Endocrine Disruptors and Human Health—Is There a Problem? An Update

Stephen H. Safe

Department of Veterinary Physiology and Pharmacology, Texas A&M University, College Station, Texas, USA

It has been hypothesized that environmental exposure to synthetic estrogenic chemicals and related endocrine-active compounds may be responsible for a global decrease in sperm counts, decreased male reproductive capacity, and breast cancer in women. Results of recent studies show that there are large demographic variations in sperm counts within countries or regions, and analyses of North American data show that sperm counts have not decreased over the last 60 years. Analyses of records for hypospadias and cryptorchidism also show demographic differences in these disorders before 1985; however, since 1985 rates of hypospadias have not changed and cryptorchidism has actually declined. Temporal changes in sex ratios and fertility are minimal, whereas testicular cancer is increasing in most countries; however, in Scandinavia, the difference between high (Denmark) and low (Finland) incidence areas are not well understood and are unlikely to be correlated with differences in exposure to synthetic industrial chemicals. Results from studies on organochlorine contaminants (DDE/PCB) show that levels were not significantly different in breast cancer patients versus controls. Thus, many of the male and female reproductive tract problems linked to the endocrine-disruptor hypothesis have not increased and are not correlated with synthetic industrial contaminants. This does not exclude an endocrine-etiology for some adverse environmental effects or human problems associated with high exposures to some chemicals. *Key words*: endocrine disruptors, human health, sperm counts, xenoestrogens.
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In 1993, Colborn et al. (*1*) pointed out that large amounts of industrial-derived endocrine-disrupting chemicals have been released into the environment since world War II, and they hypothesized that prenatal or early postnatal exposure to these compounds could result in permanent and irreversible damage to wildlife and humans. Several studies on wildlife populations have documented adverse effects that correlate with exposure to one or more putative endocrine-disrupting chemicals (*2–9*); however, in many instances it is difficult to assign causality because of the complexity of environmental contaminants and the lack of analytical data that document contaminant levels during critical windows of exposure. Nevertheless, there have been several incidents in wildlife populations that strongly correlate with exposure to specific industrial chemicals; this includes alligators in Lake Apopka, Florida, exposed to a spill of organochlorine pesticides from a chemical waste site (*5,8,9*). The alligators display a host of morphologic and hormonally related abnormalities of the male and female reproductive tracts, including reduced penis size in males. This reduced penis size in male alligators (*5,8,9*) and a report (*10*) which suggested that sperm counts had decreased globally (from 113×10^6 to 66×10^6/mL) during 1938–1990 generated considerable public, media, regulatory, and scientific concern about the possible role of environmental exposures to endocrine disruptors and their role in decreased male reproductive capacity and breast cancer in women. In 1995, I critically reviewed the endocrine-disruptor hypothesis; based on the available data, I was highly skeptical about the causal linkage between exposure to environmental (industrial-derived) endocrine disruptors and adverse human health effects (*11*). Some of this skepticism was related to the relatively low levels of exposure to synthetic endocrine disruptors, particularly those with estrogenic activity (xenoestrogens), as compared to high dietary concentrations of naturally occurring endocrine-active compounds in fruits and vegetables and their derived food products. Since 1995, the endocrine-disruptor hypothesis has spurred new scientific studies that address several relevant issues, and I will highlight and discuss these in this paper. In addition, the National Research Council has published a comprehensive report on "Hor-monally Active Agents in the Environment" (*12*).

Wildlife and Laboratory Animal Studies

The effects of environmental endocrine disruptors on wildlife populations are being extensively investigated; adverse developmental and reproductive effects have been primarily linked to organochlorine compounds such as polychlorinated biphenyls (PCBs), polychlorinated dibenzo-*p*-dioxins (PCDDs), and polychlorinated dibenzofurans (PCDFs), as well as alkylphenols derived from alkylphenol ethoxylate (AE) surfactants. Persistent organochlorine pollutants (POPs), including both pesticides such as DDT/DDE and PCBs, were among the first industrial compounds identified in the environment. Moreover, with improvement of analytical techniques, an ever-increasing number of structurally diverse POPs have been detected in environmental samples at low concentrations (*2,6,13,14*). The use and production of DDT and PCBs were restricted and banned in most countries in the 1970s; however, these compounds are still the most abundant POPs in most wildlife and human samples, even though their concentrations have significantly decreased over the past 30 years (*14–16*). Lower concentrations of POPs in the Great Lakes region are correlated with "dramatic improvements in reproductive success and significant increases in populations of cormorants, gulls, terns, herons and other predatory birds in the Great Lakes basin" (*16*).

