doi: http://dx.doi.org/10.5016/1806-8774.2003v5p45

FJR PAUMGARTTEN

Fundação Oswaldo Cruz, BRAZIL

Adverse Health Consequences of Environmental Exposure to 'Endocrine Disruptors'

Contents

Abstract

During the last decade concern has grown on the possible adverse health effects of chemicals which are capable of interacting with the endocrine system. Concerns on the effects of 'endocrine disruptors' (EDs) are largely based on reports of adverse effects on wildlife reproduction and on the plausible hypothesis that exposure to these substances is responsible for an increased incidence of certain estrogen-sensitive types of cancer, reproductive tract disorders and poor sperm quality. Most environmental EDs have proved to possess rather weak hormone-like effects, much weaker than those of physiological hormones, in *in vitro* and *in vivo* assays. Since EDs are found at relatively low levels in the environment, health risks posed by them would critically depend on the possibility of non-monotonic dose-effect relationships, on the relevance of low dose effects and on the

Correspondence

Francisco José Roma Paumgartten
Laboratorio de Toxicologia Ambiental , Departamento de Ciências Biológicas, Escola Nacional de Saúde Pública, Fundação Oswaldo Cruz, Av Brasil 4036, Manguinhos, 21040-361, Rio de Janeiro, RJ, Brazil.
E-mail: paum@ensp.fiocruz.br

The author is recipient of a research fellowship from The Brazilian National Research Council (CNPq).

type of interaction between different EDs. Results suggesting a synergistic interaction with combinations of xenoestrogens were not further confirmed by other laboratories and by their own authors. A few studies have provided data suggesting that exposure to low doses of xenoestrogens during prenatal development induces alterations in estrogen-sensitive tissues which are apparent in adulthood. These findings, however, need to be confirmed by independent research groups. No consistent epidemiological evidence has been provided indicating that environmental xenoestrogens (*e.g.* DDT) increase breast cancer risk. The instigating hypothesis that environmental EDs could adversely affect human health therefore remains to be confirmed by further experimental and epidemiological studies.

Key words: endocrine disruption, DDT, breast cancer, reproductive disorders, Bisphenol A, estrogen receptor, low-dose effects.

Invited Mini-review

Introduction

Over the last years no other topic of toxicology has been more debated than the issue of endocrine disruptors. According to USEPA an 'endocrine disruptor' (ED) would be any '*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* ' (IPCS-WHO, 2002). In other words, endocrine disruptor would be any endocrine toxicant or any xenobiotic compound that causes adverse effects by interacting with the endocrine system. Although the discipline of Endocrine Toxicology has rarely – if ever – been recognized as such, endocrine-mediated toxic effects have been known since a long time ago. The term endocrine disruptor, on the other hand, is very new. It was apparently coined in 1991, during the Wingspread Conference held in Racine, Wisconsin, USA, and organized by Dr Theo Colborn, currently an outstanding member of the World Wildlife Fund organization (Soto & Sonnenschein, 2002).

The Webster's dictionary gives to '*disrupting'* meanings such as '*breaking asunder (into pieces)*', '*splitting*' and '*separating by force*'. Since alterations of endocrine function induced by most putative EDs are rather subtle, usually much weaker than those caused by the physiological hormones, 'endocrine disruptor' seems to be a somewhat tendentious term. Alternative and more neutral terms for labeling this particular group of xenobiotic compounds would be either 'endocrine-active chemicals / substances' or 'endocrine toxicants'.

Although there are a large variety of possibilities in terms of chemically-induced alterations of endocrine system functions, most of environmental EDs identified so far are xenobiotic substances that proved to possess a certain degree of estrogenic (the so-called 'xenoestrogens') and or antiandrogenic actions, and a few other substances (like

some PCB congeners) that have been demonstrated to antagonize effects of thyroid hormones. Since xenoestrogens are the most abundant type of EDs, the present review on the possible adverse effects of environmentally found EDs will focus mainly on this subset of endocrine active substances.

Paving the Way for Wingspread: Roots of Today's Concerns about EDs

Today's concerns on the possible health consequences of exposure to EDs are largely based, on one side, on reports that chemicals with estrogenic and or antiandrogenic actions - at levels currently found in the environment - are capable of inducing adverse effects on wildlife reproduction and, on the other side, on the plausible hypothesis that human exposure to these substances might have been partially responsible for a secular increase in the incidence of certain estrogen-sensitive types of cancer, reproductive tract disorders and reductions of male fertility.

