Environmental and Dietary Estrogens and Human Health: Is There a Problem?

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Recent reports have suggested that background levels of industrial chemicals and other environmental pollutants may play a role in development of breast cancer in women and decreased male reproductive success as well as the reproductive failures of some wildlife species (1–6). These suggestions have been supported by articles in the popular and scientific press (7–13) and by a television documentary (14) which have described the perils of exposure to endocrine-disrupting chemicals such as estrogenic organochlorine pesticides and pollutants. During the past two decades, environmental regulations regarding the manufacture, use, and disposal of chemicals have resulted in significantly reduced emissions of most industrial compounds and their by-products. Levels of the more environmentally stable organochlorine pesticides and pollutants are decreasing in most ecosystems including the industrialized areas around the Great Lakes in North America (15–18). Decreased levels of organochlorine compounds correlates with the improved reproductive success of highly susceptible fish-eating water birds in the Great Lakes region (19). This article reviews key papers that have been used to support the hypotheses that environmental estrogens play a role in the increased incidence of breast cancer in women and decreased sperm counts in males. Environmental/dietary estrogens and antiestrogens are identified and intakes of "estrogen equivalents" are estimated to compare the relative dietary impacts of various classes of estrogenic chemicals.

Role of Estrogens in Breast Cancer and Male Reproductive Problems

Concerns regarding the role of environmental and dietary estrogens as possible contributors to the increased incidence of breast cancer were fueled by several reports that showed elevated levels of organochlorine compounds in breast cancer patients (20–24). The results presented in Table 1 summarize some of these studies that compare levels of organochlorine compounds in breast tissue or serum from breast cancer patients and controls. Polychlorinated biphenyls (PCBs) and 1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene (DDE) are the two most abundant organochlorine pollutants identified in all human tissues with high frequencies. In one Scandinavian study, levels of DDE or PCBs in adipose tissue from breast samples were not significantly different in breast cancer patients compared to controls (20). In another study in Finland, β-hexachlorocyclohexane levels were elevated in breast cancer patients (21); however, this compound was not detected in adipose tissue of some individuals in the patient and control groups and has a relatively low frequency of detection in human tissue samples. Falek and co-workers reported that PCB levels were elevated in mammary adipose tissue samples from breast cancer patients in Connecticut (22). In contrast, serum levels of DDE (but not PCBs) were significantly elevated in breast cancer patients enrolled in the New York University Women’s Health Study (23). DDE (but not PCB) levels were also elevated in estrogen receptor (ER)-positive but not ER-negative breast cancer patients from Quebec compared to levels in women with benign breast disease (24). It was initially concluded by Wolff and co-workers that "these findings suggest that environmental chemical contamination with organochlorine residues may be an important etiologic factor in breast cancer" (22). The correlations reported in the two U.S. studies (22,23) heightened public and scientific concern regarding the potential role of these compounds in development of breast cancer. These observations undoubtedly reinforced advocacy by some groups for a ban on the use of all chlorine-containing chemicals. However, the proposed linkage between PCBs and/or DDE and breast cancer is questionable for the following reasons:

• Most studies with PCBs indicate that these mixtures are not estrogenic, and the weak estrogenic activity observed for lower chlorinated PCB mixtures may be due to their derived hydroxylated metabolites;

• p,p'-DDE, the dominant persistent metabolite of 1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethane (p,p'-DDT), is not estrogenic, and levels of α,α'-DDT, the estrogenic member of the DDT family, are low to nondetectable in most environmental samples;

