ENDOCRINE DISRUPTERS:

A Scientific Perspective

AMERICAN COUNCIL
ON SCIENCE AND HEALTH

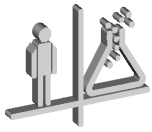
Endocrine Disrupters:
A Scientific Perspective

Prepared by
The American Council on Science and Health

Project Coordinator
Alicia Lukachko, M.P.H.

Art Director
Yelena Ponirovskaya

July 1999



AMERICAN COUNCIL ON SCIENCE AND HEALTH
1995 Broadway, 2nd Floor, New York, NY 10023-5860
Tel. (212) 362-7044 • Fax (212) 362-4919
URL: http://www.acsh.org • E-mail: acsh@acsh.org

ACSH GRATEFULLY ACKNOWLEDGES THE COMMENTS AND CONTRIBUTIONS OF THE FOLLOWING REVIEWERS

Joseph F. Borzelleca, Ph.D.
Virginia Commonwealth University

C. Jelleff Carr, Ph.D.
Regulatory Toxicology and Pharmacology

Donald G. Cochran, Ph.D.
Virginia Polytechnic Institute and State University

Ralph W. Fogleman, D.V.M.
Consultant in Toxicology and Regulatory Affairs

Arthur Furst, Sc.D., Ph.D.
University of San Francisco

Ronald E. Gots, M.D., Ph.D.
International Center for Toxicology and Medicine

Gordon W. Gribble, Ph.D.
Dartmouth College

Michael A. Kamrin, Ph.D.
Michigan State University

Ruth Kava, Ph.D., R.D.
American Council on Science and Health

Roger P. Maickel, Ph.D.
Purdue University

A. Alan Moghissi, Ph.D.
Institute for Regulatory Science

Gilbert Ross, M.D.
American Council on Science and Health

Stephen H. Safe, D.Phil.
Texas A&M University

Wallace I. Sampson, M.D.
Stanford University

Roy F. Spalding, Ph.D.
University of Nebraska

Robert A. Squire, D.V.M., Ph.D.

Martha Barnes Stone, Ph.D.
Colorado State University

Mark J. Utell, M.D.
University of Rochester Medical Center

Elizabeth M. Whelan, Sc.D., M.P.H., M.S.
American Council on Science and Health

James J. Worman, Ph.D.
Rochester Institute of Technology

ACSH would also like to thank Daland R. Juberg, Ph.D., for his work as technical consultant.

Table of Contents

Figures

Tables

Executive Summary

For years researchers have been investigating the hypothesis that trace levels of such industrial chemicals as pesticides, chlorinated compounds, and heavy metals are hazardous to human health. Although studies have failed to establish a causal relationship, some scientists and activist groups continue to emphasize the role of trace levels of synthetic chemicals in human illness. This continuing focus may be attributed, in part, to our increased ability to detect low levels of chemicals in the environment. It may also stem, however, from a collective—and often irrational—fear of such substances.

In this report the American Council on Science and Health (ACSH) explores the endocrine disrupter hypothesis, which asserts that certain (primarily man-made) chemicals act as, or interfere with, human hormones (specifically estrogens) in the body and thus cause a range of defects and diseases related to the endocrine system. This report also evaluates the possible implications of endocrine disrupters—more appropriately called "endocrine modulators"—for human health.

The following points are central to ACSH's analysis:

- High doses of some environmental contaminants have produced toxic effects in certain wildlife species. In some instances the effects appear to involve the endocrine system. Humans, however, have comparatively much lower exposures to these suspected endocrine modulators. This fact is crucial to assessing the potential risks, if any, associated with these substances.
- To date no consistent, convincing association has been made between exposures to synthetic chemicals in the environment and increased cancer in hormonally sensitive human tissues (breast and prostate tissues, for example). While a chemical may cause cancer in certain laboratory animals when given at high doses, it does not necessarily cause cancer in humans—who, as indicated above, have much lower exposures to synthetic environmental chemicals.
- Humans are exposed through their diet to estrogenic substances (substances having an effect similar to that of the human hormone estrogen) found in many plants. Dietary exposures to these plant estrogens (phytoestrogens) are presumably greater than are exposures to suspected synthetic endocrine modulators. No adverse health effects have been associated with the overwhelming majority of these dietary exposures.
- There currently is a trend in most environmental sectors (i.e. air, water, and soil) toward decreasing concentrations of many environmental contaminants, including several that are suspected of being endocrine disrupters.
- Some of the key research findings that propelled the endocrine dis-

rupter hypothesis have been retracted, are not reproducible, or have not been reproduced.
- The available human epidemiological data do not show any consistent, convincing evidence of increases in detrimental health effects related to industrial chemicals suspected of disrupting the endocrine system.

When examining the endocrine disrupter hypothesis, as with any other hypothesis, it is important to validate studies and novel findings before the media and others publicize them prematurely, exaggerate the evidence, and create undue alarm. Unfortunately, once irrational fears have been aroused, it becomes difficult to distinguish real risk from hypothetical risk.