Estrogen-like effects of an environmental pollutant were described as early as in 1950. Burlington and Lindeman (1950) reported that DDT, at rather high doses, caused atrophy of testes and feminization of secondary sex characters of White Leghorn cockerels, an effect that was then attributed to an estrogen-like effect of this insecticide and its persistent metabolite DDE. Kelce *et al.* (1995) demonstrated, however, that DDE is a potent androgen receptor antagonist, a mechanism that could also explain Burlington & Lindeman's findings.

Later on, in the 1960s and 1970s, reproductive failures of avian species on the top of food chains, which almost led to the extinction of *Falco peregrinus* and other birds-of-prey, were attributed to a DDT-induced eggshell thinning (EST). Although DDT-EST has been one of the most cited examples of endocrine disruption in wildlife, the mechanism by which this insecticide reduces eggshell thickness is far from being entirely understood. It should be pointed out, however, that current hypothesis on mechanisms underlying DDE-induced EST, such as an inhibition of a Ca-ATPase (Kolaja & Hinton, 1977), and or a blockade of prostaglandin synthesis in the eggshell gland (Lundholm, 1993), do not necessarily involve endocrine-mediated actions. Recently, the latter possibility has received a great deal of attention because it was shown that prostaglandins play an important role in the control of birds reproduction.

In the 1980s, the decreased reproductive success of a previously flourishing population of alligators in Lake Apopka, Florida, USA, had also called attention on the possibility of endocrine-mediated toxic effects of environmental pollutants. Lake Apopka had been highly contaminated with dicofol and its metabolites (DDD, DDE and chloro-DDT) and other compounds by a major chemical spill, and shortly thereafter (1980-1984) it was noted that the population of alligators (*Alligator mississippiensis*) declined by 90% (Guillette *et al.*, 1994). It was also observed that these alligators had elevated levels of organochlorine residues, including pp'DDE and PCBs, and showed abnormal plasma levels

of steroid hormones, gonadal malformations, reduced phallus length, and other alterations. Since alligators were exposed to a mixture of pollutants, it is not clear which chemical(s) is(are) responsible for the observed alterations. Although this case has been considered as a typical example of endocrine disruption in wildlife, the mechanism by which these changes were produced still remains to be completely elucidated.

Abnormalities such as masculinisation of sexual secondary characteristics, altered plasma sex steroids levels, smaller eggs and reduced egg production were noted in fish populations in the vicinity of sites where kraft mill effluents were discharged in certain USA rivers (Taylor & Harrison, 1999). β-sitosterol found in pine tree wood was shown to produce, under laboratory conditions, similar estrogen-like effects in fish. In this case, however, still remains to be elucidated to what extent other chemicals present in the kraft mill effluents also contribute for the adverse effects observed in river fish.

All the foregoing cases of reproductive disorders in birds and wildlife species have been taken as typical examples of chemically-induced endocrine disruption.

Supporting Evidence from Experimental Studies

Most of putative EDs seem to act by mimicking or antagonizing the actions of physiological hormones on their receptors. Laboratory data on the capacity of individual chemicals to induce or to inhibit hormone-like actions, in *in vitro* as well as in *in vivo* test systems, has generally shown that they act only at concentrations (or doses) orders of magnitude higher than those levels found in the environment. On the yeast-based estrogen receptor assay (YES), for example, environmental xenoestrogens have proved to be much weaker than the physiological hormone β-estradiol. YES assay EC_{50}s for nonylphenol, bisphenol A, methoxyclor and DDE were $5x10^3$, $15x10^3$, $5x10^6$ and 24×10^6 times higher than that of β-estradiol. Owing to this very weak action on the estrogen receptor, eventual health risks posed by environmental xenoestrogens would critically depend on the type of interaction between them (*e.g.* addition, synergism or antagonism), on the dose-response relationships (*e.g.* an inverted U-shaped dose–effect curve and relevance of low dose effects) as well as on the existence of developmental windows of increased susceptibilities.

Types of Interactions between EACs: Additive, Synergistic or Antagonistic Effects?