It has been hypothesized that organochlorine pesticides and other environmental and dietary estrogens may be associated with the increased incidence of breast cancer in women and decreased sperm concentrations and reproductive problems in men. However, elevation of organochlorone compounds such as dichlorodiphenyl-dichloroethylene (DDE) and polychlorinated biphenyls (PCBs) in breast cancer patients is not consistently observed. Reanalysis of the data showing that male sperm counts decreased by over 40% during 1940 to 1990 indicated that inadequate statistical methods were used and that the data did not support a significant decline in sperm count. Humans are exposed to both natural and industrial chemicals which exhibit estrogenic and antiestrogenic activities. For example, bioflavonoids, which are widely distributed in foods, and several industrial compounds, including organochlorine pesticides and various phenolic chemicals, exhibit estrogenic activity. Humans are also exposed to chemicals which inhibit estrogen-induced responses such as the aryl hydrocarbon receptor (AhR) agonist 2,3,7,8-tetrachlorodibenzo-p-dioxin and related chlorinated aromatics, polynuclear aromatic hydrocarbon combustion products, and indole-3-carbinol, which is found in cruciferous vegetables. Many of the weak estrogenic compounds, including bioflavonoids, are also antiestrogenic at some concentrations. A mass balance of dietary levels of industrial and natural estrogens, coupled with their estimated estrogenic potencies, indicates that the dietary contribution of estrogenic industrial compounds is 0.0000025% of the daily intake of estrogenic flavonoids in the diet. Moreover, dietary levels of antiestrogen equivalents (industrial or natural) are significantly higher than the estrogen equivalents of organochlorine pesticides. The suggestion that industrial estrogenic chemicals contribute to an increased incidence of breast cancer in women and male reproductive problems is not plausible. Key words: antiestrogens, dietary estrogens, estrogen equivalents, pesticides, organochlorine biphenyls, TCDD. Environ Health Perspect 103: 346–351 (1995)

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Table 1. Organochlorine levels in breast cancer patients

| Country       | Organochlorine compound                                      | Patient group (n)                  | Levels          | Reference |
|---------------|--------------------------------------------------------------|------------------------------------|-----------------|-----------|
| Finland       | β-Hexachlorocyclohexane levels elevated in breast cancer patients (breast tissue) | Breast cancer patients (24)        | 0.13 ± 0.06 ppm | (21)      |
|               |                                                              | Controls (16)                      | 0.08 ± 0.03 ppm |           |
| Norway        | DDT and PCB levels comparable in patients and controls (breast tissue) | Breast cancer patients (18)        | 6.47 ± 2.35 ppm PCB | (20)      |
|               |                                                              | Controls (35)                      | 5.12 ± 2.38 ppm PCB; |           |
|               |                                                              |                                    | 1.97 ± 2.24 ppm DDT |           |
| USA (Connecticut) | PCB levels elevated in breast cancer patients (breast tissue) | Breast cancer patients (20)        | 1069 ± 894 ppm PCB | (23)      |
|               |                                                              | Controls (20)                      | 1105 ± 424 ppb PCB |           |
| USA (New York) | DDE levels elevated in breast cancer patients (serum)        | Breast cancer patients (58)        | 11.0 ± 9.1 ng/mL | (22)      |
|               |                                                              | Controls (171)                     | 7.7 ± 6.8 ng/mL |           |
| USA (California) | PCB and DDE levels comparable in patients and controls (serum) | Breast cancer patients (150)       | 4.4 ± 1.8 ppb PCB; | (27)      |
|               |                                                              |                                    | 43.3 ± 25.9 ppb DDE |           |
|               |                                                              |                                    | 4.8 ± 2.5 ppb DDE |           |
|               |                                                              |                                    | 43.1 ± 23.7 ppb DDE |           |
| Canada (Quebec) | DDE levels increased in estrogen receptor-positive patients (breast tissue) | Breast cancer patients (9)         | 2132 ± 2080 ppm | (24)      |
|               |                                                              | Controls (17)                      | 765 ± 527 ppm   |           |

- Epidemiology studies of individuals occupationally exposed to relatively high levels of DDT (25) or PCBs (26) do not show a higher incidence of breast cancer; and
- No single class of organochlorine compounds was elevated in all studies, suggesting that other factors may be critical for development of breast cancer.

Krieger and co-workers (27) recently reported results from a nested case-control study of women from the San Francisco area which showed that there were no differences in serum DDE or PCB levels between breast cancer patients and control subjects. The authors concluded that "the data do not support the hypothesis that exposure to DDE and PCBs increases risk of breast cancer" (27; p. 589). This was duly noted in Time magazine (28) by a three-line statement in "The Good News" section. Moreover, combined analysis of the 6 studies which report PCB and DDE levels in 301 breast cancer patients and 412 control patients showed that there were no significant increases in either DDE or PCB levels in breast cancer patients versus controls (29).

