Natural and anthropogenic environmental oestrogens: the scientific basis for risk assessment*

Breast cancer: evidence for xeno-oestrogen involvement in altering its incidence and risk

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Abstract: This review specifically addresses whether environmental oestrogen xenobiotics increase breast cancer risk, and thus contribute to the gradual and persistent rise in breast cancer incidence since 1940. Xeno-oestrogens are a structurally diverse group of chemicals that includes organochlorine pesticides, herbicides, pollutants, industrial chemicals, and metabolites of potent carcinogens. They possess oestrogenic activity, and when compared to that of 17β-oestradiol, their oestrogenic potency ranges from weak (10^{-3}) to extremely weak (10^{-6}), using a variety of *in-vivo* and *in-vitro* endpoints. It is evident that the sequestering of xeno-oestrogens in mammalian adipose tissue and their gradual release may not be a property of all xeno-oestrogens. Long-term animal carcinogenicity studies of individual xeno-oestrogens [e.g., dichlorodiphenyl trichloroethane (DDT), dichlorodiphenyl dichloroethane (DDE), dieldrin, aldrin, polychlorinated biphenyls (PCBs), phthalates] are revealing. Only atrazine has been shown to have the mammary gland as a marginal target site for cancer. A number of xeno-oestrogens (DDT, DDE, PCBs) induce lymphomas and tumours in the liver and lung, and in various murine species. Human neoplasms induced by individual xeno-oestrogens largely reflect those induced in animal studies, with possible additional associations of pancreatic and haematologic cancers. Earlier small case-control studies lent credence to an association of xeno-oestrogens and breast cancer. Subsequent larger prospective case-control studies from the USA, Europe, and Mexico, however, do not support this relationship. It is concluded from the evidence presented that xeno-oestrogens do not play a significant role in human breast cancer aetiology, its subsequent development, or in the gradual rise in breast cancer incidence.

INTRODUCTION

There is some reluctance in entering a controversial area in which there appears to be so much vested interest, emotion, and politics [1, 2]. The area we speak of concerns whether environmental oestrogen xenobiotics increase breast cancer risk and thus have contributed to the gradual and persistent rise in breast cancer incidence since 1940 [3]. Although not intended to be comprehensive, this review provides a summary of the most pertinent literature. It is realized that the issue is complex and definitive answers remain elusive. As in any area of study, gaps in knowledge exist, and many of those will be addressed. Nevertheless, there are sufficient data currently available at least to begin making balanced, rational judgements. Xeno-oestrogens may affect breast cancer risk by either their carcinogenic/mutagenic or oestrogenic properties. Both of these aspects will be addressed in this review. At the risk of sounding

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'politically correct', we would like to make it clear from the outset that we strongly support the restriction and/or elimination of the use of any environmental xenobiotics established to be harmful either to wildlife or to the public. This said, it is time for a dispassionate dissemination of the state of knowledge regarding the possible role(s) that environmental oestrogen xenobiotics may play in increasing breast cancer risk in order to begin specifically to address and attempt to resolve this important issue.

PROPERTIES OF OESTROGEN XENOBIOTICS

There are well over 1500 environmental xenobiotics, many of which have been of concern, as they possess oestrogenic activity. In a variety of *in-vivo* and *in-vitro* assays, their oestrogenic potency ranges from weak (10^{-3}) to extremely weak (10^{-6}), when compared with 17β-oestradiol (E_2), the main natural human oestrogen. Representative xeno-oestrogens are listed in Table 1. This structurally diverse group of chemicals includes organochlorine pesticides, herbicides, pollutants, industrial chemicals such as phenols and phthalates, and metabolites of potent carcinogens. While these so-called endocrine disruptors may act at various levels within the endocrine system, such as hormone synthesis, metabolism, degradation, and transport, most of their endocrine disruptive effects have been concentrated on their interaction with the oestrogen receptor (ER), and subsequent target tissue cell growth and regulation. Although not always sufficiently considered, many of these chemicals also possess significant cytotoxic, mutagenic, and/or carcinogenic activities [4–7], independent of their hormonal effects. Whether correct or not, many of the xeno-oestrogens listed, particularly, o, p-DDT and its analogues, β-HCH, PCB, and bisphenol A, have served as representative chemicals of this group and, therefore, they have been more intensively investigated.