The lack of quick results and definite answers can be frustrating, both to the public and to policymakers, who are often pressured by their constituents to impose the "precautionary principle": Act now and confirm the truth later. But we must proceed objectively, using sound scientific principles—or we will find ourselves misdirecting valuable public resources, both intellectual and financial.

Introduction

The term "endocrine disrupter" (with its associated negative connotation) has gained increased visibility as a public health issue. Some researchers and advocacy groups are concerned that exposures to trace amounts of certain man-made chemicals—those that mimic hormones—may disrupt normal physiological events involving the body's endocrine system and so result in negative health effects. More specifically, some authors now believe that exposures to these endocrine-modulating chemicals ("endocrine disrupters") can plausibly be linked to such effects as birth defects of the reproductive organs, reductions in sperm counts, and increased risk of breast, prostate, and testicular cancers.[1,2] The alleged sources of these endocrine-modulating substances range from certain plastics to pesticides.

The origins of the endocrine disrupter hypothesis can be traced to at least four notable events or reports:

- the appearance of reproductive cancers and defects in the daughters of women who had taken diethylstilbestrol (DES)—a drug prescribed in relatively large doses during the 1950s and 1960s to prevent miscarriage;
- a 1994 study that reported reproductive and other anomalies—including small phallus size, reduced hatching success, and poor survivorship—in alligators from Lake Apopka, Florida. This body of water was contaminated by a spill of the pesticide DDT (dichlorodiphenyltrichloroethane, banned from use in the United States in 1972)[3];

- a Danish study that reported a decrease in sperm counts in men from industrialized countries between 1938 and 1990[4,5]; and
- a 1996 study that contended that various combinations of environmental chemicals may act synergistically.[6]

Taken collectively, these and other reports have prompted some scientists to consider the endocrine disrupter hypothesis. While it is biologically plausible that exposures to potent estrogenic chemicals, such as DES, or very high exposures to weaker estrogenic chemicals, such as DDT, may result in toxic effects, no convincing evidence exists to support the contention that low concentrations of these estrogenlike substances cause abnormalities or disease, either in humans or in animals.

The issue of endocrine disruption—or, more accurately, of endocrine modulation—is important, if for no other reason than that it has generated public fear. Many scientists question both the credibility and the significance of the data that have been used to link human health risks to environmental levels of endocrine modulators.

While both natural and synthetic chemicals can act as hormones in the body, and while exposure to large amounts of these substances can cause adverse effects, some important questions remain: Can exposure to small concentrations of endocrine-active substances (substances capable of stimulating the endocrine system) result in adverse hormonal effects in humans? At what levels, if any, are humans exposed to endocrine modulators? If humans are, indeed, exposed to these substances, is this exposure sufficient to cause harm?

The Human Endocrine System

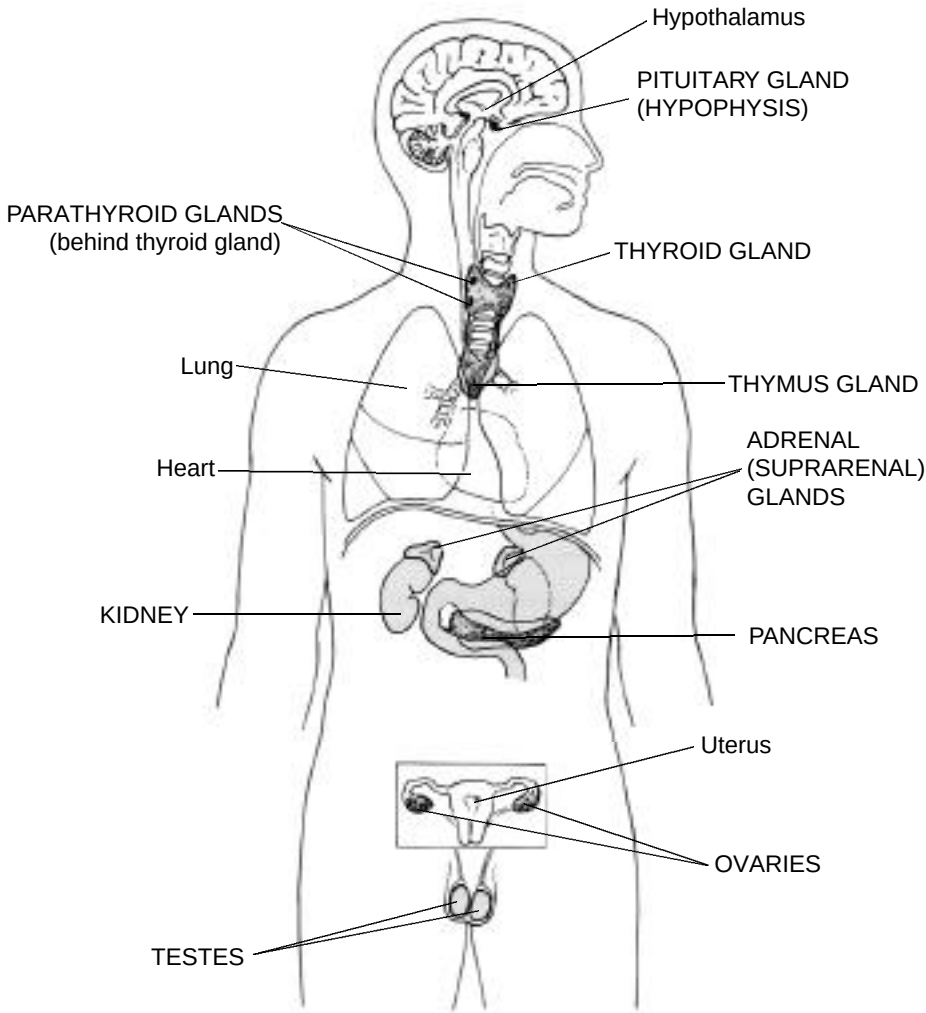
To understand the endocrine disrupter hypothesis, it is important, first, to understand the human endocrine system.* The endocrine system is one of the more complex systems in the human body. It is critical to normal growth, development, and physiological functioning and affects everything from skeletal growth to reproduction. The endocrine system is actually made up of a number of components—glands that include the adrenal cortex, the ovaries, the parathyroid, the pituitary gland, the testes and the thyroid (see Figure 1, page 8). These glands secrete hormones that activate receptors in tissues and organs throughout the body.

