Environmental Estrogens and Related Endocrine Disrupters— Are They Affecting Male Reproductive Health and Increasing Breast Cancer in Women?

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Introduction

The chemical revolution during the past 60 years has resulted in dramatic improvements in the overall standard of living in developed and some less-developed countries. Consumer and industrial products derived from synthetic chemicals impact every segment of human activity, including new drugs for treatment of diseases, consumer products from plastics to new construction materials, and agricultural chemicals that have resulted in remarkable improvements in crop yields worldwide.

Despite the innumerable benefits derived from the chemical revolution, these advances in chemistry have been accompanied by numerous chemical poisonings, primarily in the workplace, and increased levels of chemical pollution in every component of the environment, including the water, air and innumerable land-based chemical dumpsites. Many of these problems associated with production and use of chemicals have been recognized, and regulatory agencies such as the U.S. Environmental Protection Agency (US-EPA) and the Food and Drug Administration have set

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increasingly strict standards for release of chemicals into the environment and for human exposures to drugs and environmental contaminants in the diet.

Decreased environmental levels of many persistent organic pollutants in areas, such as the Great Lakes, have coincided with the resurgence of fish and wildlife populations.

One specific class of chemicals, persistent halogenated aromatic pollutants, or persistent organic pollutants (POPs), have been of particular concern because these compounds not only have long environmental half-lives but also preferentially bioaccumulate in fish, wildlife, and human fatty tissue and serum. Halogenated aromatic industrial chemicals and their byproducts include a wide variety of organochlorine pesticides such as DDT and its major metabolite DDE; commercial products containing polychlorinated biphenyls (PCBs) and polybrominated diphenylethers; and combustion byproducts containing polychlorinated dibenzo-*p*-dioxin (PCDDs, dioxins) and polychlorinated dibenzofurans (PCDFs).

The detection of DDT/DDE and PCBs in the environment in the late 1960s resulted in restrictions on their uses. Both PCBs and DDT were banned in the United States and other developed countries in the late 1970s. Environmental levels of DDE have subsequently decreased by 80 to 90 percent in most locations. PCB concentrations have also significantly decreased, although levels in some highly contaminated regions are still of concern. Not surpris-

ingly, decreased environmental levels of many POPs in areas such as the Great Lakes have coincided with the resurgence of fish and wildlife populations.[1]

Despite these improvements in environmental quality, several scientific publications in the early 1990s suggested that POPs and other synthetic chemicals may be causal endocrine disruptors responsible for a worldwide decrease in male reproductive capacity and the increased incidence of breast cancer in women.[2] Colborn and coworkers pointed out that a large number of synthetic industrial chemicals exhibit a wide range of endocrine disruptive effects in wildlife populations and in laboratory animal studies.[3] Of particular concern were those chemicals that exhibited estrogenic activity, because previous studies with the potent estrogenic drug diethylstilbestrol (DES) in both laboratory animals and humans demonstrated that *in utero* and early postnatal exposures resulted in both toxic and carcinogenic responses in reproductive tracts of male and female offspring. Thus, based in part on results observed in the children of women treated with DES, it was hypothesized that synthetic estrogens (or xenoestrogens), other endocrine-disruptive chemicals (EDCs), and possibly natural estrogenic compounds may be responsible for decreased male reproductive capacity, including decreased sperm quality, increased incidence of testicular cancer in young males, and increases in hypospadias and cryptorchidism in newborn males.[4]

The endocrine disruptor hypothesis stimulated considerable public, regulatory, and scientific concern regarding our exposures to these compounds, resulting in numerous articles in the popular press and television programs, including “Assault on the Male” (BBC *Horizon*) and “Fooling with

Nature" (PBS *Frontline*). In addition, the U.S. Congress passed the Food Quality Protection Act, which mandates that the US-EPA develop screening and testing procedures for EDCs. More importantly, several research programs were initiated worldwide to further identify and characterize xenoestrogens and other EDCs, and also to determine the magnitude of decreased male reproductive capacity and the association of synthetic chemicals with this problem.