Table 1. Environmental oestrogen xenobiotics

Pesticides	Pollutants	Industrial chemicals
Dieldrin	PCB (Aroclor)	Phthalates
Endosulfan	TCDD (Dioxins)	Alkyphenols
Toxaphene		Bisphenol A
Chlordane		Nonylphenol
o,p-DDT		
p-p′-Methoxychlor	**Herbicides**	**Carcinogen metabolites**
Vinclozolin	Atrazine	1-OH-Benzo[α]pyrene
Chlordecone (Kepone)		9-OH-Benzo[α]pyrene
Mirex		3,9-Di-OH-benz[α]anthracene
β-Hexachloro- cyclohexane (β-HCH)		BP-9,10-dihydrodiol
Heptachlor		BP-7,8-dihydrodiol

Recently, it has been recognized that human exposure to xeno-oestrogens is the result of mixtures of these chemicals. Such realization poses the possibility that combinations of xeno-oestrogens may lead to markedly enhanced oestrogenic activity, appreciably greater than the low potency of each individual xeno-oestrogen. A now erroneous study [8], employing a yeast system, generated considerable interest since it reported a remarkable synergism of xeno-oestrogen mixtures in relation to their oestrogenic potency. Unfortunately, there is now ample evidence from many independent groups that the oestrogenic effects of xenobiotic mixtures are merely additive or, at most, only a few-fold higher than those observed when xeno-oestrogens are tested individually in both *in-vitro* and *in-vivo* systems [9–11]. With respect to oestrogenic burden, the latter findings have served to dampen the potential oestrogenic impact of combined, multiple types of xeno-oestrogen exposure in humans. Table 2 depicts some of the major naturally occurring phyto-oestrogens and oestrogen mycotoxins. They have been included in this review because they are capable of modulating xeno-oestrogen binding to the ER and thus any potential deleterious oestrogenic effects elicited by these xenobiotics.

Table 2. Plant-derived oestrogenic compounds

Phyto-oestrogens	Oestrogen mycotoxins
Coumesterol	α-Zearalanol
Genistein	β-Zearalanol
Daidzein	Zearalenone
Phlorein	Zearalanone
Apigenin	
Diosgenin	
Anethols	
Ferulic acid	
Sitosterol	
Quercetin	

ANIMAL STUDIES

Oestrogenicity

In nearly 50 years of research concerning the oestrogenic action of environmental xeno-oestrogens, a vast amount of information has accumulated. There is little doubt that, employing a variety of test parameters under appropriate conditions and doses, xeno-oestrogens exhibit distinct and significant oestrogenicity.

The first xeno-oestrogens identified to possess significant oestrogenic activity; that is, increased uterine weight in rats and mice, were technical grade dichlorodiphenyl trichloroethane (DDT) and methoxychlor [12–14]. Subsequent studies showed that most of the oestrogenic activity of DDT resided in o,p′-DDT, a significant but relatively modest contaminant (~17%) [15]. In addition to increased uterine weight, these xeno-oestrogens also elicited rises in uterine glycogen, RNA, DNA, protein, progesterone receptor, and ornithine decarboxylase activity [15, 16]. A number of DDT metabolites also exhibited hormonal activity, but they were about 10^3 to 10^4 less oestrogenic than E_2 [17]. Chlordecone (Kepone) was shown to bind rat uterine ER, and to increase nuclear ER retention, nuclear DNA, as weel as uterine weight when administered at ≈4 mg/100 gm of body weight [20]. Moreover, chlordecone, mirex, dieldrin, and aldrin induced persistent vaginal oestrus and anovulatory cycles in rats after neonatal treatment [19].