The endocrine system is one of the body's key communication networks. The endocrine system uses hormones as carriers of critical information. Hormones produced by endocrine glands throughout the body travel through the blood and influence the function of other organs.

* The human endocrine system comprises a number of systems. For the purposes of the present discussion, however, we will refer to these systems collectively as the "endocrine system."

Hormones affect human emotions as well as such processes as sperm production in men and the menstrual cycle in women. Estrogen, progesterone, and testosterone are some of the key hormones in the human endocrine system. The primary estrogen in the human body is 17b-estradiol. This hormone represents the standard by which "estrogen activity"—the ability of a substance to elicit estrogen's hormonal response—is measured.

FIGURE 1. THE HUMAN ENDOCRINE SYSTEM: SELECTED GLANDS AND ASSOCIATED STRUCTURES/ORGANS.*



* Adapted from Tortora GJ, Anagnostakos NP. *Principles of Anatomy and Physiology*. 5th ed. New York: Harper & Row, Publishers; 1987:398.

Hormones occur naturally in the human body, and they are essential to normal functioning. Too much of them can be harmful, however; an overabundance of unopposed estrogen, for example, can promote uterine tumors.

In addition to responding to human hormones, the human endocrine system also responds to a wide variety of external environmental stimuli and internal chemical signals. Exercise, pregnancy, malnutrition, and such pharmaceuticals as oral contraceptives and antithyroid medication can profoundly affect hormonal systems. Even seasonal changes of light and temperature can alter the body's endocrine system.

Some synthetic chemicals have been shown to influence the endocrine system. These so-called endocrine disrupters, however, are much less potent in terms of their ability to prompt a hormonal response than are naturally occurring estrogens. Because the human body is continually exposed to much higher concentrations of its own, stronger, hormones, the extent to which trace levels of chemicals in foods, other consumer products, and the environment can influence endocrine activity (if, indeed, they can at all) remains speculative. As we learn more about endocrine modulators, determining the relative potency of these substances in comparison to the standard human estrogen 17b-estradiol will continue to be critical.

What Is an Endocrine Disrupter?

The U.S. Environmental Protection Agency (EPA) defines an "endocrine disrupter" as "an exogenous agent [one originating outside the body] that interferes with the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body that are responsible for the maintenance of homeostasis, reproduction, development, and/or behavior."[7] The vagueness of this description reflects the uncertainty surrounding the specific mechanisms of endocrine modulation.

The term "endocrine disrupter" is often used interchangeably with the terms "environmental estrogen" and "endocrine modulator." There are subtle but important differences among the meanings of these three terms, however.

The term "endocrine disrupter" suggests that the effects of such substances are negative. But it is also conceivable that typical exposures to these hormonally active substances may lead to benign, or even beneficial, outcomes.

The term "environmental estrogens" is problematic. It omits the possibility that substances other than estrogen—that is, androgens (male hormones), anti-androgens, and anti-estrogens—may affect the endocrine system.

In light of these subtle but significant distinctions, the term "endocrine modulator" is a preferable description for such substances.

The initial concern over endocrine-modulating substances focused on

industrial chemicals, such as polychlorinated biphenyls, or PCBs (chemicals formerly used as coolants and lubricants in electrical equipment), and on the pesticide DDT. Many of these substances are no longer produced but may still be found at trace levels in the environment. Today, industrial chemicals are still being targeted, but the category of endocrine modulators has been broadened to encompass a variety of substances. These include phytoestrogens—the estrogenlike compounds found in plants—as well as pharmaceutical and therapeutic agents (see Table 1, below).