The relatively low potencies of almost all environmental xenoestrogens suggest that these substances alone are unlikely to produce estrogen-related adverse health effects. Since humans are typically exposed to mixtures of several xenoestrogens (e.g. organochlorine pesticides), health risks posed by these compounds depend to some extent on the type of interaction between them. In 1996, Arnold and coworkers presented, in an instigating paper published in *Science*, a clear evidence that combinations of two weak environmental xenoestrogens afforded a synergistic response in the YES assay (with the human estrogen receptor, hER) as well as in the test of inhibition of [^{3}H]-17β-estradiol

binding to hER (Arnold *et al.*, 1996). As expected, such a result immediately aroused considerable interest among toxicologists, environmentalists and regulatory agencies experts. Shortly thereafter, however, several independent researchers employing not only the same *in vitro* test (YES) but also the *in vivo* uterotrophic assay failed to confirm Arnold and colleagues' findings (Ashby *et al.*, 1999, Ramamoorthy *et al.*, 1997). John A. McLachlan, the paper's senior author, sent to *Science* a letter formally withdrawing the report and recognizing that he and his research group had not been able to replicate their earlier results (McLachlan, 1997). A possible scientific misconduct of the authors was further investigated by a Tulane University committee the conclusions of which were that Arnold *'provided insufficient data to support the major conclusions of Science paper*', and that McLachlan '*did not participate in, or have any knowledge of any scientific misconduct'*. Since then, although additive effects have been consistently observed by several researchers, no scientifically valid evidence of synergistic interactions between xenoestrogens has been reported.

Windows of Higher Susceptibility to EDs during Pre- and Postnatal Development

Experimental data supporting the existence of developmental periods of higher susceptibility to xenoestrogens have been provided by a few rodent studies. Ana Soto, Frederik vom Saal and Ibrahim Chahoud, and their respective research groups, have published some of the most exciting findings supporting the view that exposure to rather low levels of EDs during critical periods of pre- and or postnatal development may result in permanent alterations of hormone-sensitive tissues.

Markey *et al.* (2001), for instance, found that female CD1 mice exposed *in utero* to low doses of an environmental xenoestrogen (bisphenol A) showed changes in the histoarchitecture and secretory functions of mammary glands which were still apparent long time after exposure had ceased, *i.e.*, at 1 and 6 months of age.

Frederik vom Saal and coworkers, on the other hand, reported that male offspring of mice treated with diethylstilbestrol from pregnancy day 11 to 17 exhibited a prostate enlargement in adulthood, apparent at lower doses but not at higher doses (i.e. according to an inverted U dose-response curve) (vom Saal *et al.*, 1997). Similar prostate enlargement and a reduction in the efficiency of sperm production in mice prenatally-exposed to low levels of bisphenol A were also described by the same authors (Nagel *et al.*, 1997). Ashby *et al.* (1999), however, failed to confirm the previously reported effects of DES and bisphenol A on the prostate gland of mice exposed *in utero*.

Along the same line, Ibrahim Chahoud and coworkers have recently found that postpubertal female Sprague-Dawley rats prenatally-exposed to low doses of bisphenol A showed striking morphological changes in the vagina, and a lack of expression of full-length estrogen receptor alpha in this tissue during estrus (Schoenfelder *et al.*, 2002). Contrasting with this altered expression of estrogen receptor alpha in the estrus, no difference between controls and BPA-treated females was noted in the diestrus

(Schoenfelder *et al.*, 2002).

Although the foregoing studies have provided interesting data suggesting that exposure to low doses of xenoestrogens during prenatal development may induce long lasting alterations in estrogen-sensitive tissues that are apparent much later in adulthood, all of them still need to be confirmed by independent research groups.

Non-monotonic Dose-response Relationships and the Relevance of 'Low-dose Effects'

The ED issue has highlighted a kind of biological response which had been neglected by toxicologists for a long time; i.e. hormesis or an stimulatory effect at low doses followed by inhibition at higher doses or vice-versa. Several studies have suggested that EDs can exhibit a kind of hormetic behavior, as for example the inverted U dose-response curve found by vom Saal *et al.* (1997) for xenoestrogens-induced prostate enlargement in mice.