There has been particular concern about the discharge and environmental persistence of AEs and their alkylphenol degradation products, which have been identified in relatively high concentrations in industrial sewage effluents and in sediments in lakes and rivers in Europe (*4,17–21*). Concentrations of these compounds in North American rivers and sediments tend to be lower. Soto et al. (*20*) showed that nonylphenols extracted from polystyrene were estrogenic, and Jobling and Sumpter (*17*) showed that the estrogen-regulated yolk protein, vitellogenin, was induced in male fish collected near sewage outflows in the United Kingdom. Moreover, Fairchild et al. (*22*) hypothesized that the estrogenic effects of nonylphenol, a solvent/emulsifier (an AE) used in pesticide spraying, may be related to declines of Atlantic salmon in Atlantic Canada. The widespread estrogenized fish populations in British rivers and estuaries have been extensively investigated (*23–25*) and were initially linked to nonylphenols and related compounds; however, the recent identification of etiologic agents from sewage treatment effluents that

Address correspondence to S.H. Safe, Department of Veterinary Physiology and Pharmacology, Texas A&M University, College Station, TX 77843-4466 USA. Telephone: (409) 845-5988. Fax: (409) 862-4929. E-mail: ssafe@cvm.tamu.edu

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received mainly domestic wastes was somewhat surprising (*23,24*). The major estrogenic components were the natural hormones 17β-estradiol (E_2) and estrone, with minor amounts of the birth control pill ingredient 17α-ethinylestradiol. Routledge et al. (*23*) concluded that

> environmentally relevant concentrations of natural steroidal estrogens are sufficient to account for the levels of vitellogenin synthesis observed in caged male fish placed downstream of certain [sewage treatment works] effluent discharges in British rivers.

Thus, although initial concern regarding the estrogenic disruption of fish in U.K. rivers focused on synthetic estrogenic AE surfactants, human and possible animal discharges were the major sources of these environmental endocrine disruptors. This highlights the difficulties in assigning causality to environmental endocrine-disrupting chemicals without thoroughly investigating all potentially active agents.

Strong support for the endocrine-disruptor hypothesis has come from laboratory animal studies where increasing numbers of synthetic chemicals have been shown to exhibit estrogenic/antiestrogenic, androgenic/antiandrogenic, and other endocrine-like activities (*6,26–33*). Included in this list of chemicals is *p,p'*-DDE, a major environmental contaminant that has been shown to exhibit antiandrogenic activity in both *in vivo* and *in vitro* models (*28*). Research from several laboratories has shown that *in utero* exposure to extremely low doses of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD; ≤ 1 μg/kg), an aryl hydrocarbon receptor (AhR) agonist, can result in a host of neurodevelopmental and reproductive tract problems in juvenile and adult rodent offspring (*26,27,30–32*).

Studies on *in utero* exposure to the estrogenic drug diethylstilbestrol (DES) have served as an important model for delineating problems associated with exposure to estrogenic compounds in both animal models and in humans; DES-induced effects on the male and female reproductive tracts strongly support the endocrine-disruptor hypothesis (*34,35*). Bisphenol A, an important intermediate in the production of polycarbonates, is a weakly estrogenic industrial compound in most, but not all, assays (*36–38*). For example, bisphenol A induces mammary gland growth in Noble rats at doses as low as 0.1 mg/kg/day; this is similar to the dose required for the potent estrogen DES to induce the same response (*34*). The estrogenic activity of bisphenol A in CF-1 mice has also generated controversy (*39–41*); vom Saal et al. (*39*) reported that fetal exposure to low doses of bisphenol A (2 or 20 μg/kg/day) resulted in increased prostate weight in the male offspring. Results for bisphenol A, E_2, and DES all gave low dose inverted U-shape dose–response curves for this effect; at higher doses, decreased prostate weight was observed in the offspring (*39,40*). In contrast, Cagen et al. (*41*) did not observe this low dose effect for bisphenol A or DES in CF-1 mice. Thus, the "low dose" hypothesis for this response should be resolved for bisphenol A and other estrogenic compounds.