Researchers are also examining the effects of hormone residues, among them the residues associated with birth-control pills, that enter the environment from sewage treatment processes.[8] Endogenous estrogens (those such as 17b-estradiol that are produced naturally by the human body) resist degradation in the course of typical sewage treatment. Such estrogens may also appear in effluents as a result of human excretion.[9]

TABLE 1. A SAMPLING OF SUBSTANCES ASSOCIATED WITH ENDOCRINE-MODULATION POTENTIAL.

Industrial or Commercial Chemicals	Pesticides, Fungicides, Herbicides	Medical or Pharmaceutical Agents	Phytoestrogen-Containing Foods
PCBs	DDT	DES	cabbage
alkyl phenols and polyeth-oxylates	Methoxychlor	RU-486	soybeans
dibenzofurans and dioxins	Chlordecone	the “pill”	sprouts
Bisphenol A	Vinclozolin	estrogen replacement therapy	legumes
	Trifluralin	Tamoxifen	
	Parathion	testosterone-enhancing drugs	

Putting Things into Perspective

Aside from the exposure itself, perhaps the most important factors related to any exposure to a substance are potency and dose. These two factors are critical in any attempt to assess the potential risk of endocrine modulators.

"Potency" can be defined as the ability of a chemical to elicit a response (in this case, a hormonal response). The "dose" is the actual amount of the substance being received. These toxicological concepts are distinct, yet related. A high dose of weak substance "A," for example, may cause the same level of response, whether harmful or benign, as a low dose of the more potent substance "B." Received at equal doses, these two substances may yield significantly different levels of response. What differentiates substance "A" from substance "B" is relative potency.

Most environmental endocrine disrupters are very weak relative to 17b-estradiol, the primary human estrogen (see Table 2, page 12). Furthermore, human exposures to industrial chemicals, including those chemicals suspected of being endocrine disrupters, generally occur at very low doses.

The principles of potency and dose likely explain why some studies have shown deleterious effects in certain wildlife exposed to massive levels of such suspected endocrine modulators as DDT. The harmful effects seen in these cases may not have resulted from the mere existence of the chemicals involved but, rather, from the overwhelming doses that occurred.

Similarly, the chemical DES—a drug formerly prescribed to prevent miscarriage—is a potent estrogen. DES has many times the strength of endocrine modulators found in the environment. It is likely that this property of DES—its great potency—was a major factor in the detrimental effects associated with its use (see page 17).[10]

Chlorinated compounds such as PCBs and DDT have been the objects of much scientific study, perhaps because of their persistence in the environment. But while these substances are not easily broken down, either in the body or in the environment, their persistence alone does not signal harm—and they are not potent estrogens.

Assessing a chemical's potency relative to that of 17b-estradiol is crucial. This major human estrogen is very potent. The comparison of a chemical to 17b-estradiol therefore offers a good perspective on the chemical's possible risks to humans.

It is also important to compare such compounds to the many other types of hormonally active substances to which humans are exposed. For example, many natural phytoestrogens and estrogen supplements are more potent and are taken in higher doses than are man-made chemicals commonly encountered by humans in trace amounts. Some studies have suggested that phytoestrogens potentially play a role in preventing meno-

Table 2. RELATIVE POTENCIES OF SELECTED ESTROGENIC SUBSTANCES AS COMPARED WITH ESTRADIOL USING A YEAST-BASED ESTROGEN RECEPTOR ASSAY.*

Chemical	**Estrogenic Potency Ratio** ***(Ratio of the potency of the chemical to that of estradiol)***
Estradiol (the primary human estrogen)	1 *Represents the greatest estrogenic potency and the standard by which estrogen activity is measured*
DES (a drug previously prescribed to prevent miscarriage)	.64 (1/1.57) *DES is .6 times (slightly more than half) as potent as estradiol.*
Coumestrol (a phytoestrogen—an estrogenlike compound found in plants)	.01 (1/77.00) *Coumestrol is 77 times less potent than estradiol.*
p-Nonylphenol (a chemical used in certain plastics)	.0002 (1/5,000) *p-Nonylphenol is five thousand times less potent than estradiol.*
Bisphenol A (a chemical used in certain plastics)	.00007 (1/15,000) *Bisphenol A is fifteen thousand times less potent than estradiol.*
ß-Sitosterol (a natural plant chemical used as an anticholesterol agent)	.000004 (1/220,000) *ß-Sitosterol is two hundred and twenty thousand times less potent than estradiol.*
Methoxychlor (a pesticide)	.0000002 (1/5,000,000) *Methoxychlor is five million times less potent than estradiol.*
o,p´-DDT (a pesticide banned from use in the U.S. in 1970)	.0000001 (1/8,000,000) *DDT is eight million times less potent than estradiol.*
o,p´-DDE (a breakdown product of the pesticide DDT)	.00000004 (1/24,000,000) *DDE is twenty-four million times less potent than estradiol.*

* Adapted from Gaido KW, Leonard LS, Lovell S, et al. Evaluation of chemicals with endocrine modulating activity in a yeast-based steroid hormone receptor gene transcription assay. *Texicol Appl Pharmacol.* 1997b;143:205–212.