Decreased Male Reproductive Capacity and the Role of EDCs

Sperm Counts and Quality

In 1992, Carlsen and coworkers[5] reported in the *British Medical Journal* results of their analysis of 61 sperm count studies published during the period between 1940 and 1990. The studies were carefully selected, and they reported that there was a linear decrease in sperm counts from 113 million per milliliter in 1940 to 66 million per milliliter in 1990. This represented a nearly 50 percent decline in sperm counts.

This observation, coupled with reports on other increased male reproductive tract abnormalities, including cryptorchidism, hypospadias, and testicular cancer, led to publication of a paper in the medical journal *Lancet* entitled "Are Oestrogens Involved in Falling Sperm Counts and Disorders of the Male Reproductive Tract?"[6] The authors, Richard Sharpe, a reproductive biologist from the University of Edinburgh, and Niels Skakkebaek, a physician-scientist from the University of Copenhagen, answered the question by stating, "We argue that the increasing incidence of reproductive tract abnormalities in the human male may be related to increased oestrogen exposure *in utero* and

we identify mechanisms by which this exposure could occur."

Subsequent research has both supported and criticized the initial meta-analysis studies, and more importantly, several groups have investigated temporal changes in sperm counts and quality among patients in various clinics in developed countries. In 1995, Auger and coworkers[7] published one of the first reports on the time-dependent changes in sperm quality of over 1,000 patients in a fertility clinic in Paris. This study showed that the mean concentration of sperm decreased by 2.1 percent per year, from 86 million per milliliter in 1973 to 60 million per milliliter in 1992.

However, a subsequent study[8] in Toulouse, France using a similar study group and analysis procedures concluded, "Sperm concentration has not changed with time in the Toulouse area" (1977-1992). Moreover, in 1992, sperm counts in Toulouse and Paris varied from 83 million per milliliter to 60 million per milliliter, respectively, suggesting that male sperm counts in various regions of France may be significantly different.

In the meantime, several subsequent studies at clinics in various countries indicated either decreased or unchanged sperm counts. For example, Irvine and coworkers[9] examined 577 volunteer semen donors at the Center for Reproductive Biology in Edinburgh, Scotland, and they chose to analyze their results by year of birth (i.e. birth cohort analysis). Most of their data on sperm quality suggested that there was a decrease with earlier year of birth. For example, although overall sperm concentration in this group was 104.5 million per milliliter, concentrations in the birth cohorts 1959 or earlier, 1960-1964, 1965-1969, and 1970-1974 were 117.9 million, 114.4 million, 91.3 million, and

93.9 million per milliliter, respectively. It was concluded, "This study provides direct evidence that semen quality is deteriorating," and "it is consistent with the hypothesis advanced by Sharpe and Skakkebaek that environmental or other factors acting during fetal and perinatal life can have profound effects on subsequent adult reproduction function."

Rasmussen and coworkers[10] investigated sperm quality of male partners of women with tubal infertility who were treated at the Odense University Hospital in Odense, Denmark. Their results were in direct contrast to those reported by the Scottish group, which found, "When four birth cohorts were compared, a later year of birth was not associated with any change in sperm concentration or semen volume."

These results demonstrated that geographical location *(i.e. demography) might be an important determinant of sperm counts.*

It is well-known that differing methods for semen analysis can give different results, and there are many other factors that can cause variability in semen counts, making it difficult to directly compare results from one study to another. Handelsman[11] reviewed semen analysis of men donating sperm from 1980 to 1995 at the Royal Prince Alfred Hospital in Sydney and did not observe changes in semen quality over time or by birth cohort analysis.