Decreased Male Reproductive Capacity and Endocrine Disruptors

Sperm counts. The concern over decreased sperm counts and male reproductive capacity was triggered by a paper on the meta-analysis of 61 sperm count studies which concluded that "There has been a genuine decline in semen quality over the past 50 years" (*10*). This study (*10*) and a subsequent paper (*42*) hypothesized that

> We argue that the increasing incidence of reproductive abnormalities in the human male may be related to increased oestrogen exposure *in utero*.

PCBs and TCDD-like compounds, as well as DDE, may also contribute to this problem (*42,43*). The validity of the meta-analysis (*10*) was quickly debated (*44–48*), but more importantly, new research on this problem was initiated throughout the world. Results of single location and laboratory studies gave highly variable results. Some reports showed that over the last 15–25 years, there were significant decreases in sperm quantity, whereas other studies showed either no declines or slight increases (*49–58*). Auger et al. (*49*) investigated semen quality among fertile men in Paris and reported that

> The mean concentration of sperm decreased by 2.1% per year from 86×10^6 per milliliter in 1973 to 60×10^6 per milliliter in 1992.

In contrast, using a similar approach, Bujan et al. (*50*) reported that from 1977 to 1992, "sperm concentration has not changed with time in the Toulouse area." In 1996, Fisch et al. (*59*) reported that semen quality of 1,283 men from three sperm banks in the United States had not declined over the last 25 years (1970–1995). The surprising results of this study were the large demographic differences in sperm counts: sperm donors from New York had the highest number ($131.5 \pm 3.5 \times 10^6$/mL, mean ± SEM), followed by Minnesota ($100.8 \pm 2.9 \times 10^6$/mL) and California ($72.7 \pm 3.1 \times 10^6$/mL).

In a separate study, Paulsen et al. (*54*) reported no change in sperm counts in Washington State between 1972 and 1993 (46.5×10^6/mL to 52×10^6/mL); by accounting for geographic differences in an analysis of 29 U.S. studies from 1938 to 1996, Saidi et al (*60*) reported "no significant change in sperm counts during the last 60 years." Geographic differences in sperm counts have been reported in French men (*61*) and Danish men (*62*) and also in a Canadian study among 11 academic fertility centers (*63*). The latter report shows that among 48,968 samples of sperm taken from Canadian men between 1984 and 1996, there was a significant overall downward trend in sperm counts (*63*); however, when the data from 1975 to 1983 were included, "there was no significant trend in sperm density" (*63*). The analysis of data from the individual centers (1984–1996) showed that 6 centers had a downward trend and 5 centers had small but insignificant increases in sperm counts. However, the most remarkable results from these studies were the differences (geographic) between centers: in 1984, sperm counts ranged from 51×10^6/mL to 121×10^6/mL, and in 1996, these values ranged from 48×10^6/mL to 137×10^6/mL (*63*). The predictive value of sperm count data taken from self-selected volunteers is clearly subject to multiple variables including measurement methods, temperatures, time of day, and seasonal variability. Handelsman (*52*) reported that mean sperm counts taken from five different sets of volunteers at the same hospital in Sydney, Australia, varied from 142×10^6/mL to 63×10^6/mL, which exceeded the differences in the decline in sperm counts reported in the 1992 meta-analysis by Carlsen et al. (*10*). Handelsman (*52*) concluded that

> This highlights the invalidity of extrapolating similar findings on sperm counts of selected volunteers to the general male community or in using such study groups to characterize sperm counts in supposedly healthy men.

These data suggest that we do not know if sperm counts are actually up or down. Our knowledge of sperm counts and their temporal variability in normal populations is minimal, and the contributions of the environment (i.e., lifestyle, diet, contaminants, etc.) are also unknown.

Hypospadias and cryptorchidism. Cryptorchidism is a condition in which one or both testicles have not descended, and hypospadias occurs when the urethral opening is displaced. Both of these responses have been observed in male offspring of rodents exposed *in utero* to estrogenic and antiandrogenic compounds (*64,65*). Weidner et al. (*66*) reported a significantly increased risk of cryptorchidism, but not hypospadias, among male offspring of female (but not male) gardeners. This study suggests a possible link between *in utero* exposure to agricultural chemicals used in gardening; however, the identity of potential toxic chemicals and their mode of action are unknown.