Using the classical assay, direct comparison of uterotrophic activity of various organochlorine xeno-oestrogens in the rat indicated the following increase in uterine weight after s.c. daily injections for three days: chlordecone ≥ E_2 >>> o,p′-DDT > mirex [20]. It is evident, however, from these data that these xeno-oestrogens, including chlordecone, are very weak oestrogens since the organochlorines were administered at markedly higher concentrations than E_2. Interestingly, neither o,p′-DDT nor mirex, both exhibiting lower affinity for the rat uterine ER, did not increase uterine weight at dose levels that were maximally effective for chlordecone. A comparison of the dose levels of chlordecone and E_2 for maximal or half maximal ER translocation indicated that doses of chlordecone required to elicit equal stimulation of uterine growth were 10 000 times higher than those of E_2. Bisphenol A, a monomer of polycarbonate plastics, used widely in the food-packaging industry and dentistry, is capable of stimulating prolactin secretion, cell proliferation of the uterus and vagina, and uterine c-*fos* mRNA levels in Fisher 344 but not in SD female rats (**21**), and MCF-7 cell proliferation (**22**). However, there is a general consensus that bisphenol A is an extremely weak oestrogen requiring 2000- to 5000-fold higher concentrations compared to E_2 to exhibit these responses. It has been suggested that xeno-oestrogens may have sustained oestrogenic actions by their ability to concentrate in fat and to be released gradually over prolonged periods. However, it is now evident that not all xeno-oestrogens share this property. In a recent study, β-hexachloro-cyclohexane (β-HCH), o,p′-DDT, and E_2 were compared for their ability to be released from fat stores after a 48-hr fast [23]. Significantly, only β-HCH showed significant release

from fat in both fed and fasted mice using increased mouse uterine weight as an endpoint. It seems most pertinent to extend such studies to other species, as well as to other xeno-oestrogens administered either individually or as mixtures, to ascertain their relative rates of release from adipose tissue.

Carcinogenicity

Long-term animal carcinogenicity studies of many individual xeno-oestrogens have been revealing. Surprisingly, very few have the mammary gland as their target site for cancer. Employing technical grade DDT, male hamsters, a species highly susceptible to oestrogen-induced neoplasms in the kidney, liver, and pituitary [24], were resistant to any of the carcinogenic effects of moderate to high doses of DDT [25]. However, a number of reports have indicated that, in feeding studies, both DDT and dichlorodiphenyldichloroethane (DDE) are hepatocarcinogens in various strains of mice [26, 27] and in rats [28]. Moreover, significant increases in lymphomas and lung tumours, but no mammary tumours, were detected in male and female mice after administration of DDT by different routes [29]. Polychlorinated biphenyls (PCBs, Aroclor 1260, 1254) are hepatocarcinogenic in Sprague-Dawley (SD) and Fisher rats (females ≥ males) [7, 30]. Commercial PCBs (Kanechlors 500, 400, and 300) have also been shown to be hepatocarcinogens in mice [7]. Another class of chemicals, the phthalates or their esters, were administered to different murine species. Reproductive toxicities were observed, but no mammary tumours [31]. Organochlorine pesticides, dieldrin and aldrin, exhibited the same hepatocarcinogenic effects as DDT in these species [32, 33]. On the other hand, the herbicide atrazine, when fed at high doses, resulted in a significant but modest rise in mammary tumours in Fischer 344 male rats (from 2% in untreated controls to 17% in atrazine-treated animals), but none in females [34]. It is unclear, however, whether this tumourigenic effect of atrazine is due to an inherent carcinogenic activity of this herbicide or to its weak oestrogenic activity, although this latter property is now being questioned [35]. Interestingly, subsequent feeding of 0.05% DDT to 2-acetamidophenanthracene-treated SD male rats promoted mammary gland tumour development [36]. However, in the widely used rat 3,9-dihydroxybenz[α]anthracene (DMBA)-mammary tumour model, DDT was shown to be protective against DMBA-induced mammary gland tumour formation in female rats [37]. Moreover, it has recently been shown that 100 and 500 mg/kg doses of benzylbutyl phthalate inhibited female rat mammary gland DMBA-DNA adduct formation 72% and 92%, respectively, as well as DMBA-induced mammary tumour incidence (37%), compared with DMBA-treated controls [38]. These latter findings are inconsistent with a role for xeno-oestrogens in increasing mammary cancer development.

It has been known for two decades that hydroxylated metabolites of potent carcinogens, such as DMBA, benzopyrene (BP), and dibenz[α,h]anthracene (DBA) possess oestrogenic properties. The basis for this is that a molecular similarity exists between carcinogenic polynuclear aromatic hydrocarbons (PAHs) and oestrogens [39]. For example, DMBA metabolites have been shown to bind rat uterine ER [40]. Moreover, DMBA increases the weight of the uterus equal to E_2 at 2×10^3 excess concentration [41]. There is also evidence that DMBA itself may bind to ER [42], which may apply to other PAHs as well. The weak oestrogenicity of some PAH metabolites, however, is overwhelmed by the considerable potency of these chemicals as mammary gland carcinogens in a variety of murine species.