Interpreting Table 2

Humans are continually exposed to their own naturally produced estrogens, primarily one called estradiol. These estrogens, like other hormones, influence the human endocrine system and are essential to human functioning and good health. When assessing chemicals (i.e., so-called "endocrine disrupters") for their estrogenic potency or their ability to elicit a hormonal response similar to that of estrogen, it is helpful to compare them with the human estrogen estradiol. In this way, estradiol can be used as the standard by which estrogen activity or potency is measured.

In Table 2 the potency of selected chemicals with endocrine-modulating activity (as assessed by a yeast-based estrogen receptor assay) is compared with the potency of estradiol. As can be seen in the table, the chemicals suspected of disrupting the human endocrine system and thereby causing adverse health effects are many times less potent than the estrogens produced by the human body. Moreover, levels of human exposure to these endocrine-modulating chemicals are very low when compared with levels of exposure to estradiol.

pausal symptoms and in reducing the incidence of certain cancers of the breast, colon, prostate, rectum, and stomach.[11–19] There is not sufficient evidence to prove that these effects are associated with phytoestrogens, however.

Studies have also indicated that postmenopausal hormone replacement results in health benefits that extend beyond the treatment of menopausal symptoms such as hot flashes. Long-term hormone replacement therapy (HRT) has clearly been shown to prevent osteoporotic bone fractures in postmenopausal women. HRT has also been shown to have beneficial effects on cholesterol profiles, and it may also prevent heart disease in older women.[14]

These few examples serve to remind us of the myriad bodily responses that hormonally active substances may elicit.

Clearly, a wide range of effects, both positive and negative, are associated with hormonally active substances. Evidence has suggested that environmental chemicals may not only be acting as estrogens, but also as anti-estrogens, androgens, and anti-androgens.[20,21,22] Researchers thus must explore various mechanisms of action when evaluating endocrine modulation.

Evidence or Assumption: The Studies Behind the Hypothesis

Laboratory Research

The endocrine disrupter hypothesis gained momentum after laboratory tests using various types of cells showed that certain substances may have caused positive estrogenic responses in the systems in which they were tested. Scientists screened many compounds for their hormonal activity and their potency relative to 17b-estradiol. In 1997 researchers Gaido and associates reported a wide variation in the estrogenic strength of these compounds.[23] Chemicals such as DDT and the insecticide methoxychlor were found to be roughly one million times less potent than 17b-estradiol, the benchmark human estrogen.

The most potent synthetic estrogen, DES, has been studied extensively in a variety of laboratory tests. DES, as measured by a yeast-based estrogen receptor assay, is slightly more than half as potent as estradiol (see Table 2, page 12). The effects of DES on human and animal offspring exposed to the chemical *in utero* (in the womb) have been well characterized. Numerous rodent studies have demonstrated that sufficiently large doses of DES produce a spectrum of adverse effects in the offspring of exposed mothers. These effects include sperm abnormalities, infertility, and vaginal cancer.[24]

The class of chemicals known as PCBs has also been implicated as endocrine modulators. Laboratory tests have shown that a few PCBs appear to have a slight degree of estrogenic activity. Yet, in one study only one out of a series of PCB types showed estrogenlike effects at approximately 1 millionth the potency of the human estrogen 17b-estradiol.[25]

Other studies assessing PCB exposure in rats have reported effects on mating behavior, on menstrual cycling, and on reproductive success. The doses of PCBs that caused these effects were much higher, however, than concentrations of PCBs to which humans would be exposed from environmental sources.[26] In 1996 researchers Cooke and colleagues reported that certain types of PCBs may both inhibit and stimulate reproductive functions in laboratory rats, depending on whether the PCBs are administered in infancy or in adulthood.[27]

Studies in rats have compared the effect of 17b-estradiol to that of the synthetic chemical p-nonylphenol, another so-called endocrine disrupter.[28] Adverse reproductive changes appeared at relatively low doses—10 parts per million (ppm)—of estradiol, but a 1998 study by Cunny and associates reported that p-nonylphenol did not cause any estrogenic activity at dietary concentrations as high as 2,000 ppm.[29] All of these studies illustrate the importance of estrogen potency in the occurrence of adverse effects.

One of the more well-publicized laboratory research investigations on endocrine modulators came from Tulane University. In a 1996 study, a

group of Tulane researchers used a simple yeast estrogen assay to screen combinations of environmental estrogens for estrogenic potency.[6] The researchers reported that certain endocrine modulators, while weakly estrogenic on their own, were more than 1,000 times as potent when combined.

The synergistic effect reported by the Tulane researchers created considerable alarm. Yet, several laboratories failed to replicate this finding.[30–34] Even some of the original researchers could not duplicate their initial work. As a result, they formally retracted their study.[35] But despite this lack of evidence, this "synergism myth" still persists—and fuels many of the misperceptions about endocrine modulators that exist today.