Sharpe and Skakkebæk (*42*), suggested that decreased male reproductive capacity may be related to exposure to endocrine disruptors (*42*), and pointed out that some studies reported increases in hypospadias and cryptochidism in male infants. Paulozzi (*67*) analyzed international trends in rates of cryptorchidism and hypospadias from several different countries and categorized regions by gross domestic product (in 1984). Hypospadias increased in more affluent areas but not in less affluent areas up to 1985, whereas no increases have been observed since 1985. Before 1985, there were also region-specific trends in rates of cryptorchidism (increases in two U.S. and one South American system); however, since 1985, rates have actually declined in most systems (*67*). Thus, the specter of a global decrease in male reproductive capacity is not supported by international trends for hypospadias or cryptorchidism; however, like the sperm count data, there is some evidence that incidence of these problems is also dependent on demography.

Testicular cancer. Testicular cancer is one of the major types of cancer in young men, and there is evidence suggesting a prenatal etiology (*68*). Cryptorchidism is one of the known risk factors for testicular cancer, suggesting that *in utero* or early postnatal exposure to estrogens or antiandrogens may contribute to development of this tumor in young men (*68–72*). Testicular cancer is generally increasing in most countries, and it was suggested that *p,p′*-DDE, an antiandrogen, could play a role in the development of this cancer (*43*). However, Ekbom et al. (*15*) pointed out that DDE concentrations in breast milk in the four Scandinavian countries are not significantly different, whereas the incidence of testicular cancer (1985–1989) varies from $14.5/10^5$ males in Denmark (highest) to $3.6/10^5$ males in Finland (lowest). Moreover, as the overall incidence of testicular cancer has increased in all Scandinavian countries during the last 25–30 years, there has been an 80–90% decrease in average breast milk DDE concentrations, showing an inverse relationship between testicular cancer and DDE concentration (*15*). Similar inverse correlation can be observed in most other developed countries, including the United States (*73*). Many countries in similar regions (e.g., bordering the North Sea) do not have major differences in human or environmental concentrations of persistent organochlorine pollutants, and differences in production and human exposure to other synthetic chemicals are unlikely. Environmental exposures have not been linked or correlated with testicular cancer, and the environmental and lifestyle factors, including diet and occupational exposures, that are responsible for this disease are unknown and should be investigated.

Sex ratios and endocrine disruptors. A recent study (*74*) reported that accidental exposure to high concentrations of TCDD in Seveso resulted in lower sex ratios (male/female) at birth; this observation has been noted for high level occupational exposures to some chemicals (*74–76*). There is evidence from several countries, including a recent U.S. study, that in the past few decades there have been small but significant decreases in sex ratios (*77–79*). The potential role of male/female sex ratios as sentinel health indicators "that may be linked to environmental factors" was proposed by Davis et al. (*80*), based on their observations that the proportion of males born in Denmark (1950–1994), The Netherlands (1950–1994), Canada (1970–1990), and the United States (1970–1990) had decreased. However, in the United States, although the overall sex ratio decreased from 1.053 in 1969 to 1.049 in 1995, this small decline was observed only for Caucasians but not African Americans (*77*); the authors concluded that "environmental exposures are unlikely to account for the observed trends." In a more recent comprehensive study, Vartainen et al. (*81*) examined sex ratios in Finland over the past 250 years. From 1751 to 1920, there was an increase in male/female birth ratios, and with the exception of pre- and post-World War I and II years, there has been a decline in these ratios since 1920. The authors concluded that

> the present data do not support the hypothesis that agricultural or industrial environmental estrogens play any significant role

because, in Finland, major production and exposures to these types of chemicals occurred after 1950. James (*82*) initially proposed that newborn sex ratios may be a useful indicator of male reproductive hazard but has subsequently concluded that "population sex ratios at birth are not useful monitors of reproductive hazard."

Fertility. Temporal changes in human fertility have not been extensively investigated; however, a recent study in Sweden (*83*) concluded that

> a decrease in male fertility cannot be ruled out … but if present, it is minor and totally outweighed by other favorable developments.