The second major link between environmental/dietary estrogens and human disease was precipitated by an article published in the Lancet, in which Sharpe and Skakkebaek (5) hypothesized that increased estrogen exposure may be responsible for falling sperm counts and disorders of the male reproductive tract. Unlike the proposed link between environmental estrogens and breast cancer, this hypothesis was not based on experimentally derived measurements of increased levels of any estrogenic compounds in males. Previous studies with diethylstilbestrol, a highly potent estrogenic drug, showed that in utero exposure results in adverse effects in male offspring (30), and the authors hypothesized that in utero exposure to environmental/dietary estrogens may also result in adverse effects in male offspring. A critical experimental component supporting the authors' hypothesis was their analysis of data from several studies which indicated that male sperm counts had decreased by over 40% during the past 50 years (31). These observations, coupled with the hypothesis that environmental estrogens including organochlorine chemicals were possible etiologic agents, were reported with alarm in the popular and scientific press (7–12) and in a BBC television program entitled "Assault on the Male: A Horizon Special" (14). Subsequent and prior scientific studies have cast serious doubts on both the hypothesis (5) and the observed decrease in male sperm counts (31). In 1979, Mackled and Wang (32) reported that there had been no decline in sperm counts, and reanalysis of the data presented by Carlsson and co-workers showed that sperm counts had not decreased from 1960 to 1990 (33). Thus, during the time in which environmental levels of organochlorine compounds were maximal, there was not a corresponding decrease in sperm counts. Moreover, a reevaluation of the sperm concentration data was recently reported by Brownwich et al. (34) in the British Medical Journal, and their analysis suggested that the decline in sperm values in males was a function of the choice of the normal or reference value for sperm concentrations. The authors contend that their analysis of the data does "not support the hypothesis that the sperm count declined significantly between 1940 and 1990" (34: p. 19).

These results suggest that the increasing incidence of human breast cancer is not related to organochlorine environmental contaminants and that decreases in sperm counts is hardly debatable. Nevertheless, human populations are continually exposed to a wide variety of environmental and dietary estrogens, and these compounds clearly fit into the category of "endocrine disrupters." The remainder of this article briefly describes the different structural classes of both environmental and dietary estrogens and quantitates human exposures to these compounds.

**Synthetic Industrial Chemicals with Estrogenic Activity**

The estrogenic activities of different structural classes of industrial chemicals were reported by several research groups in the late 1960s and 1970s in which \( o,p' \)-DDT and other diphenylmethane analogs (Fig. 1) and the insecticide kepone were characterized as estrogens (35–38). Subsequent studies have confirmed the estrogenic activity of \( o,p' \)-DDT and related compounds (39) whereas the \( p,p' \)-substituted analogs were relatively inactive (36,37). In addition, \( p,p' \)-methoxychlor and its hydroxylated metabolites elicit estrogenic responses (39,40). Ecobichon and Comeau (41) investigated the estrogenic activities of commercial PCB mixtures (Aroclors) and individual congeners in the female rat uterus and reported estrogenic responses for some Aroclors and individual congeners. Studies in this laboratory showed that a number of commercial PCBs did not significantly increase secretion of procathepsin D, an estrogen-regulated gene product, in MCF-7 human breast cancer cells (42). It should be noted that several hydroxylated PCBs bind to the ER, and it is possible that para-hydroxylated PCB metabolites may be the active estrogenic compounds associated with lower chlorinated PCBs (43). A recent study reported that several additional organochlorine pesticides including endosulfan, toxaphene, and dieldrin exhibit estrogenic activity and induce proliferation of MCF-7 human breast cancer cells (44).
Other industrial chemicals or intermediates that have been identified as estrogenic compounds include bisphenol-A (Fig. 1), a chemical used in the manufacture of polycarbonate-derived products (45); phenol red, a pH indicator used in cell culture media (46); and alkyl phenols and their derivatives, which are extensively used for preparation of polyethoxylates in detergents (47,48).

**Natural Estrogenic Compounds**

Human exposure to estrogenic chemicals is not confined to xenoestrogens derived from industrial compounds. Several different structural classes of naturally occurring estrogens have been identified, including plant bioflavonoids (Fig. 1) and various mycotoxins including zearealenone and related compounds (49–52). The plant bioflavonoids include different structural classes of compounds which contain a flavonoid backbone: flavones, flavanones, flavonols, isoflavones, and related condensation products (e.g., coumestrol). The estrogenic activities of diverse phytoestrogenic flavonoids and mycotoxins have been extensively investigated in *in vivo* models, *in vitro* cell culture systems, and in ER binding assays, and most of these compounds elicit multiple estrogenic responses in these assays. In addition, a number of plant foodstuffs contain 17β-estradiol (E₂) and estrone (51,52).