Observations in Wildlife

The endocrine disrupter hypothesis was propelled further by several wildlife studies—particularly those involving high exposures to chemicals—that reported reproductive abnormalities in some species. In most such cases, however, the types and magnitude of the exposures are not known. It is therefore difficult to make useful comparisons to humans.

One widely cited wildlife report involved alligators in Lake Apopka, Florida. This lake had been contaminated by a nearby spill of DDT; and the resident alligators were found to have, among other adverse health effects, reduced hatching success, small phallus size, and shortened lifespans.[3] Researchers also reported that alligator eggs from Lake Apopka contained levels of DDT and DDE (a breakdown product of DDT) that were 5 to 8 times higher than the levels found in eggs taken from two reference sites elsewhere in Florida.[36]

While this highly contaminated site provided a good opportunity to study the possible relationship between synthetic chemicals and wildlife populations, the Lake Apopka observations must be interpreted within the context of dose. As mentioned above, the adverse effects noted in these animals likely resulted from toxic levels of chemical exposure. Lake Apopka is not representative of the vast majority of habitats elsewhere in the United States or in the world, and the status of ecosystem health should not be assessed and judged by this anomalous example.

The Great Lakes have received considerable attention from wildlife biologists and population ecologists because of these lakes'importance as a large freshwater resource and as a home to many aquatic and terrestrial species. A number of studies have examined the relationships between reproductive and developmental impairments in a variety of Great Lakes species and the industrial chemicals found in the lakes.[37–42] Evidence that specific industrial chemicals have caused negative effects in a few select species is, at best, weak.

In 1987 researchers Peakall and Fox reported on the decline of the reproductive capacity of herring gulls in the Great Lakes in the 1960s and early 1970s, a period during which chemical deposits were presumably at

their highest.[43] Peakall and Fox concluded that by the end of the 1970s the gulls'reproduction had returned to normal. Studies in the 1990s have reported a relationship between residues of dioxinlike substances and reproductive and developmental problems in several fish-eating bird populations in the Great Lakes region.[39,44]

Most current hypotheses linking reproductive and developmental effects in Great Lakes wildlife to endocrine disrupters come at a time when levels of contamination in the Great Lakes have declined significantly from the levels seen in previous decades.[45,46] A recent International Joint Commission (IJC) review of the Great Lakes Basin reported that environmental media—air, water, and soil—show decreasing levels of persistent toxic substances and that once-affected animal species have recovered significantly.[39,43,47] Two other comprehensive reviews have concluded that, by most measures, the health of the Great Lakes ecosystem has improved.[48,49]

Apparently, there is a threshold level of contamination below which various populations of animal species can thrive and prosper. For recovering species in the Great Lakes region, levels of environmental contaminants are evidently beneath the apparent threshold.

Runoffs from sewage treatment plants and pulp and paper mills have also been considered possible sources of endocrine modulators. Some scientists have reported, for example, that sewage treatment effluents lead to estrogenic effects in rainbow trout.[50]

Numerous chemicals have been suspected of being responsible for these effects, but some evidence indicates that the human hormones estrone and 17b-estradiol and breakdown products of the oral contraceptive pill that have passed through sewage treatment facilities may be causing endocrine-related effects in some fish populations.[51] The ecological significance of these effects is unclear, however, as some aquatic species—rainbow trout, for example—appear to exhibit a hormonal response while others, such as carp, do not.

Other scientists have linked pulp mill runoff to a range of developmental disorders in fish.[52,53,54] The effects resulting from such effluents (and the lethality of such effects) have been reduced by the use of treatment facilities at many mills, but various effects on fish reproduction persist.[54,55] Interestingly, these responses have been observed at mills regardless of the treatment of effluents or of the mills'use of chlorine to bleach pulp.[56,57] This suggests that the reproductive disorders may be caused by naturally produced organic compounds released from the wood during pulping rather than by chlorinated substances as first suspected.

Endocrine-related effects in wildlife are not a widespread phenomenon, but contaminated hotspots may affect certain species. While wildlife observations may raise questions about the potential effects in humans of endocrine modulators, the usefulness of wildlife observations as warning signals is limited. Differences in exposure and in susceptibility to environmental chemicals complicate extrapolations from wildlife to humans.

Human Associations

Some of the concern about the effects of endocrine modulators on humans began after adverse reproductive effects were associated with the use of the prescription drug DES. The observation of recent trends in hormonally related cancers (such as prostate cancer) and other hormonally sensitive events (sperm production, for example) have also been proposed by some as evidence of endocrine disruption.

Adverse Reproductive Effects of DES

During the 1950s and 1960s, diethylstilbestrol (DES)—a synthetic pharmaceutical—was available to women as a prescription drug for the prevention of miscarriage. Then, years after its introduction, DES was found to cause sexual deformities, sterility, and increased incidence of vaginal cancer in some of the daughters of women who had used the drug. [58–61]

Given the potency of DES as an estrogen (it is roughly equal in potency to 17b-estradiol), and the fact that DES was administered to women during pregnancy (and therefore during fetal development), DES may have specifically affected the reproductive and endocrine systems of the offspring of those women who took it. It is crucial to note, however, that both the potency of DES and the dosage at which it was prescribed were extremely high as compared to usual levels of endocrine-modulating chemicals to which humans may be exposed.