Moreover, Handelsman and his colleagues recruited five groups of semen donors for male contraception research studies during the period 1987-1994, and

the median sperm concentrations in groups 1-5 were 103 million, 142 million, 84 million, 67 million, and 63 million per milliliter, respectively. He concluded, "the inconsistency of these estimates illustrates the magnitude of bias (up to 100 percent) in sperm output that may occur in recruiting groups of self-referred volunteers within a single center." Moreover, Handelsman argues that self-selected volunteers that have been used in nearly all semen quality studies are not appropriate for estimating sperm output in so-called randomly selected normal male populations.

In 1996, Harry Fisch, a physician at Columbia-Presbyterian Medical Center in New York, and his coworkers published a paper in *Fertility and Sterility* on the analyses of semen from 1,283 men who banked sperm prior to vasectomy.[12] There was a slight but significant *increase* in sperm concentration from 77 million per milliliter in 1970 to 89 million per milliliter in 1994, whereas sperm volume and motility were unchanged.

This study was the first to demonstrate another important variable that had not been recognized in previous reports, including the meta-analysis paper by Carlsen and coworkers.[13] Individuals analyzed by Fisch and coworkers came from sperm banks in New York, Minnesota, and California, and their mean sperm concentrations were 131.5 million, 100.8 million, and 72.7 million per milliliter, respectively. These results demonstrated that *geographical location* (i.e. demography) might be an important determinant of sperm counts. This finding has been confirmed by recent studies in France, Denmark, and Canada.[14]

The importance of demography was particularly evident in a study of semen quality in 11 fertility centers across Canada.[15] Overall, there was a decrease in

semen concentration from 1984 to 1996; however, when the data from earlier studies (1975-1983) were taken into account, there was no significant trend in sperm density. However, it was apparent that there were dramatic differences in sperm densities between the 11 centers. For example, in 1984 the mean sperm densities ranged from a low of 51 million per milliliter to a high of 121 million per milliliter and an even larger degree of variability was observed in 1996 (43 million to 137 million per milliliter).

Current evidence showing the importance of demography and other factors does not support the hypothesis that there has been a global decline in sperm counts or semen quality.

A recent study by Skakkebaek and coworkers[16] at the University of Copenhagen showed that mean sperm concentrations increased from 53.0 million per milliliter in 1977 to 72.7 million per milliliter in 1995. However, they also observed consistent seasonal variations, with higher values observed in samples collected during the winter and spring and lower values in summer and fall. Many of the co-authors of this report also co-authored the meta-analysis study by Carlsen and coworkers,[17] and they concede that geographical differences in semen quality may also be important, even though they do not cite the extensive evidence showing the importance of demography.

In summary, the issue of declining sperm counts has been the subject of in-

tense scientific debate; however, current evidence showing the importance of demography and other factors does not support the hypothesis that there has been a global decline in sperm counts or semen quality. None of these studies has addressed the issue of exposures to estrogens or other environmental contaminants. However, since organochlorine contaminant concentrations are comparable within regions as large as the United States and Canada, it is unlikely that these trace environmental levels of these compounds play a role in modulating semen quality.

Testicular Cancer

The hypothesis that there is a global increase in problems of the male reproductive tract is supported by the increasing incidence of testicular cancer in most countries. Since this type of cancer is predominant in young males, it is possible that *in utero*/early postnatal exposures to chemicals or other initiators may be etiologic agents for this disease.

A paper by Kelce and coworkers[18] showed that *p,p'*-DDE, the persistent metabolite of DDT, was an antiandrogen in both cell culture and rodent models. Since androgens play an important role in development of the male reproductive tract, it was speculated that this compound might contribute to male reproductive problems. This issue was addressed by Ekbom and coworkers,[19] who compared breast milk DDE levels vs. incidence of testicular cancer in Scandinavia. Rates of testicular cancer are particularly high in Denmark (14.5 per hundred thousand males from 1985 to 1989), whereas lower rates were observed in Norway (12.6 per hundred thousand), Sweden (8.1 per hundred thousand), and Finland (3.6 per hundred thousand). However, breast milk DDE lev-

els in the 1960s were *not* significantly different in the four Scandinavian countries, suggesting the prior *in utero* exposure to *p,p'*-DDE does not correlate with the different rates of testicular cancer in Scandinavia. This report also showed that DDE levels have decreased by 90 percent from their 1960s levels due to restricted use of this pesticide, thus, there was an *inverse* correlation with the increasing incidence of testicular cancer.