Since most putative xenoestrogens exhibit weak estrogen activity in different test systems, non-monotonic dose-effect relationships as well as low doses effects seem to be important characteristics for a possible detrimental effect on human health. By low dose effect is generally meant the effect of a dose below the conventional No Observed Adverse Effect Level (NOAEL) and or a response to a dose compatible with current environmental exposures. As previously mentioned, adverse consequences of prenatal exposure to low doses of xenoestrogens have been demonstrated by different authors (vom Saal *et al.*, 1997; Markey *et al.*, 2001; Shoenefelder *et al.*, 2002). Witorsch (2002), however, has recently pointed out that such low dose effects noted in rodents are unlikely to occur in humans. According to this author, owing to the high levels of physiological estrogens sustained by the human fetus throughout pregnancy, any additive effect of a relatively weak environmental estrogen such as bisphenol A would have a little impact.

Lack of Evidence from Epidemiological Studies. Exposure to Environmental Xenoestrogens and Risk of Breast Cancer: The DDT Story

The incidence of breast cancer increased steadily from the 1940s to the 1990s in many industrialized countries in Western Europe and North America and it is quite possible that, at least in part, this increase had been due to improved screening methods. The contribution of estrogen-related risk factors, however, can not be ruled out. Evidences from a great number of epidemiological studies support the current view that breast cancer risk increases with a higher life-time exposure to endogenous estrogens. For instance, among the known estrogen-related risk factors for breast cancer are conditions such as:

- an earlier menarcha and or a delayed menopause;
- not having children, having fewer pregnancies and or a delay of first pregnancy;
- postmenopausal obesity (it is known that the fat tissue converts androgens to estrogens);

- postmenopausal hormonal (estrogen) replacement therapy;
- risk of breast cancer is markedly reduced by oophorectomy at an young age.

Owing to this estrogen-dependence of some mammary gland tumors, a possible relationship between a higher exposure to putative xenoestrogens like DDT (and its metabolite DDE) and an increased risk for breast cancer has been investigated by a number of epidemiological studies.

Concerns on a causal relationship between exposure to DDT and breast cancer were highlighted by a large study published by Wolff and coworkers in 1993. These authors described that blood levels of DDE in women with breast cancer were higher than those measured in healthy controls of the same age (Wolff *et al.*, 1993). After this report, a substantial number of studies were performed to confirm a possible association between DDT and breast cancer. In a rather large cohort of Danish women, Hoyer *et al. (*1998) found a significantly increased dose-related risk of breast cancer for exposure to dieldrin, but not for exposure to DDT/DDE and PCBs. Two retrospective case-control studies also found a positive association between DDT/DDE and breast cancer (Olaya-Contreras *et al.*, 1998; Romieu *et al.*, 2000). Nonetheless, a much larger number of retrospective case-control studies, including both pre- and postmenopausal women, did not confirm the existence of such an association between DDT/DDE and breast cancer (Lopez-Carrillo *et al.*, 1997; Dello Iacovo *et al.*, 1999; Mendonça *et al.*, 1999; Zheng *et al.*, 1999; Aronson *et al.*, 2000; Bagga *et al.*, 2000; Demers *et al.*, 2000; Millikan *et al.*, 2000; Stellman *et al.*, 2000; Ward *et al.*, 2000; Wolff *et al.*, 2000[a], Wolff *et al.*, 2000[b]). Two retrospective studies including only post-menopausal women, among which breast cancer tend to be more estrogen-dependent, gave negative results as well (van't Veer *et al.*, 1997; Moyisch *et al.*, 1998). Furthermore a combined analysis of five US studies showed no relationship between higher levels of DDE and increased breast cancer risk (Laden *et al.*, 2001[a], Laden *et al.*, 2001[b]).

Altogether the foregoing findings from epidemiological studies indicate that concerns on a possible association between exposure to DDT and human breast cancer are not justified. The story of a possible relationship between exposure to DDT and breast cancer, nevertheless, has not come to an end yet. The possibility exists that populations studied so far had been exposed to DDT levels below the threshold for increasing risk of breast cancer. To date, epidemiological studies have enrolled only environmentally-exposed women, exhibiting rather low blood levels of DDE. Blood levels of DDT/DDE resulting from occupational exposures are, as a rule, much higher than those found in the general population. Timing of exposure also seems to be a relevant variable that was not taken into account in previous studies. Levels of DDT/DDE have been measured only in adult women. It is quite possible that exposures to DDT earlier in life (i.e in prenatal and neonatal periods, childhood and adolescence), during mammary gland differentiation and growth, and not those in adulthood, are the critical ones for increasing breast cancer risk.