Akre et al. (*83*) observed declining infertility among successive birth cohorts, and "this strongly argues against a substantial deterioration in sperm quality." This was explained by the decreasing incidence of gonorrhea between 1970 and 1992. Previous studies that demonstrated adverse effects of DES on male and female offspring are unquestionable (*34,35*); however, Wilcox et al. (*84*) reported that fertility of DES-exposed males was not significantly different from males in a control group. DES was not used in Finland, but in a recent study, Hemminki et al. (*85*) reported reproductive effects of *in utero* exposure to estrogen and progestin drugs on male and female offspring. There were some differences in times of birth between controls and hormone- or drug-exposed individuals (e.g., time to first birth after marriage, mean time between first and second live birth); however, the overall fertility in both groups was similar. Hemminki et al. (*85*) concluded that

> Estrogen- and progestin-containing drugs as used in the study population did not have much impact on the fertility of offspring.

Thus, pharmacologic doses of estrogenic drugs did not affect fertility, and it is unlikely that much lower concentrations of weakly estrogenic industrial compounds would affect fertility. Thus, with the exception of testicular cancer, data from more recent studies suggest that there does not appear to be a worldwide decrease in disorders of the male reproductive tract.

Xenoestrogens and Breast Cancer

In 1992–1993, two studies from Connecticut and New York reported higher concentrations of PCBs and DDE, respectively, in breast cancer patients as compared to controls (*86,87*); this generated the hypothesis that xenoestrogens, such as PCBs and DDE, were preventable causes of breast cancer (*88*). This hypothesis was supported by the two studies on breast cancer patients (*86,87*) and also by *in vitro* metabolic data on chemical-induced metabolism of E_2 to 2-hydroxyestrone (2-OHE1) and 16α-hydroxyestrone (16α-OHE1) metabolites in MCF-7 human breast cancer cells (*89*). The hypothesis of Davis et al. (*88*) was criticized on several counts (*11*), and new research on the role of organochlorine contaminants in the incidence of breast cancer has clarified some of these issues.

PCB and DDE concentrations in breast cancer patients. I was particularly skeptical about the biologic plausibility of the xenoestrogen hypothesis because occupational exposures to high concentrations of PCBs or DDE have not been associated with increased risk for breast cancer (*11*). In rodent carcinogen-induced mammary cancer models, DDE and 3,3′,4,4′-tetrachlorobiphenyl both increased and decreased mammary tumor formation and growth (*90–93*), and the increase in mammary tumor formation was primarily associated with altered carcinogen metabolism (*91,92*). Both TCDD and higher chlorinated PCB mixtures inhibited formation of spontaneous mammary tumors in 2-year-old female

Sprague-Dawley rats (*33,94*); this was consistent with the antiestrogenic activity associated with AhR agonists in breast cancer (*95,96*).

Several recent studies on DDE and PCB concentrations in breast cancer patients versus controls have been carried out in Europe, Asia, North and South America, and most studies indicate that levels of these organochlorine contaminants are not significantly different in the two groups (Table 1) (*97–106*). These data are consistent with an earlier report by Krieger et al. (*107*) in a California cohort. Several studies have also investigated risk for breast cancer and correlations with other organochlorine compounds or other parameters. For example, Moyisch et al. (*101,106*) reported an odds ratio (OR) of 1.8 for women (parous women who had never lactated) with high concentrations of hexachlorobenzene (HCB), but Zheng et al. (*108*) did not observe higher concentrations of HCB in patients in Connecticut (304 cases and 186 controls) and concluded that

> our study does not support a positive association between environmental exposure to HCB and risk of breast cancer.

In a study in Copenhagen, Hoyer et al. (*102*) reported that although correlations for PCBs were not observed, the pesticide dieldrin was associated with an increased risk for breast cancer. The authors concluded that

> these findings support the hypothesis that exposure to xenoestrogens may increase the risk of breast cancer.

Dieldrin is an exceedingly weak estrogen in most assays, and the biologic plausibility that trace concentrations of this contaminant play a role in breast cancer is minimal. Some recent studies have combined differences in DDE or PCB concentrations with drug-metabolizing enzyme polymorphisms in breast cancer patients and control groups (mixtures and congeners) to further investigate correlations with breast cancer (*106*); this approach in future studies may lead to new insights.