It seems unlikely that persistent organochlorine compounds such as PCBs and DDT/DDE contribute to increases in testicular cancer.

It seems unlikely that persistent organochlorine compounds such as PCBs and DDT/DDE contribute to increases in testicular cancer because environmental levels are similar in many developed countries (such as Scandinavia), whereas there are large country-specific differences in the incidence of testicular cancer in young men. These results do not exclude a role for other environmental factors (including chemicals); however, these have not been identified.

Fertility and Sex Ratios

Decreased fertility has also been considered as a possible outcome of decreased sperm counts and male reproductive capacity. Laboratory animal studies with mice show that *in utero* exposure to DES decreases fertility in male offspring. Wilcox and coworkers[20] investigated the fertility of 253 sons of women exposed to DES in a Chicago hospital (1950-1952) and 241

unexposed males from the same clinical trial. The incidence of deformed genitalia was three times higher among the DES sons, which was consistent with other DES exposure studies.

Fertility of both groups was determined by a questionnaire and by determining the length of time to conception, a standard measure of fertility. The results showed that *in utero* exposure to high doses of diethylstilbestrol "did not lead to impairment of fertility or sexual function in adult men" 40 years after their initial exposures.

A more recent study[21] examined the effect of *in utero* exposure to estrogens and progestins that were administered to women in Helsinki from 1954 to 1963. (Note: DES was not used in Finland.) The results of this retrospective cohort study showed that *in utero* exposure to relatively high doses of estrogens or progestins did not impact overall male or female fertility of the offspring. Thus, high-dose *in utero* exposure to estrogens and DES did not affect fertility of offspring, suggesting that exposures to trace levels of weakly estrogenic EDCs are unlikely to affect fertility.

Male to female newborn sex ratios undergo temporal and seasonal variations and may be useful as indicators of exposure to some environmental/occupational chemical toxins. For example, a report from Seveso, Italy, indicated that there was a significant decline in male/female sex ratios in births (1977-1984) among individuals exposed to high levels of TCDD as a result of an industrial accident on July 10, 1976 that released large amounts of TCDD into the environment.[22] Davis and coworkers[23] have proposed that decreased male/female ratios of newborns may be "a sentinel health event" that may be linked to environmental factors. This proposal was based, in part, on the observation that

male/female sex ratios in the United States, Canada, Denmark, and the Netherlands have slightly decreased during the past 20 to 40 years.

Marcus and coworkers[24] also observed that in the United States between 1969 and 1995, there was an overall decline in the male/female sex ratio from 1.053 to 1.049; however, this decline was primarily observed in Caucasians. In contrast, among African-Americans there was an increase in this ratio among newborns. The researchers concluded that environmental exposures are unlikely to account for the observed trends.

The possible link between environmental chemicals and drugs with changing birth ratios was also investigated in Finland. This study used data accumulated over 250 years.[25] Their results showed an increase in male/female sex ratios in the years from 1751 to 1920. With the exception of increased ratios during and after World Wars I and II, there has been a decline in this ratio since 1920. Since the downward trend of this ratio preceded the high levels of environmental contamination observed from 1950 to the late 1970s, the researchers concluded, "We were not able to confirm that chemical-ization (in the sense of exposure to agricultural and industrial chemicals) is a significant source of changes in sex ratio."

Hypospadias and Cryptorchidism

Hypospadias are characterized by a displaced urethral opening on the penis and cryptorchidism is a condition in which one or both testicles do not descend into the scrotum. Based on limited studies, it was hypothesized that increased incidences of both defects were part of an overall global decrease in male reproductive capacity.[26] A recent study summarized international

trends in both developmental defects in various countries, and the results again showed that demography was an important factor.[27]

These data suggest that human populations are not threatened with a global decline in sperm counts or decreased male reproductive capacity. There may be some problems in specific areas, but these have not been correlated with exposures to EDCs.