Declining Sperm Counts

A hypothesis that has received much attention links endocrine modulators to declining sperm counts. A 1992 Danish analysis of studies made on human semen between 1938 and 1991 found an overall decline of 50 percent in the sperm counts of men from industrialized countries.[4] This work prompted other investigators to speculate that the reported drop was caused by *in utero* exposure to chemicals with hormonal—that is, estrogenic—activity.[5] This notion was partly based on previous research that had demonstrated that *in utero* exposure to the highly potent estrogen DES (see above) could impair male sexual development.[61]

In recent years, however, both the Danish research and this hypothesis have lost some support. A number of recent reports have contradicted the assertions of declining semen quality.[62–65] One report indicates that the original Danish analysis was heavily influenced by reports from New York State. Without those reports, no significant decrease in sperm counts existed. Other reports revealed substantial geographical variation in sperm counts within the United States. One investigation of men in the Seattle area found no decline in semen quality over the past 21 years. So, despite some biological plausibility for tying sperm counts to endocrine-modulating chemicals, evidence does not support this link.

PCBs, DDT, and Breast Cancer

In 1992 researchers Falck and colleagues reported elevated levels of PCBs, DDT, and DDE in a group of 20 women with breast cancer when those women were compared with a control population of women with benign breast disease.[66] Then, in 1993, the New York University Women's Health Study examined another group of women and found an association between breast cancer and serum DDE but not between breast cancer and PCBs.[67] For many, these studies provided important evidence that the low levels of organochlorine residues suspected of "disrupting" the endocrine system increased the risk of breast cancer in women.

In 1994 some of the same investigators ran a follow-up study of 150 breast cancer patients and 150 controls (women without breast cancer). This time the researchers found that blood levels of organochlorine contaminants such as DDE and PCBs were not significantly elevated in the patients with breast cancer. The researchers concluded that "the data do not support the hypothesis that exposure to DDE and PCBs increases the risk of breast cancer."[68]

Epidemiological studies of women exposed to PCBs at work—presumably at levels higher than those they would have encountered from general environmental sources—have not shown an increased incidence of breast cancer.[69] Additionally, in a 1995 review of organochlorine compounds such as PCBs and DDT and their relationship to breast cancer, endometrial cancer, and endometriosis (overgrowth of the uterine lining), researchers Ahlborg and associates concluded that no such relationship could be "supported by the existing *in vitro*, animal, and epidemiological evidence."[70]

Thus, while early studies suggested that a link existed between organochlorine compounds and breast cancer, larger, more rigorous, and more recent studies have indicated that these compounds do not appear to be risk factors for breast cancer.[71]

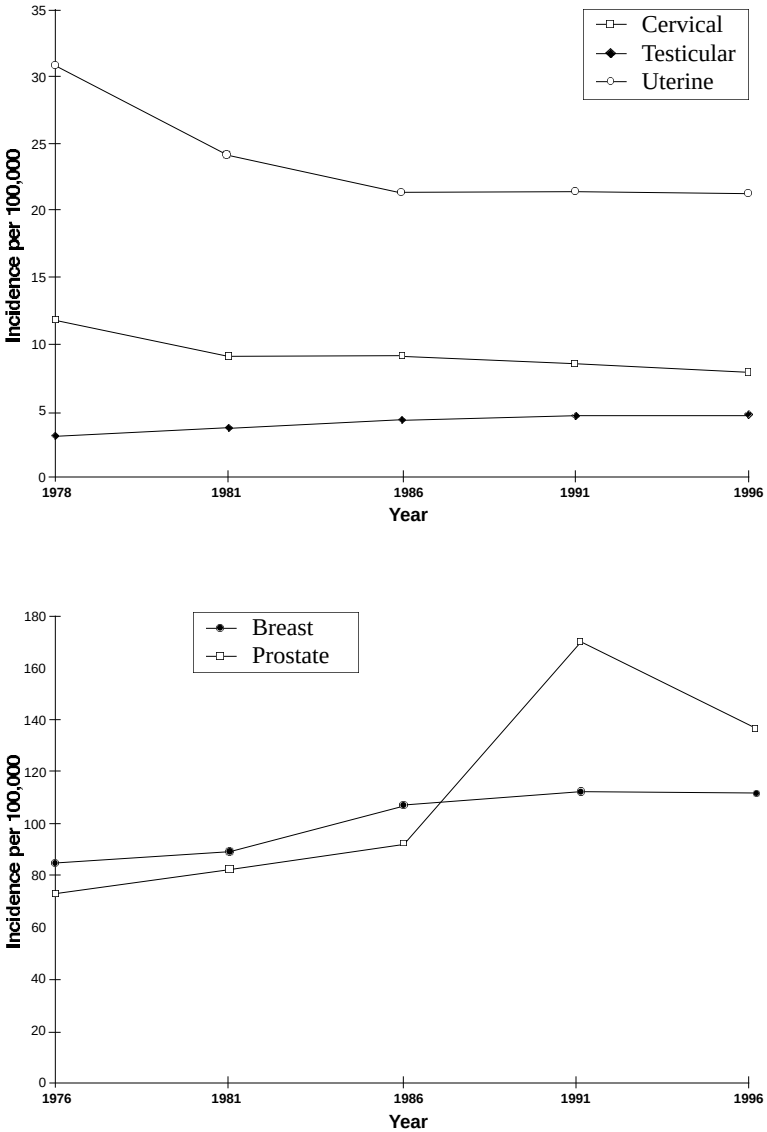
Considering the many known risk factors for breast cancer, the lack of a clear response for the disease to high doses of DES, and the continuing decline in exposures to environmental contaminants, it is unlikely that endocrine modulators are measurably influencing breast cancer rates.