Estrogen metabolite ratios. Bradlow et al. (*89*) investigated the effects of various chemicals, including several organochlorine pesticides, on the metabolism of E_2 to 2-OHE1 and 16α-OHE1 in MCF-7 human breast cancer cells and concluded that "the ratio of 16α-OHE1/2-OHE1 may provide a marker for the risk of breast cancer." PCBs, DDE, and other weakly estrogenic pesticides induced higher 16α-OHE1/2-OHE1 ratios, and these data were initially used to support the xenoestrogen hypothesis in early reports showing higher concentrations of PCBs or DDE in breast cancer patients versus controls. The predictive utility of the ratio was based on reports that 16α-OHE1 was highly estrogenic and higher levels of this metabolite were observed in a small cohort of breast cancer patients (*89,109,110*). In contrast, 2-OHE1 exhibits partial antiestrogenic activity and was labeled by Bradlow et al. as "the 'good' estrogen" (*110*). In my laboratory, we used the radiometric assay, as previously described (*89*), to investigate the effects of a diverse spectrum of estrogens, antiestrogens, and mammary carcinogens on estrogen metabolism (*111,112*). The results showed that the metabolite ratios in our study were not predictive of carcinogens, estrogens, or antiestrogens, and metabolite ratios varied with the concentration of some compounds in this assay. For example, the triphenylethylene antiestrogen 4′-hydroxytamoxifen decreased the ratio, whereas the potent steroidal antiestrogen ICI 182,780 increased the ratio; we also observed other inconsistencies between compounds with similar effects on mammary cancer (*111,112*). We concluded that induction of this metabolite ratio in MCF-7 breast cancer cells was not predictive for a wide variety of chemicals that may affect breast cancer *in vivo* (*112*). Some additional studies question the use of the urinary 16α-OHE1/2-OHE1 ratio as a predictor of risk for breast cancer (*113–115*). In a recent study, Ursin et al. (*115*) reported that in 66 postmenopausal breast cancer patients and 76 control subjects,

> the ratio of 2-OHE1 to 16a-OHE1 was 1.1% higher in the patients (p = 0.84) contrary to the hypothesis.

The authors concluded that

> this study does not support the hypothesis that the ratio of the two hydroxylated metabolites (2-OHE1/16α-OHE1) is an important risk factor for breast cancer.

Endocrine Disruptors in the Diet

The potential adverse role of endocrine disruptors in the diet during critical periods of development will depend not only on intake concentrations of these compounds but also on their concentrations in serum and in the fetus. Intake concentrations of synthetic estrogenic compounds and AhR agonists are low as compared to dietary intakes of natural phytoestrogens and AhR-active compounds (e.g., indole-3-carbinol) in fruits and vegetables (*11*). In one collaborative study, we compared the estrogenic potency of one glass of red wine (200 mL) with the corresponding potency of the estimated daily intake of organochlorine pesticide residues in food (*116*) (Figure 1). The reconstituted mixture in this study included the following weakly estrogenic organochlorine contaminants: 1,1,1-trichloro-2-(*p*-chlorophenyl)-2-(*o*-chlorophenyl)ethane, 1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)ethane, 1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethylene, endosulfan-1, endosulfan-2, *p,p′*-methoxychlor, and toxaphene. The relative proportion of each chemical in the mixture resembled the composition reported in a recent U.S. Food and Drug Administration market basket survey (*117*). Using a series of seven *in vitro* assays, the calculated estrogen equivalents (EQs) in extracts from 200 mL red cabernet wine varied from 0.15 to 3.68 µg/day. In contrast, the EQs for consumption of organochlorine pesticides (2.44 µg/day) varied from nondetectable to 1.24 ng/day. These data, coupled with EQs for other foods (*118*), demonstrate that dietary intakes of naturally occurring phytoestrogens far exceed intakes of organochlorine xenoestrogens. However, these data should not be overinterpreted because organochlorine compounds bioaccumulate and can be identified in serum and because dietary intake levels of other xenoestrogens are unknown.

Table 1. Recent reports on PCB and DDE concentrations in breast cancer patients versus control groups.