Reductions in Sperm Concentration and EDs

Possible changes in human reproductive performance, particularly temporal and geographic trends towards declining sperm counts, have played a key role in the debate about health consequences of environmental exposure to EDs. An hypothesis was advanced by Sharpe and Skakkebaek (1993) suggesting that estrogens are involved in falling sperm counts and disorders of the male reproductive tract.

A possible decline of sperm quality was highlighted by a meta-analysis based on 61 articles which concluded that sperm concentration decreased from 113 x 10^6 /ml to 66 x 10^6 /ml within a period of 50 years between 1938 and 1991 (Carlsen *et al.*, 1992). Moreover, Auger *et al.* (1995) examined ejaculate samples stored in a Paris sperm bank, and found that sperm concentration decreased by 2.1% a year, from 89x10^6 /ml in 1973 to 60x10^6 /ml in 1992.

Several other papers have reported results of retrospective analyses of semen quality data but, owing to differences in experimental design, origin of samples and sample sizes, it is not possible to conclude whether there are real trends toward declining sperm count. An extensive review of sperm quality studies recently performed by IPCS came to a somewhat vague conclusion: '*although.... published data suggests that there could be temporal and geographical variations in human sperm production, it is not possible to conclude that the phenomenon is real and, if so, to what extent reductions in sperm count may affect fertility'* (IPCS-WHO 2002).

Therefore, it remains to be proven that presence of EDs in the environment could be inducing a decrease in male fertility in the human population.

Concluding Remarks

Most of environmental xenoestrogens have low affinity for the estrogen receptor and very weak estrogenic activity in *in vitro* and *in vivo* test systems, usually orders of magnitude lower than that of estradiol. Lack of evidence of synergistic interaction between xenoestrogens seems to mitigate, at least in part, concerns on their possible adverse effects. Although there has been no consistent epidemiological evidence that exposure to DDT and other environmental xenoestrogens causes adverse health effects in humans, studies performed so far have not investigated the effects of exposures earlier in life, during pre and postnatal development. A few rodent studies have indicated that prenatal exposure to relatively low doses of xenoestrogens can induce alterations in estrogen-sensitive tissues still apparent in adulthood. Such instigating findings apparently support today's concerns on the health risks posed by these substances. Most of these findings, however, have not been confirmed by independent research groups. Owing to interspecies differences in pregnancy physiology, it also remains to be answered whether or not – and to what extent - such rodent findings could be extrapolated to humans.

References

Arnold SF, Klotz DM, Collins BM, Vonier PM, Guillette LJ Jr, McLachlan JA. Synergistic activation of estrogen receptor with combinations of environmental chemicals. Science 1996;272:1489-92.

Aronson KL, Miller AB, Woolcott CG, Sterns EE, McCready DR, Lickley LA, Fish EB, Hiraki GY, Holloway C, Ross T, Hanna WM, SenGupta SK, Weber JP. Breast adipose tissue concentrations of polychlorinated biphenyls and other organochlorines and breast cancer risk. Cancer Epidemiol Biomark Prev 2000;9:55-63.

Ashby J, Tinwell H, Hasemann J. Lack of effects for low dose levels of bisphenol A and diethylstilbestrol on the prostate gland of CF1 mice exposed in utero. Regul Toxicol Pharmacol 1999;30:156-66.

Auger J, Kunstmann JM, Czyglik F, Jouannet P. Decline in semen quality among fertile men in Paris during the past 20 years. N Engl J Med 1995;332:281-5.

Bagga D, Anders KH, Wang HJ, Roberts E, Glaspy JA. Organochlorine pesticide content of breast adipose tissue from women with breast cancer and control subjects. J Natl Cancer Inst 2000;92:750-3.

Burlington H, Lindeman VF. Effect of DDT on testes and secondary sex characters of White Leghorn cockerels. Proc Soc Exp Biol Med 1950;74:48-51.

Carlsen E, Giwercman A, Keiding N, Skakkebaek NE. Evidence for decreasing quality of semen during past 50 years. Brit Med J 1992;305:609-13.