CULTURED HUMAN BREAST CELL LINES

The relative binding affinities (RBA) for the ER of o,p′-DDT and methoxychlor were assessed in human breast MCF-7 cells and compared with natural and synthetic oestrogens [43]. At equal molar concentrations, the RBA obtained for DES or E_2 was 70%, while those for o,p′-DDT and methoxychlor were 0.04% and 0.004%, respectively. These data indicate that, in order to obtain equivalent oestrogenic effects, doses 1000- to 10 000-fold higher for o,p′-DDT and 10 000- to 100 000-fold higher for methoxychlor are required when compared with either E_2 or DES. It was also shown that the pesticides endosulfan, toxaphene, and dieldrin were weakly oestrogenic in the same human breast cancer cell line [44]. These findings have been confirmed by more recent reports [9, 10, 45]. After an initial screen using the yeast assay system, various phthalates were tested for their ability to stimulate proliferation of MCF-7 and ZR-75 human breast cancer cell lines [46]. These data indicate that, of the phthalates tested, the

butyl-benzyl derivative was the most mitogenic. Three other phthalates exhibited weaker mitogenic activities, while the rest showed little cell proliferative activity. Importantly, no additive or synergistic effects were detected when the most potent phthalates were mixed with a dose of E_2 capable of inducing a small mitogenic response. It is noteworthy that the most potent phthalate, however, was 1×10^6 times less potent than E_2.

Extending these studies in MCF-7 cells, a recent report [47] showed that PCBs (Aroclor 1221 and 1254) moderately stimulated the growth of MCF-7 human breast cancer cells at relatively high doses (10 µM), while, when the two Aroclor congeners were combined, no additional increase in MCF-7 cell proliferative activity was observed. Heptachlor, at the same high dose, exhibited only a minimal change in the ability to stimulate the growth of MCF-7 cells compared with untreated cultured cells. In the same study, however, both o,p′-DDT and p,p′-DDT stimulated cell growth at equivalent doses (1 µM). Interestingly, p,p′-DDT was more potent than o,p′-DDT, particularly at higher concentrations (10 µM). Moreover, a modest synergistic effect on MCF-7 cell growth was observed when p,p'-DDT and o,p'-DDT were combined.

The pesticide β-HCH, a stable isomer found in lindane (γ-HCH), exerted oestrogenic effects on MCF-7 cells which were evidently not mediated via the classic pathway of binding to and activating ER, but nevertheless required the presence of ER [48]. It was also shown in this study that o,p′-DDT and β-HCH stimulate MCF-7 and T47D (both ER-positive cell lines) cell proliferation in a dose-dependent manner, but this was not found in the ER-negative cell lines MDA-MB231, MDA-MB468, and HS578T. Moreover, both pesticides increased the steady-state level of oestrogen-mediated pS2 mRNA in MCF-7 cells. Unlike o,p′-DDT and E_2 ligands, β-HCH was found not to bind ER over a large range of concentrations, and nuclear retention of ER in the presence of β-HCH was not observed. It is evident that the mechanism of action of β-HCH differs markedly from other xeno-oestrogens.

A number of alkyl phenols, particularly 4-octylphenol and 4-hydroxyphenoxycarboxylic acid, stimulate the growth of MCF-7 and ZR-75 oestrogen-responsive cells in culture [49]. The most potent of this class of chemicals, 4-octylphenol, is able to stimulate these cell lines to an extent similar to that of E_2, albeit at a 1000-fold greater concentration.

It has been suggested that the oestrogenic actions of xeno-oestrogens *in vivo* would be expected to be insignificant relative to endogenous oestrogens, prescribed oestrogens, and dietary phyto-oestrogens [45, 50]. While phyto-oestrogens may have relatively short biological half-lives relative to most xeno-oestrogens, their continuous ingestion in the diet may allow them to modulate the effects of these xenobiotics in man as well as in animals by lessening xeno-oestrogen interactions with ER in target tissues. At least one report has shown that phyto-oestrogens and oestrogen mycotoxins are able to inhibit markedly the growth of MCF-7 cells induced by individual pesticides (e.g., DDT, endosulfan, chlordane) or various mixtures of these chemicals [51].