Reference	DDE		PCBs		Serum fat (concentration)
	Cases (*n*)	Control (*n*)	Cases (*n*)	Control (*n*)	
vant' Veer et al. (*98*)	1.35 (265)	1.51 (341)			✔ (µg/g)
Hunter et al. (*99*)	6.01 ± 4.56 (236)	6.97 ± 4.56 (236)	5.08 ± 7.51 (236)	5.16 ± 2.26 (236)	✔ (ng/mL)
Schecter et al. (*100*)	2.33 ± 0.46 (21)	2.37 ± 0.58 (21)	–	–	✔ (ng/mL)
López-Carrillo et al. (*97*)	4.75 (141)	4.07 (141)	–	–	✔ (ng/mL)
Liljegren et al. (*104*)	0.767 (43)	1.026 (35)	1.205 (43)	1.149 (335)	✔ (µg/g)
Guttes et al. (*103*)	0.805 (45)	0.496 (20)	0.625 (45)	0.505 (20)	✔ (µg/g)
Moysich et al. (*101*)	11.47 (154)	10.77 (192)	4.24 (154)	4.12 (192)	✔ (ng/mL)
Hoyer et al. (*102*)	10.2 (240)	9.5 (477)	8.6 (240)	8.7 (472)	✔ (ng/mL)
Helzlsouer et al. (*105*)	11.5 ± 7.1 (235)	13.6 ± 10.6 (235)	7.9 ± 6.4 (235)	9.7 ± 3.6 (235)	✔ (ng/mL)
Moysich et al. (*106*)	7.9 ± 6.4 (105)	9.7 ± 3.6 (105)	2.1 ± 2.0 (105)	2.2 ± 1.9 (105)	✔ (ng/mL)

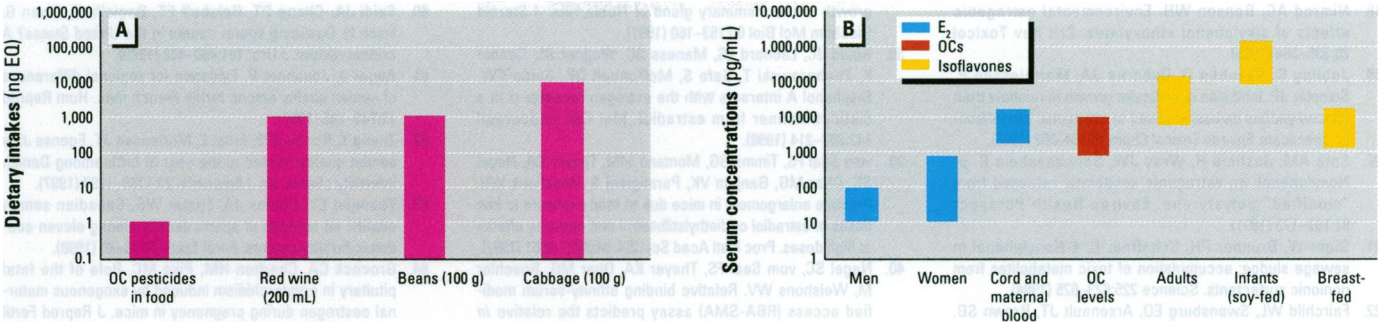

Figure 1. (*A*) Estrogen equivalents (EQs) in various food products and organochlorine compounds (OCs) (*117*) and (*B*) range of human serum concentrations of natural estrogens, isoflavones, and OCs (*116,119*) in different groups. EQs (ng) were 0–1 for OC pesticides in food, 200–3,000 for red wine, 200–1,000 for beans, and 24,000 for cabbage.

Recent reports have investigated serum concentrations of some phytoestrogens (*119,120*), and these can be compared to endogenous hormone and organochlorine xenoestrogen serum concentrations in human populations. A recent study on women in Long Island, New York, showed that total serum concentrations of organochlorine pesticides plus PCBs were < 10 ng/mL (*121*); these values correspond to serum concentrations from women sampled within the last 5–10 years (Table 1). Setchell et al. (*119*) recently summarized serum concentrations of endogenous estrogenic hormones in men, women, and children as well as concentrations of estrogenic isoflavones in various groups. Serum concentrations of estradiol in men, women, and neonates are variable (between 10 and 500 pg/mL); however, concentrations in maternal blood and cord blood are similar to concentrations of organochlorine compounds (10,000 pg/mL). On the basis of the low estrogenic potencies of these xenoestrogens, it is unlikely that their effects as estrogens are important. This does not exclude endocrine- and estrogen-independent toxic actions of organochlorine compounds that are currently being investigated in several laboratories. Serum concentrations of estrogenic isoflavones (primarily genistein, daidzein, and equol) can range from 552,000 to 1,755,000 pg/mL (mean = 988,000 pg/mL) in soy-fed infants; these are approximately 100-fold higher than organochlorine concentrations (*119*). High isoflavone concentrations (~ 100,000 pg/mL) have also been detected in Japanese men (*119,120*). Thus, on the basis of current analytical data, soy-fed infants are the group with the highest exposure to estrogenic compounds during critical periods of development. Most studies associate consumption of phytoestrogen-containing foods with health benefits (*122,123*); however, as reported by Setchell et al. (*119*),

> To allay increasing concerns about soy-based formulas, long-term follow-up studies are needed to assess the potential beneficial or adverse effects of phyto-oestrogen exposure in early life.