**Environmental and Dietary Antiestrogens**

Several different structural classes of chemicals found in the human diet also exhibit antiestrogenic activity (Fig. 2) (13). 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) and related halogenated dibenzo-p-dioxins (PCDDs), dibenzo furans (PCDFs), and PCBs are also an important class of organochlorine pollutants that elicit a diverse spectrum of biochemical and toxic responses (53). These chemicals act through the aryl hydrocarbon receptor (AhR)-mediated signal transduction pathway, which is thought to play a role in most of the responses elicited by these compounds. AhR agonists such as TCDD have been characterized as antiestrogens using rodent and cell models similar to those used for determining the estrogenic activity of dietary and environmental chemicals. In the rodent model, TCDD and related compounds inhibit several estrogen-induced uterine responses including increased uterine wet weight, peroxidase activity, cytosolic and nuclear progesterone receptor (PR) and ER binding, epidermal growth factor (EGF) receptor binding, EGF receptor mRNA, and c-fos mRNA levels (54–58). In parallel studies, the antiestrogenic activities of TCDD and related compounds have also been investi-
flower) and exhibits antiiogenetic and anticancer (mammary) activities (70,73).

Bioflavonoids have been extensively characterized as weak estrogens and therefore may also be active as antiestrogens at lower concentrations. The interaction between estrogens and flavonoids depends on their relative doses or concentrations, the experimental model, and the specific estrogen-induced endpoint. Markaverich and co-workers (74) reported that the estrogenic bioflavonoids quercetin and luteolin (Fig. 1) inhibited E2-induced proliferation of MCF-7 human breast cancer cells and E2-induced uterine wet weight increase in 21-day-old rats. Similar results were also observed in this laboratory for quercetin, reserpine, and naringenin. For example, the flavonoid naringenin inhibited estrogen-induced uterine hypertrophy in female rats and estrogen-induced luciferase activity in MCF-7 cells transfected with an E2-responsive plasmid construct containing the 5'-promoter region of the p52 gene and a luciferase reporter gene (unpublished results). In contrast, a recent study (75) reported that coumestrol, genistein, and zearalenone were not antiestrogenic in human breast cancer cells. The antiestrogenic activities of weak dietary and environmental estrogens require further investigation; however, it is clear that at subestrogenic doses, some of these compounds exhibit antiestrogenic activities in both in vitro and in vivo models.

**Mass/Potency Balance**

The uptake of environmental or dietary chemicals that elicit common biochemical/toxic responses can be estimated by using an equivalency factor approach in which estrogen equivalents (EQs) in any mixture are equal to the sum of the concentration of the individual compounds (ECi) times their potency (EP) relative to an assigned standard such as diethylstilbestrol (DES) or E2 (51). The total EQs in a mixture would be:

\[ \text{EQ} = \sum (\text{ECi} \times \text{EP}) \]

A similar approach is being used to determine the TCDD equivalents (TEQs) of various mixtures containing halogenated hydrocarbons (76). Verdeal and Ryan (51) have previously used this approach with DES equivalents assuming that the oral potency of E2 is 15% that of DES. Winter (77) has estimated the dietary intake of pesticides based on FDA's total diet study, which includes estimates of food intakes and pesticide residue levels in these foods. The results presented in Table 2 summarize the estimated exposure of different groups to estrogenic pesticides. For example, 14- to 16-year-old males were exposed to a total of 0.0416 μg/kg/day of the estrogenic pesticides, DDT, dieldrin, endosulfan, and p.p'-methoxychlor (note: the DDT value represents p.p'-DDE and related metabolites, which are primarily nontoxic). Thus, the overall dietary intake of these compounds by this age group was 2.5 μg/day.

The relative potencies of dietary and xenosterogens are highly variable. The results of in vitro cell culture studies suggest that estrogenic potencies of bioflavonoids relative to E2 are 0.001 to 0.0001 (75,78) whereas Soto and co-workers (44) have assigned an estrogen potency factor of 0.000001 for the estrogenic pesticides. These relative estrogen potency factors for bioflavonoids and pesticides may be lower when derived from in vitro studies since pharmacokinetic factors and metabolism may decrease bioavailability. Thus, a more accurate assessment of dietary/environmental EQs requires further data from dietary feeding studies that use these compounds under the same experimental protocols.

The results in Table 3 summarize human exposure to dietary and environmental estrogens and the estimated daily dose in terms of EQs. The relative estrogen intakes for various hormonal drug therapies were previously estimated by Verdeal and Ryan (51); the average estimated daily intake of all flavonoids in food products was 1020 and 1070 mg/day, respectively.

