (UNEP) and World Health Organisation (WHO); 2013.

13. * Colborn T, Dumanoski D, Myers JP: *Our stolen future*. USA: Dutton; 1996.
Sequel to reference 8 detailing escalating observed losses of wildlife populations from environmental chemicals and implications for human health.

14. Horiguchi T: **Masculinization of female gastropod mollusks induced by organotin compounds, focusing on mechanism of actions of tributyltin and triphenyltin for development of imposex**. *Environ Sci* 2006, **13**:77–87.

15. Guillette Jr LJ, Gunderson MP: **Alterations in development of reproductive and endocrine systems of wildlife populations exposed to endocrine-disrupting contaminants**. *Reproduction* 2001, **122**:857–864.

16. Jobling S, Nolan M, Tyler CR, Brighty G, Sumpter JP: **Widespread sexual disruption in wild fish**. *Environ Sci Technol* 1998, **32**:2498–2506.

17. Dodds EC, Goldberg L, Lawson W, Robinson R: **Estrogenic activity of certain synthetic compounds**. *Nature* 1938, **141**:247–248.

18. Stanczyk FZ, Archer DF, Bhavnani BR: **Ethinyl estradiol and 17β-estradiol in combined oral contraceptives: pharmacokinetics, pharmacodynamics and risk assessment**. *Contraception* 2013, **87**:706–727.

19. Mattox JH, Shulkman LP: **Combined oral hormone replacement therapy formulations**. *Am J Obstet Gynecol* 2001, **185**: S38–S46.

20. Kolok AS, Ali JM, Rogan EG, Bartelt-Hunt SL: **The fate of synthetic and endogenous hormones used in the US beef and dairy industries and the potential for human exposure**. *Curr Environ Health Rep* 2018, **5**:225–232.

21. Rhen T, Cidlowski JA: **Antiinflammatory action of glucocorticoids – new mechanisms for old drugs**. *N Engl J Med* 2005, **353**:1711–1723.

22. Lonning PE: **Endocrinology and treatment of breast cancer**. *Clin Endocrinol Metabol* 2004, **18**:1–130.

23. Kristensen DM, Hass U, Lesné L, Lottrup G, Jacobsen PR, Desdoits-Lethimonier C, Boberg J, Petersen JH, Toppari J, Jensen TK, Brunak S, Skakkebaek NE, Nellemann C, Main KM, Jégou B, Leffers H: **Intrauterine exposure to mild analgesics is a risk factor for development of male reproductive disorders in human and rat**. *Hum Reprod* 2011, **26**:235–244.

24. Smith OW: **Diethylstilboestrol in the prevention and treatment of complications of pregnancy**. *Am J Obstet Gynecol* 1948, **56**: 821–834.

25. Herbst AL, Ulfelder H, Poskanzer DC: **Adenocarcinoma of the vagina: association of maternal stilboestrol therapy with tumor appearance in young women**. *N Engl J Med* 1971, **284**:878–881.

26. * Harris RM, Waring RH: **Diethylstilboestrol - a long-term legacy**. *Maturitas* 2012, **72**:108–112.
Review of the legacy of DES.

27. Feng S, Cao Z, Wang X: **Role of aryl hydrocarbon receptor in cancer**. *Biochim Biophys Acta* 2013, **1836**:197–210.

28. Soto AM, Sonnenschein C, Chung KL, Fernandez MF, Olea N, Serrano FO: **The E-SCREEN assay as a tool to identify estrogens: an update on estrogenic environmental pollutants**. *Environ Health Perspect* 1995, **103**:113–122.

29. Safe S, Wormke M: **Inhibitory aryl hydrocarbon receptor - estrogen receptor cross-talk and mechanisms of action**. *Chem Res Toxicol* 2003, **16**:807–816.

30. White R, Jobling S, Hoare SA, Sumpter JP, Parker MG: **Environmentally persistent alkylphenolic compounds are estrogenic**. *Endocrinology* 1994, **135**:175–182.

31. Jobling S, Reynolds T, White R, Parker MG, Sumpter JP: **A variety of environmentally persistent chemicals, including some phthalate plasticizers, are weakly estrogenic**. *Environ Health Perspect* 1995, **103**:582–587.

32. Krishnan AV, Stathis P, Permuth SF, Tokes L, Feldman D: **Bisphenol-A: an estrogenic substance is released from polycarbonate flasks during autoclaving**. *Endocrinology* 1993, **132**:2279–2286.

33. Rubin BS: **Bisphenol A: an endocrine disruptor with widespread exposure and multiple effects**. *J Steroid Biochem Mol Biol* 2011, **127**:27–34.

34. Darbre PD, Harvey PW: **Parabens can enable hallmarks and characteristics of cancer in human breast epithelial cells: a review of the literature with reference to new exposure data and regulatory status**. *J Appl Toxicol* 2014, **34**:925–938.

35. Darbre PD, Aljarrah A, Miller WR, Coldham NG, Sauer MJ, Pope GS: **Concentrations of parabens in human breast tumours**. *J Appl Toxicol* 2004, **24**:5–13.

36. Kuratsune M, Yoshimura T, Matsuzaka J, Yamaguchi A: **Epidemiologic study on vusho, a poisoning caused by ingestion of rice oil contaminated with a commercial brand of polychlorinated biphenyls**. *Environ Health Perspect* 1972, **1**: 119–128.

37. Jensen TK, Vierula M, Hjollund NH, Saaranen M, Scheike T, Saarikoski S, Suominen J, Keiski A, Toppari J, Skakkebaek NE: **Semen quality among Danish and Finnish men attempting to conceive. The Danish first pregnancy planner study team**. *Eur J Endocrinol* 2000, **142**:47–52.

38. * Skakkebaek NE, Rajpert-De Meyts E, Main KM: **Testicular dysgenesis syndrome: an increasingly common developmental disorder with environmental aspects**. *Hum Reprod* 2001, **16**:972–978.
Landmark publication in directing attention to a collection of male reproductive problems linked to EDC exposures.

39. Barker DJP: **Fetal origins of coronary heart disease**. *BMJ* 1995, **311**:171–174.

40. * Darbre PD: **Endocrine disruptors and obesity**. *Curr Obes Rep* 2017, **6**:18–27.
Overview of obesogens and hypothesis of their role in increasing body burdens of EDCs.

41. Colborn T, Clement C: *Chemically-induced alterations in sexual and functional development: the wildlife/human connection*. Princeton, NJ: Princeton Scientific Publishing Co Inc; 1992.

42. * Vandenberg LN, Colborn T, Hayes TB, Heindel JJ, Jacobs Jr DR, Lee DH, Shioda T, Soto AM, vom Saal FS, Welshons WV, Zoeller RT, Myers JP: **Hormones and endocrine-disrupting chemicals: low-dose effects and nonmonotonic dose responses**. *Endocr Rev* 2012, **33**:378–455.
Extensive review of the literature demonstrating the many differing non-monotonic responses of EDCs.

43. Darbre PD, Fernandez MF: **Environmental oestrogens and breast cancer: long-term low-dose effects of mixtures of various chemical combinations**. *J Epidemiol Community Health* 2013, **67**:203–205.

44. * Reif DM, Martin MT, Tan SW, Houck KA, Judson RS, Richard AM, Knudsen TB, Dix DJ, Kavlock RJ: **Endocrine profiling and prioritization of environmental chemicals using ToxCast data**. *Environ Health Perspect* 2010, **118**:1714–1720.
Incorporation of EDCs into ToxCast in the USA.