Summary

Environmental concentrations of persistent organochlorine compounds have been decreasing over the past two decades, and this correlates with remarkable advances in the detection of exceedingly low levels of these compounds in human populations. Undoubtedly, correlational studies of human diseases with tissue and serum concentrations of organochlorine compounds will continue, and due to the large number of these compounds, positive correlations with some diseases will undoubtedly be made. It is important that interpretation of data obtained from these studies consider biologic plausibility and temporal trends in concentrations as well as additional correlative results from other reports.

Results of recent studies suggest that there is not a global decrease in male reproductive capacity and that an etiologic role for xenoestrogens in female breast cancer is unlikely. It is possible that new scientific evidence may reinforce or weaken these conclusions; it is also important to carefully validate and replicate findings before media announcements that may contribute to unnecessary fear and worry by the public. A recent book, *The Culture of Fear* (*124*), has addressed some of the issues regarding unreasonable fears by the public; it states,

> We compound our worries beyond all reason. Life expectancy in the United States has doubled during the twentieth century. We are better able to cure and control diseases than any other civilization in history. Yet, we hear that phenomenal numbers of us are dreadfully ill.

The role of endocrine disruptors and human disease has not been fully resolved; however, at present the evidence is not compelling.

Note: A recent paper by many of the same coauthors of the sperm count meta-analysis study (10) *have now reported "a significant increase in mean sperm concentration from 53.0 × 10^6/mL in 1977 to 72.7 × 10^6/mL in 1995" among donors to the Central Sperm Bank in Copenhagen* (125).

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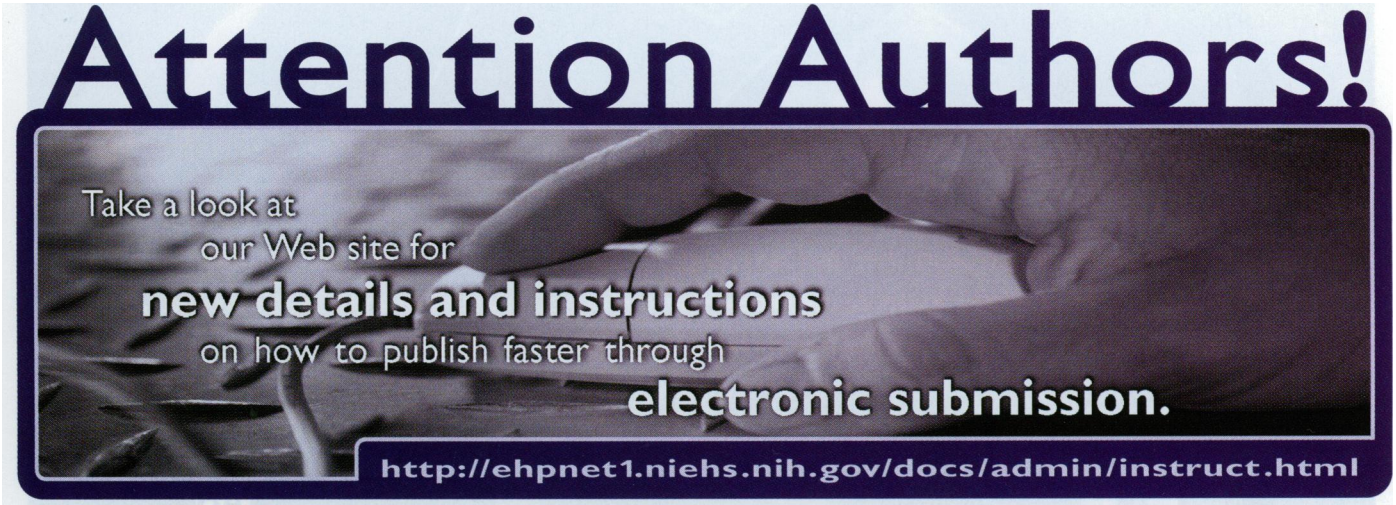
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