### Table 2. Estimated dietary intake of estrogenic pesticides by different age groups based on food intake and pesticide levels in these foods (77)

| Pesticide | 6–11 months | 14–16 years | 21 days |
|-----------|-------------|-------------|--------|
| DDT (total) | 0.077 | 0.0260 | 0.0103 |
| Dieldrin | 0.0014 | 0.0016 | 0.0016 |
| Endosulfan | 0.0274 | 0.0135 | 0.0210 |
| p.p'-Methoxychlor | 0.0005 | 0.0005 | 0.0001 |

**Maximum exposure: 60 x 0.0416 = 2.5 μg/day.**

### Table 3. Estimated mass balance of human exposures to environmental and dietary estrogens and antiestrogens (51,52,77,79)

| Source | Estrogen equivalents (μg/day) |
|--------|-------------------------------|
| Estrogens | \[ IC1 \] |
| Morning after pill | 333,500 |
| Birth control pill | 16,675 |
| Post-menopausal therapy | 3,260 |
| Flavonoids in foods (1,020 mg/day x 0.0001) | \[ IC1 \] |
| Environmental organochlorine estrogens (2.5 x 0.00001) | 0.0000025 |

| Antiestrogens | TCDD antiestrogen equivalents (μg/day) |
|---------------|----------------------------------------|
| TCDD and organochlorines (80–120 pg/day) | \[ 0.000098 – 0.000202 \] |
| PAHs in food (1.2–5.0 x 106 pg/day; relative potency = 0.001) | \[ 0.001230 – 0.009530 \] |
| Indolo[3,2-b]carbazole in 100 g brussels sprouts | \[ 0.000250 – 0.001282 \] |

\[ 0.025 – 1.28 \times 106 pg/day; relative potency = 0.001 \]

\[ 0.001 \]

\[ 0.0000025 \]

\[ 0.00261 \]

\[ 0.0000025 \]

\[ 0.00261 \]
human serum; however, the estrogenic \textit{o,p'-DEDE} and \textit{o,p'-DDT} analogs and other weakly estrogenic organochlorine compounds are not routinely detected in serum samples. A recent study identified several hydroxylated PCB congeners in human serum. All of the hydroxylated compounds were also substituted with chlorine groups at both adjacent meta positions (81). Based on results of previous structure–activity studies (43) for hydroxylated PCBs, these compounds would exhibit minimal estrogenic activity; however, further studies on the activity of hydroxylated PCBs are warranted.

**Summary**

The hypothesized linkage between dietary/environmental estrogens and the increased incidence of breast cancer is unproven; there is a lack of correlation between higher organochlorine levels in breast cancer patients compared to controls (Table 1) and the low levels of organochlorine EQs in the diet (Table 3). Higher levels of bioflavonoids are unlikely to contribute to increased breast cancer incidence because these compounds and the foods they are associated with tend to exhibit anticarcinogenic activity (82,83). The hypothesis that male reproductive problems and decreased sperm counts are related to increased exposure to environmental and dietary estrogens is also unproven. As noted above, dietary exposure to xenoestrogens derived from industrial chemical residues in foods is minimal compared to the daily intake of EQs from naturally occurring bioflavonoids. Moreover, there are serious questions regarding the decreased sperm counts reported by Carlsen and co-workers. Reanalysis of Carlsen et al.’s data suggests that there has not been a decrease in sperm counts in males over the past 30 years (33) and possibly over the past 50 years (34). Thus, in response to articles in the popular and scientific press such as “The Estrogen Complex” (7) and “Eccancers: Do Environmental Factors Underlie a Breast Cancer Epidemic?” (8), the results would suggest that the linkage between dietary or environmental estrogenic compounds and breast cancer has not been made, and further research is required to determine the factors associated with the increasing incidence of this disease.

**Note added in proof** A recent study (84) reported a 2.1% decrease in sperm concentrations in France from 1973 to 1979.