In a somewhat related effect, toxaphene was shown to inhibit markedly the E_2-induced ER-dependent transactivation and to suppress oestrogen-mediated pS2 RNA and protein expression in MCF-7 cells [52].

HUMAN EPIDEMIOLOGICAL STUDIES

The hypothesis that xeno-oestrogens, particularly organochlorine chemicals, increase the risk of breast cancer in general, non-occupationally exposed populations stems in part from an evident inability to explain completely the high incidence of breast cancer in women in industrialized countries. Support for this supposition has been provided by the presence of pesticides and industrial pollutants in human serum, breast milk, and adipose tissue [53–58]. However, these findings are not necessarily unexpected because of the well-established high lipid solubility properties of most xeno-oestrogens. A recent examination of 36 human breast adipose samples from Connecticut women ages 50–80 years old indicated that all the tissue samples contained residues of β-HCH, oxychlordane, p,p'-DDE, and p,p'-DDT, as well as the nine PCB congeners tested, in the pg/g range [59]. In contrast, only p,p'-DDE and two congeners of PCB were detected in the serum. On a lipid-adjusted basis, p,p'-DDE concentration was 19 to 27 times greater than those of oxychlordane and β-HCH, respectively, and 6.9- to 255-fold

greater than those of the PCB congeners studied. The retention of xenobiotic residues, whether oestrogenic or not, in human tissues is clearly a potentially serious worldwide problem [60–63].

Earlier case-control studies appeared to lend support to the contention that xeno-oestrogens may be involved in contributing to the gradual rise in breast cancer incidence [53, 55, 58]. Although these studies may contain some design flaws and the sample sizes were small, they reported higher DDE, β-HCH, or PCBs levels in serum/plasma or adipose tissue samples among breast cancer patients compared to samples with benign breast disease. Dewailly, *et al.* [58] data suggest that women with ER-positive beast cancer have a higher body burden of DDE than women with benign breast disease. In a prospective study in New York, serum levels of these same xeno-oestrogens were compared in 58 women given a diagnosis of breast cancer within one to six months after blood sampling in 1985 to 1991 and 171 controls [57]. The New York study concluded that breast cancer was strongly associated with DDE in serum but not with PCBs. Subsequently, in a larger prospective case-control study (150 breast cancer patients and 150 controls) selected from a cohort of San Francisco Bay Area women who provided serum samples from 1964 to 1971, little association was found between organochlorine serum levels (DDT, DDE, PCBs) and the risk of breast cancer [64]. In addition to Caucasian women, the latter study also included African-American and Asian women. These studies differed somewhat from a report published at the same time in which a positive association of serum organochlorine levels was shown in African Americans and Caucasians, but not in Asians [65]. A large European multi-centre case-control study of 265 postmenopausal women with breast cancer and 341 hospital controls from five European countries found lower adipose tissue levels of DDE concentrations in breast cancer case patients compared with controls and therefore concluded that DDE does not increase the risk of breast cancer in postmenopausal women [66]. The ban on DDT since 1972 and the cessation of PCB production in 1977 may be problematic in developing causal associations in future studies because the levels of these xeno-oestrogens in the USA have been declining [67]. However, in Mexico, where DDT is still widely used to control malaria, a recent study performed in Mexico City becomes particularly relevant [68, 69] because the DDT levels may be somewhat higher than those reported in the USA. In a case-control study involving 141 confirmed breast cancer cases and a corresponding number of age-matched controls, there were no significant differences in DDT/DDE serum levels between the two groups. This study, therefore, supported the conclusions of both the San Francisco Bay area and the multi-centre European studies. In the largest single area study to date, employing the Nurses' Health Study population, 240 breast cancer cases were compared with an equal number of controls. Again, neither DDE nor PCB serum levels were significantly different between the two groups studied; this study therefore does not support the hypothesis that DDT and PCBs increase the risk of breast cancer [67]. Perhaps some confounding problems are that p,p′-DDE possesses significantly weaker oestrogenic activity than o,p′-DDT, that serum levels may not necessarily be accurate indications of xeno-oestrogen tissue exposures, and that the sequestered DDT may not be released from adipose storage sites [21]. In regard to the latter point, although β-HCH is generally found in lower concentrations than DDT [59], the higher serum levels of β-HCH in breast cancer patients may be a more relevant finding than the sequestered DDT in the tissues [70]. In a review of breast cancer incidence in women occupationally exposed to PCBs [71], it was concluded that there was no increased incidence of breast cancer. In summary, based on the larger, more recent case-control studies, at this time it can only be concluded that xeno-oestrogens do not have a major impact on human breast cancer incidence, contrary to conclusions made in earlier reports.