For example, hypospadias in New Zealand occurred at approximately one-half the rate observed in Canada. Finland had the lowest rate of hypospadias among Scandinavian countries, and the rate was nearly threefold higher in Sweden. Large demographic differences were also observed for cryptorchidism, and this variability did not correlate with any obvious chemical contaminant gradient. Moreover, since 1985, the incidence of hypospadias in most countries has been relatively stable, whereas cryptorchidism has declined in most regions. Thus, the initial argument that the increasing incidence of hypospadias and cryptorchidism supported the endocrine disruptor hypothesis[28] is not borne out by worldwide trends for these birth defects.

Summary

These data suggest that human populations are not threatened with a global decline in sperm counts or decreased male reproductive capacity. There may be some problems in specific areas, but these have

not been correlated with exposures to EDCs. Demography appears to be an important determinant for male reproductive capacity. It will be a significant scientific challenge to determine factors that are responsible for these region-dependent differences.

Breast Cancer and Xenoestrogens

The suggestion that estrogenic compounds may be causing a global decrease in male reproductive capacity was paralleled by a hypothesis by other scientists that these same compounds were also "preventable" causes of breast cancer.[29] Because it is well-known that a woman's overall lifetime exposure to estrogens is a major risk factor for sporadic breast cancer, it seemed reasonable that additional exposure to xenoestrogens would increase the risk.

Two papers published in 1992 and 1993 that compared levels of PCBs and DDE in breast cancer patients versus controls were cited as support for the xenoestrogen hypothesis.[30] In a group of women from Connecticut, PCB levels were higher in tissue from breast cancer patients compared to a control group, and DDE levels were higher in serum from breast cancer patients versus a control group in New York.

These results prompted widespread concern regarding the potential impacts of organochlorine pesticides and pollutants and their possible role in breast cancer. However, there have been many questions regarding their role as xenoestrogens in breast cancer. For example, neither DDT/DDE or PCBs have been linked to increased incidence of breast cancer in individuals (e.g. workers) highly exposed to these compounds. Studies in laboratory animals provide only minimal support for the estro-

genic role of these compounds in development of mammary tumors. In fact, a recent paper shows that commercial PCBs *inhibit* formation of breast tumors in female Sprague-Dawley rats and thereby exhibit antitumorigenic activity.[31]

Subsequent studies in several countries have partially resolved the controversy regarding DDE/PCBs and breast cancer. Levels of these organochlorine compounds were *not* significantly different in breast cancer patients versus control groups of patients in the San Francisco Bay area, 11 states associated with the Nurses Health Study, five European countries, Mexico City, or many other areas.[32]

Neither DDT/DDE or PCBs have been linked to increased incidence of breast cancer in individuals (e.g. workers) highly exposed to these compounds.

The role of environmental contaminants, diet, and genetic factors may combine to protect against or enhance development of breast cancer in women. Future studies on these complex interactions will not only help identify risk factors but also suggest possible chemoprevention strategies.

Natural Estrogens and Xenoestrogens

One of the major problems in assessing risks associated with exposure to xenoestrogens is the lack of information on our overall dietary intake of these compounds, their estrogenic potencies, and their persistence in the body. While it is true that several weakly estrogenic organochlorine pesticides have been identified in a typical "food basket" survey, the maxi-

mal overall intake of these compounds is relatively low—less than 3 micrograms a day (3.0 mg/day). Moreover, their estrogen equivalent intake is a tiny fraction of this daily amount. The estrogenic potency of a single glass of red wine (1.0 mg estrogen equivalents) is at least 1,000 times higher than the estrogen equivalents associated with daily dietary intakes of organochlorine pesticides in food.[33] Many other food products contain "natural" estrogenic compounds, including high levels of phytoestrogens (such as flavonoids) in fruits, nuts, and vegetables.