**References**

1. Hunter DJ, Kelsey KT. Pesticide residues and breast cancer: the harvest of a Silent Spring. J Natl Cancer Inst 85:598–599 (1993).
2. Colborn T, vom Saal FS, Soto AM. Developmental effects of endocrine-disrupting chemicals in wildlife and humans. Environ Health Perspect 101:372–384 (1993).
3. Thomas KB, Colborn T. Organochlorine endocrine disruptors in human tissue. In: Chemically induced alterations in sexual development: the wildlife/human connection (Colborn T, Clement C, eds). Princeton, NJ:Princeton Scientific Publishing, 1992:365–394.
4. El-Bayoumy K. Environmental carcinogens that may be involved in human breast cancer etiology. Chem Res Toxicol 5:585–590 (1993).
5. Sharpe RM, Skakkebaek NE. Are oestrogens involved in falling sperm counts and disorders of the male reproductive tract. Lancet 341:1392–1395 (1993).
6. Davis DL, Bradlow HL, Wolff M, Woodruff T, Hoel DG, Anton-Culver H. Medical hypothesis: xenestrogens as preventable causes of breast cancer. Environ Health Perspect 101:372–377 (1993).
7. The estrogen complex. Newsweek March 21:76–77 (1994).
8. Raloff J. Eccancers: do environmental factors underlie a breast cancer epidemic? Sci News 146:10–14 (1994).
9. Raloff J. That feminine touch. Sci News 145:56–58 (1994).
10. Raloff J. The gender benders. Sci News 145:24–27 (1994).
11. Hileman B. Environmental estrogens linked to reproductive abnormalities and cancer. Chem Eng News Jan 31:19–23 (1994).
12. Stone R. Environmental estrogen stirs debate. Science 265:308–310 (1994).
13. Safe SH. Dietary and environmental estrogens and antiestrogens and their possible role in human disease. Environ Sci Pollut Res 1:29–33 (1994).
14. Assault on the male. Horizon, 30 October 1993. London:British Broadcasting Company.
15. Sole M, Porte C, Pastor D, Albiges J. Long-term trends of polychlorinated biphenyls and organochlorinated pesticides in mussels from the western Mediterranean coast. Chemosphere 28:897–903 (1994).
16. Robinson PE, Mack GA, Remmers J, Levy R, Mohadjer L. Trends of PCB, hexachlorobenzene, and benzene hexachloride levels in the adipose tissue of the U.S. population. Environ Res 53:175–192 (1990).
17. Turle R, Noestrom RJ, Collins B. Comparison of PCB quantitation methods: re-analysis of archived specimens of herring gull eggs from the Great Lakes. Chemosphere 22:201–213 (1991).
18. Schmitt CJ, Zajicek JL, Peterman PH. National contaminant biomonitoring program: residues of organochlorine chemicals in U.S. freshwater fish, 1976–1984. Arch Environ Contam Toxicol 19:749–781 (1990).
19. Giesty JP, Ludwig JP, Tillitt DE. Deformities of birds in the Great Lakes region: assigning causality. Environ Sci Technol 28:128A–135A (1994).
20. Unger M, Kier H, Bliicher-Toft M, Olsen J, Clausen J. Organochlorine compounds in human breast fat from deceased with and without breast cancer and in biopsy material from newly diagnosed patients undergoing breast surgery. Environ Res 34:24–28 (1984).
21. Musculo-Rahaman H, Häskén E, Pyysalo H, Antervo K, Kauppila R, Pantzar P. Occurrence of β-hexachlorocyclohexane in breast cancer patients. Cancer 66:2124–2128 (1990).
22. Falck F, Ricci A, Wolff MS, Godbold J. Deckers P. Pesticides and polychlorinated biphenyl residues in human breast lipids and their relation to breast cancer. Arch Environ Health 47:143–146 (1992).
23. Wolff MS, Toniole PG, Leel EW, Rivera M, Dubin N. Blood levels of organochlorine residues and risk of breast cancer. J Natl Cancer Inst 85:648–652 (1993).
24. DeWaal E, Dodin S, Verreault R, Ayotte P, Sauvé L, Morin J, Brisson J. High organochlorine body burden in women with estrogen receptor-positive breast cancer. J Natl Cancer Inst 86:232–234 (1994).
25. Higginson J. DDT epidemiologic evidence. IARC Scientific Publication no. 65; Lyon:International Agency for Research on Cancer, 1985:107–117.
26. Brown DP. Mortality of workers exposed to polychlorinated biphenyls—an update. Arch Environ Health 43:333–339 (1987).
27. Krieger N, Wolff MS, Hiatt RA, Rivera M, Vogelman J, Orentreich N. Breast cancer and serum organochlorines: a prospective study among white, black, and Asian women. J Natl Cancer Inst 86:589–599 (1994).
28. The good news. Time, 2 May 1994:20.
29. Ole J, Reeves G. Organochlorines in the environment and breast cancer. Br Med J 308:1520–1521 (1994).
30. Stillman RJ. In utero exposure to diethylstibestrol: adverse effects on the reproductive tract and reproductive performance in male and female offspring. Am J Obstet Gynecol 142:905–921 (1982).
31. Carlsen E, Giwercman A, Keiding N, Skakkebaek NE. Evidence for the decreasing quality of semen during the past 50 years. Br Med J 305:609–612 (1992).
32. MacLeod J, Wang Y. Male fertility potential in terms of semen quality: a review of the past, a study of the present. Fertil Steril 31:103–116 (1979).
33. Ramilow M. In: The toxicology forum (proceedings of the annual winter meeting). Fairfax, UK:CASEt Associates Ltd, 1994:79.
34. Bromwich P, Cohen A. Decline in sperm counts: an artefact of changed reference range of normal. Br Med J 309:19–22 (1994).
35. Bitman T, Cecil HC, Harris SJ, Fries GF. Estrogenic activity of o,p'-DDT in the mammalian uterus and avian oviduct. Science 162:371–372 (1968).
36. Welch RM, Levin W, Conney AH. Estrogenic action of DDT and its analogs. Toxicol Appl Pharmacol 14:358–367 (1969).
37. Bitman T, Cecil HC, Estrogenic activity of DDT analogs and polychlorinated biphenyls. J Agric Food Chem 18:1088–1112 (1970).
38. Hammond B, Katzenellenbogen BS, Krauthammer N, McConnell J. Estrogenic activity of the insecticide chlordecone (Kepone) and interaction with uterine estrogen receptor. Proc Natl Acad Sci USA 76:6641–6645 (1979).
39. Robinson AK, Mukku VT, Spalding DM, Stancel GM. The estrogenic activity of DDT: the in vitro induction of an estrogen-inducible protein by o,p'-DDT. Toxicol Appl Pharmacol 76:537–543 (1984).
40. Tullner FW. Uteroestrogenic action of the insecticide methoxychlor. Science 133:647–648 (1961).
41. Ecobichon DJ, MacKenzie DO. The
2,3,7,8-Tetrachlorodibenzo-p-dioxin inhibition of 17β-estradiol-induced increases in rat uterine EGF receptor binding activity and gene expression. Mol Cell Endocrinol 72:247–252 (1990).