Dello Iacovo R, Celentano E, Strollo AM, Iazzetta G, Capasso I, Randazzo G. Organochlorines and breast cancer. A study on Neapolitan women. Adv Exp Med Biol 1999;472:57-66.

Demers A, Ayotte P, Brisson J, Dodin S, Robert J, Dewally E. Risk and aggressiveness of breast cancer in relation to plasma organochlorine concentrations. Cancer Epidemiol Biomark Prev 2000;9:161-6.

Guillette LJ, Gross TS, Masson GR, Matter JM, Percival HF, Woodward AR. Developmental abnormalities of the gonad and abnormal sex hormone concentrations in juvenile alligators from contaminated and control lakes in Florida. Environ Health Perspect 1994;102:680-8.

Hoyer AP, Grandjean P, Jorgensen T, Brock JW, Hartvig HB. Organochlorine exposure and risk of breast cancer. Lancet 1998;352:1816-20.

IPCS-WHO. Global Assessment of the State-of-the-Science of Endocrine Disruptors, Edited by T. Damstra, S. Barlow, A. Bergman, R. Kavlock and G van der Kraak. International Programme on Chemical Safety (WHO/PCS/EDC702.2), Geneve, 2002:178.

Kelce WR, Stone CR, Laws SC, Gray LE, Kemppainen JA, Wilson EM. Persistent DDT metabolite pp'DDE is a potent androgen receptor antagonist. Nature 1995;75:581-5.

Kolaja GJ, Hinton DE. Effects of DDT on eggshell quality and calcium adenosine triphosphatase. J Toxicol Environ Health 1977;3:699-704.

Laden F, Collman G, Iwamoto K, Alberg AJ, Berkowitz GS, Freudenheim JL, Hankinson

SE, Helzlsouer KJ, Holford TR, Huang HY, Moysich KB, Tessari JD, Wolff MS, Zheng T, Hunter DJ. 1,1 Dichloro - 2,2-bis (p-chlorophenyl)ethylene and polychlorinated biphenyls and breast cancer: A combined analysis of five US studies. J Natl Cancer Inst 2001[a]; 93:768-76.

Laden F, Hankinson SE, Wolff MS, Colditz GA, Willett WC, Speizer FE, Hunter DJ. Plasma organochlorine levels and risk of breast cancer: An extended follow-up in the nurses' health study. Int J Cancer 2001[b];91:568-74.

López-Carrillo L, Blair A, López-Cervantes M, Cebrián M, Rueda C, Reyes R, Mohar A, Bravo J. Dichlorodiphenyltrichloroethane serum levels and breast cancer risk: A case control study from Mexico. Cancer Res 1997;57:3728-32.

Lundholm CE. Inhibition of prostaglandin synthesis in eggshell gland mucosa as a mechanism for pp´-DDE-induced eggshell thinning in birds - a comparison of ducks and domestic fowls. Comp Biochem Physiol C. Pharmacol Toxicol 1993;106:389-94.

Markey CM, Luque EH, Toro MM, Sonnenschein C, Soto A. In utero exposure to bisphenol A alters the development and tissue organization of the mouse mammary gland. Biol Reprod 2001;65:1215-23.

McLachlan JA. Synergistic effect of environmental estrogens: Report withdrawn. Science 1997;277:462.

Mendonça GA, Eluf-Neto J, Andrada-Serpa MJ, Carmo PAO, Barreto HHC, Inomata ON, Kussumi TA. Organochlorines and breast cancer: A case control study in Brazil. Int J Cancer 1999;83:596-600.

Millikan R, DeVoto E, Duell EJ, Tse CK, Savitz DA, Beach J, Edmiston S, Jackson S, Newman B. Dichlorodiphenyltrichloroethene, polychlorinated biphenyls and breast cancer among African-Americans and white women in North Carolina. Cancer Epidemiol Biomark Prev. 2000;9:1233-40.

Moysich KB, Ambrosone CB, Vena JE, Shields PG, Mendola P, Kostyniak P, Greizerstein H, Graham S, Marshall JR, Schisterman EF, Freudenheim JL. Environmental organochlorine exposure and postmenopausal breast cancer risk. Cancer Epidemiol Biomark Prev 1998;7:181-8.