The estrogenic potency of a single glass of red wine is at least 1,000 times higher than the estrogen equivalents associated with daily dietary intakes of organochlorine pesticides in food.

Kenneth Setchell and his coworkers[34] recently detected relatively high levels of estrogenic flavonoids in serum from adults on soy diets and infants on soy formula—groups that are among the most highly exposed to estrogenic compounds. The potential harmful effects of these natural estrogens on adults or infants during critical exposure periods is unknown; however, most studies associate consumption of diets rich in phytoestrogenic compounds with *positive* health effects.

Conclusion

The endocrine disruptor hypothesis continues to generate controversy and debate among scientists and regulators,

and it is not surprising that the media and public are confused regarding the potential impacts of these chemicals on the male reproductive tract and on breast cancer in women. It is paradoxical that on one hand, there is concern regarding *in utero*/early postnatal exposure to trace levels of industrial estrogenic compounds, whereas health-promoting estrogenic soy-derived products are being marketed for all age groups. Moreover, many pharmaceutical companies are developing selective estrogen receptor modulators (SERMs) for treatment of breast cancer and for postmenopausal problems associated with estrogen deficiency.

There has been considerable controversy regarding the low-dose effects of some xenoestrogens such as bisphenol-A, an important compound in the production of polymers/plastics. Vom Saal and coworkers have reported inverted U-shape dose response curves showing that *in utero* exposure to extremely low doses of bisphenol-A results in increased prostate weight in male offspring.[35] In contrast, this same response has not been observed in other studies using similar protocols.[36] Reasons for these differences have not been resolved; however, there is evidence from other studies that exposure to some xenoestrogens can induce some responses/changes in laboratory animals at relatively low doses.

The major emphasis of this article has been to highlight some of the latest reports on male reproductive capacity and breast cancer and also to show that the major dietary sources of endocrine-active chemicals are from plant-derived phyto-chemicals.

The National Research Council (NRC) appointed a Committee on Hormonally-Active Agents in the Environment and I was a member of this committee. A report

entitled “Hormonally Active Agents in the Environment” was released in the fall of 1999, and it is clear from this report that there were issues that divided the Committee. Despite these divisions and differences among committee members, the executive summary includes the following statements:

> Reported increases in the incidence of male reproductive disorders such as hypo-spadias (urethra opening found at the bottom rather than the top of the penis), cryptorchidism (undescended testes), and testicular cancer cannot be linked to exposures to environmental HAAs at this time. With respect to the end point most closely studied, sperm concentration, retrospective analyses of trends over the past half-century remain controversial. When the data from large regions are combined and analyzed, some data sets indicate a statistically significant trend consistent with declining sperm concentrations. However, aggregation of the data over larger geographic regions might not be an appropriate spatial scale for this analysis, given the significant geographic heterogeneity.
>
> An evaluation of the available studies conducted to date does not support an association between adult exposure to DDT, DDE, TCDD, and PCBs and cancer of the breast.[37]

The importance of geographical location on analysis of sperm count data was recently reviewed by Saidi and coworkers, and they concluded: “When accounting for this geographic difference and examining all available data, there appears to be no

significant change in sperm counts in the U.S. during the last 60 years. Further studies addressing the causes of geographic variations are needed."[38]

This pattern of geographical differences in sperm counts appears to be an important variable that requires further study.

One of the important outcomes of the endocrine disruptor hypothesis may be a renewed focus on both natural and xenoEDCs in our diet and their role in human health. At present, the evidence suggests that the dominant EDCs in our diets are naturally occurring phytochemicals, including estrogens, antiestrogens, antiandrogens, Ah receptor agonists, and retinoids. The health benefits of foods containing these compounds are well-known. However, it is possible that some dietary modifications during critical periods may be warranted. This requires further investigation.

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