57. Gallo MA, Hesse EJ, MacDonald GJ, Umbricht TH. Interactive effects of estradiol and 2,3,7,8-tetrachlorodibenzo-p-dioxin on hepatic cytochrome P-450 and mouse uterus. Toxicol Lett 32:123–132 (1986).

58. DeVito MJ, Thomas T, Martin E, Umbricht TH, Gallo MA. Anti-estrogenic action of 2,3,7,8-tetrachlorodibenzo-p-dioxin: tissue-specific regulation of estrogen receptor in CD1 mice. Toxicol Appl Pharmacol 113:284–292 (1992).

59. Gierthy JF, Lincoln DW, Gillespie MB, Seeger JI, Martinez HL, Dickerman HW, Kumar SA. Suppression of estrogen-regulated extracellular plasminogen activator activity of MCF-7 cells by 2,3,7,8-tetrachlorodibenzo-p-dioxin. Cancer Res 47:6198–6203 (1987).

60. Gierthy JF, Bennett JA, Bradley LM, Cutler DS. Correlation of in vitro and in vivo growth suppression of MCF-7 human breast cancer by 2,3,7,8-tetrachlorodibenzo-p-dioxin. Cancer Res 53:3149–3153 (1993).

61. Gierthy JF, Lincoln DW. Inhibition of post-confluent focus production in cultures of MCF-7 breast cancer cells by 2,3,7,8-tetrachlorodibenzo-p-dioxin. Breast Cancer Res 12:227–233 (1988).

62. Biegel L, Safe S. Effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) on cell growth and the secretion of the estrogen-induced 34-, 52- and 160-kDa proteins in human breast cancer cells. J Steroid Biochem Mol Biol 37:725–732 (1990).

63. Krishnan V, Wang X, Ramamurthy P, Safe S. Effect of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in formation of estrogen-induced ER/Sp1 complexes on the cathepsin D promoter. Toxicologist 14:47 (1994).

64. Harper N, Wang X, Liu H, Safe S. Inhibition of estrogen-induced progesterone receptor in MCF-7 human breast cancer cells by aryl hydrocarbon (Ah) receptor agonists. Mol Cell Endocrinol 104:47–55 (1994).