It is particularly important not to overlook that many xeno-oestrogens are likely xenobiotic carcinogens in humans. While metabolites of xeno-oestrogens are largely less oestrogenic than their respective parent compounds, many of them may be converted to more potent reactive metabolites capable of forming covalent DNA adducts, as in the case of bisphenol A [72]. However, these effects may have more bearing in cancer causation in both animals and humans in target sites other than the breast. For instance, there appears to be a strong dose-response relationship between serum PCB concentrations and the risk of non-Hodgkin's lymphoma in both men and women [73]. Occupational exposure to DDT has been reported to be associated with lung cancer [74], as well as pancreatic cancer [75]. A recent study indicate a possible association of liver cancer risk in individuals occupationally exposed to PCBs [76]. As a result of an accident in Seveso, Italy, 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) exposure of the local population resulted in higher incidences of hepatobiliary, haematologic,

and soft-tissue neoplasms, and of non-Hodgkin's lymphomas [77]. Interestingly, consistent with TCDD antiestrogenic properties, both breast and endometrial cancer in TCDD-exposed women were below expected levels. As discussed in an earlier section, it is noteworthy that these xeno-oestrogens produce many of the same tumours in various animal species that are found in the human but, in either case, neither breast nor endometrial cancers were detected. Additionally, an interview-based study suggests that occupational exposure to unidentified herbicides may be associated with ovarian mesothelial tumours [78]. Finally, multiple myelomas have been associated with duration of occupational exposure to phthalates [79].

CONCLUSIONS

There is no doubt that whole animal and breast cancer cell line studies provide ample evidence that xeno-oestrogens possess significant oestrogenic activities when used at relatively high concentrations. However, unlike endogenous and exogenously prescribed oestrogens, which have been consistently shown to increase the risk of breast cancer [80, 81], to date, evidence concerning xeno-oestrogen exposure and breast cancer has neither been consistent nor compelling. In fact, there is now considerable evidence to the contrary. Whole animal studies employing various individual xeno-oestrogens, particularly in species that are sensitive to neoplastic transformation by oestrogen alone, are not consistent with the contention that they are importantly involved in the aetiology and subsequent development of breast cancer in females. However, it would be pertinent to extend xeno-oestrogen studies to other more appropriate (oestrogen-induced) animal tumour models, though it is unlikely that they will yield positive results given their extremely low oestrogenic properties. Although one would like to see epidemiological studies using other xeno-oestrogens (e.g., β-HCH) determining their accumulation directly in breast, breast adipose tissue, and breast cancer tissues, rather than their concentration in serum samples, expectations do not appear bright for a positive association in light of the cited, recent, larger studies. Nevertheless, while it is concluded from the evidence presented that xeno-oestrogens do not play a significant role in either human breast cancer aetiology or in the increasing rate in breast cancer incidence, one cannot exclude the possibility, however, that a small subset of women may be found affected by higher xeno-oestrogens levels in relation to breast cancer risk. It also remains an intriguing possibility that early *in-utero* or neonatal exposure to certain xeno-oestrogens may adversely affect breast cancer risk later in life. However, at present, there is a paucity of data in its support and, therefore, it remains only a speculation by those who advocate this view.

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APPENDIX

Abbreviations

BP	=	Benzo[α]pyrene
DBA	=	Dibenz[α,h]anthracene
DDE	=	Dichlorodiphenyl dichloroethane
DDT	=	Dichlorodiphenyl trichloroethane
DMBA	=	Dimethyl-benz[α]anthracene
E_2	=	17β-Oestradiol
ER	=	Oestrogen receptor
β-HCH	=	β-Hexachloro-cyclohexane
PAH	=	Polynuclear aromatic hydrocarbon
PCB	=	Polychlorinated biphenyls
SD	=	Sprague–Dawley
TCDD	=	2,3,7,8-Tetrachlorodibenzo-p-dioxin