Nagel SC, vom Saal FS, Thayer KA, Dhar MG, Boechler M, Welshons WV. Relative binding affinity-serum modified access (RBA SMA) assay predicts the relative in vivo bioactivity of the xenoestrogens bisphenol A and octylphenol. Environ Health Perspect 1997;105:70-6.

Olaya-Contreras P, Rodriguez-Villamil J, Poso-Valencia HJ, Cortez JE. Organochlorine exposure and breast cancer risk in Columbian women. Cad Saude Publica 1998;14 (sup 3):125-32.

Ramamoorthy K, Wang F, Chen IC, Safe S, Norris JD, McDonnell DP, Gaido KW, Bocchinfuso WP, Korach KS. Potency of combined estrogenic pesticides. Science 1997;275:405.

Romieu I, Hernandez-Avila M, Lazcano-Ponce E, Weber JP, Dewaillly E. Breast cancer,

lactation history, and serum organochlorines. Am J Epidemiol 2000;152:363-70.

vom Saal F, Timms BG, Montano MM, Palanza P, Thayer KA, Nagel SC, Dhar MD, Ganjan VK, Parmigiani S, Welshons WV. Prostate enlargement in mice due to fetal exposure to low doses of estradiol or diethylstilbestrol and opposite effects at high doses. Proc Natl Acad Sci USA 1997;94:2056-61.

Schoenfelder G, Flick B, Mayr E, Talness C, Paul M, Chahoud I. In utero exposure to low doses of bisphenol A lead to long-term deleterious effects in vagina. Neoplasia 2002; 4(2):98-102.

Sharpe RM, Skakkebaek NE. Are oestrogens involved in falling sperm counts and disorders of the male reproductive tract? Lancet 1993;341:1392-5.

Soto AM, Sonnenschein C. Disruptores endocrinos: Una historia muy personal y con múltiples personalidades. Gac Sanit 2002;16(3):209-11.

Stellman SD, Djordjevic MV, Britton JA, Muscat JE, Citron ML, Kemeny M, Busch E, Gong L. Breast cancer risk in relation to adipose concentrations of organochlorine pesticides and polychlorinated biphenyls in Long Island, New York. Cancer Epidemiol Biomarkers Prev 2000;9:1241-9.

Taylor MR, Harrison PTC. Ecological effects of endocrine disruption: Current evidence and research priorities. Chemosphere 1999;39:1237-48.

van't Veer P, Lobbezoo IE, Martin-Moreno JM, Guallar E, Gomez-Aracena J, Kardinaal AF, Kohlmeier L, Martin BC, Strain JJ, Thamm M, van Zoonen P, Baumann BA, Huttunen JK, Kok FJ. DDT (dicophane) and postmenopausal breast cancer in Europe: Case control study. Brit Med J 1997;315: 81-5.

Ward EM, Schulte P, Grajewski B, Andersen A, Patterson DG Jr, Turner W, Jellum E, Deddens JA, Friedland J, Roeleveld N, Waters M, Butler MA, DiPietro E, Needham LL. Serum organochlorine levels and breast cancer: A nested case-control study of Norwegian women. Cancer Epidemiol Biomark Prev 2000;9:1357-67.

Witorsch RJ. Low-dose in utero effects of xenoestrogens in mice and their relevance to humans: an analytical review of the literature. Food Chem Toxicol 2002;40:905-12.

Wolff MS, Toniolo PG, Lee EW, Rivera M, Dubin N. Blood levels of organochlorine residues and risk of breast cancer. J Natl Cancer Inst 1993;85:648-52.

Wolff MS, Berkowitz MS, Brower S, Senie R, Bleiweiss IJ, Tartter P, Pace B, Roy N, Wallestein S Weston A. Organochlorines exposure and breast cancer risk in New York City women. Environ Res 2000[a];84:151-61.

Wolff MS, Zeleniuch-Jacquotte A, Dubin N, Toniolo P. Risk of breast cancer and organochlorine exposure. Cancer Epidemiol Biomark Prev 2000[b];9:271-7.

Zheng T, Holford TR, Mayne ST, Ward B, Carter D, Owens PH, Dubrow R, Zahm SH, Boyle P, Archibeque S, Tessari J. DDE and DDT in breast adipose tissue risk of female breast cancer. Am J Epidemiol 1999;150:453-8.