65. Zacharewski T, Bandy K, McDonell P, Wu ZF. Antiestrogenic effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin on 17β-estradiol-induced p52 expression. Cancer Res 54:2707–2713 (1994).

66. Holcomb M, Safe S. Inhibition of 7,12-dimethylbenz[a]anthracene-induced rat mammary tumor growth by 2,3,7,8-tetrachlorodibenzo-p-dioxin. Cancer Lett 82:43–47 (1994).

67. Kociba RJ, Keys KE, Beger JE, Carreon RM, Wade CE, Dittenber DA, Kalnis RP, Frauson LE, Park CL, Barnard SD, Hummel RA, Humiston CG. Results of a 2-year chronic toxicity and oncogenicity study of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in rats. Toxicol Appl Pharmacol 46:279–303 (1978).

68. Bertazzi PA, Pesatori AC, Consonni D, Tironi A, Landi MT, Zocchetti C. Cancer incidence in a population accidentally exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin. Epidemiology 4:398–406 (1993).

69. Chaloupka K, Krishnan V, Safe S. Polynuclear aromatic hydrocarbon carcinogens as antiestrogens in MCF-7 human breast cancer cells. Role of the Ah receptor. Carcinogenesis 13:2223–2239 (1992).

70. Tiwari RK, Guo L, Bradow HL, Telang NT, Osborne MP. Selective responsiveness of breast cancer cells to indole-3-carbinol, a chemopreventive agent. J Natl Cancer Inst 86:126–131 (1994).

71. Vaessen HAMG, Jekel AA, Wilbers AAMM. Dietary intake of polycyclic aromatic hydrocarbons. Toxicol Environ Chem 16:281–294 (1988).

72. Menzies CA, Potrocki BB, Santodonato S. Exposure to carcinogenic PAHs in the environment. Environ Sci Technol 26:1278–1284 (1992).

73. Stoewsand GS, Anderson JL, Munson L. Protective effect of dietary brussels sprouts against mammary carcinogenesis in Sprague-Dawley rats. Cancer Lett 39:199–207 (1988).

74. Markavitch BM, Roberts RR, Alejandro MA, Johnson GA, Middleditch BS, Clark JH. Bioflavonoid interaction with rat uterine type II binding sites and cell growth inhibition. J Steroid Biochem 30:71–78 (1987).

75. Mäkelä S, Davis VL, Tally WC, Korkman J, Salo L, Vihko R, Santti R, Korach KS. Dietary estrogens act through estrogen receptor-mediated processes and show no antiestrogenicity in cultured breast cancer cells. Environ Health Perspect 102:572–578 (1994).

76. Safe S. Polychlorinated biphenyls (PCBs), dibenzo-p-dioxins (PCDDs), dibenzo(p-dioxins) and related compounds: environmental and mechanistic considerations which support the development of toxic equitability factors (TEFs). CRC Crit Rev Toxicol 21:51–88 (1990).

77. Winter CK. Dietary pesticide risk assessment. Rev Environ Contam Toxicol 127:23–67 (1992).

78. Miksicek RJ. Commonly occurring plant flavonoids have estrogenic activity. Mol Endocrinol 44:37–43 (1993).

79. Liu H, Wormke M, Safe S, Bjeldanes LF. Indolo[3,2-b]carbazole: a dietary factor which exhibits both antiestrogenic and estrogenic activity. J Natl Cancer Inst 86:1758–1765 (1994).

80. Aldercreutz H, Markkanen H, Watanabe S. Plasma concentrations of phyto-oestrogens in Japanese men. Nature 342:1209–1210 (1990).

81. Bergman A, Klasson-Wehler E, Kuroki, H. Selective retention of hydroxylated PCB metabolites in blood. Environ Health Perspect 102:464–469 (1994).

82. Verma AK, Johnson JA, Gould MN, Tanner MA. Inhibition of 7,12-dimethylbenz(a)-anthracene- and N-nitrosomethylurea-induced rat mammary cancer by dietary flavonol quercetin. Cancer Res 48:5754–5758 (1988).

83. Messina MJ, Persky V, Sennell KDR, Barnes S. Soy intake and cancer risk: a review of the in vitro and in vivo data. Nutr Cancer 21:113–131 (1994).

84. Auger J, Kuntsmann JM, Czyglik F, Jouannet P. Decline in semen quality among fertile men in Paris during the past 20 years. N Engl J Med 332:281–285 (1990).