Trends in Reproductive Cancers

Some scientists have tried to correlate the incidence of some reproductive cancers (see Figure 2, opposite) with exposures to endocrine modulators. When making such leaps, however, it is important first to assess whether the observed increase in disease is real.

An apparent rise in a particular disease may be the result of a specific agent. Such an apparent rise may also be due, however, to a change in the reporting or detection of the disease or to a study bias—meaning that the apparent rise is not a real rise at all. Even if a trend appears to be significant, many factors must be evaluated to determine the causes for the trend.

FIGURE 2. TRENDS IN INCIDENCE RATES OF BREAST, CERVICAL, PROSTATE, TESTICULAR, AND UTERINE CANCERS.*



* Adapted from Ries LAG, Kosary CL, Hankey BF, Miller BA, Edwards BK, eds. *SEER Cancer Statistics Review, 1973–1996.* Bethesda, MD: National Cancer Institute, National Institutes of Health; 1999.

These factors include changes in lifestyle risk factors such as diet and smoking, changes in sexual practices, changes in reproduction, and changes in environmental exposures. Accounting for all of these factors is often very difficult. In most cases the available evidence consists of crude correlations between trends and variable exposures to nonspecific environmental chemicals.

The incidence of testicular cancer has increased over the last 30 years.[72,73] Large differences in incidences and mortality, both in terms of geography and in terms of ethnic groups, have led some researchers to question the role that endocrine modulators might play.

The incidence of testicular cancer in white males in the United States is at least five times higher than the rate in black males.[74] But while the incidence in white males has been increasing, the trend in black males has remained neutral.

It is improbable that an environmental factor is selectively causing an increase in testicular cancer in white males. Furthermore, the rates for this disease began rising before the use of PCBs and DDT became widespread, a fact that lessens the probability of a direct effect from these chemicals. Thus, while the observed increased incidence rates are real, an association with exposure to particular environmental factors such as endocrine modulators remains to be established.[24]

A sharp increase in the incidence of prostate cancer in both black and white males in the United States occurred between 1989 and 1992.[75] This increase coincided very closely with the introduction of new diagnostic techniques, among them the Prostate Specific Antigen (PSA) and transurethral ultrasound (TRUS) tests. Diagnostic procedures therefore offer a likely explanation for the rise in reported prostate cancer incidence in the United States.[76,77]

Worldwide, the incidence of prostate cancer has generally increased; but adequate explanations for this rise—whether related to genetic, dietary, lifestyle, or environmental factors—have not surfaced.

There was a clear increase in the incidence of uterine cancer in white women in the 1970s—an increase that corresponded to the increasing use of estrogen therapy (ERT) to relieve symptoms of menopause. The addition of synthetic progesterone to estrogen therapy, however, has greatly reduced the associated risk of uterine cancer. Rates of uterine cancer have remained relatively stable over the past 10 years, and there is no evidence to suggest that endocrine modulators are contributing to the disease.

Both the incidence and the mortality rate of cervical cancer have been declining steadily in the United States since data collection began in 1973.[74] As with cancers of several other hormonally sensitive tissues, the argument that environmental contaminants acting as weak estrogens influence the incidence of cervical cancer is not supported. This is particularly evident when the downward trend in cervical cancer is considered.

In short, the epidemiological data on cancers of hormonally sensitive

tissues and the data on sperm counts in men do not provide consistent or convincing evidence of an effect associated with exposure to those chemicals accused of being "endocrine disrupters."

The EPA's Response to the Issue of Endocrine Modulators

In 1997 the Office of Prevention, Pesticides, and Toxic Substances of the U.S. Environmental Protection Agency (EPA) issued a *Special Report on Environmental Endocrine Disruption: An Effects Assessment and Analysis.* The report stated:

> The EPA is aware of and concerned about information indicating the possibility of adverse impacts on human health and the environment associated with exposure to endocrine disrupters. At the present time, however, there is little knowledge of, or agreement on the extent of the problem. Based on the current state of the science, the Agency does not consider endocrine disruption to be an adverse endpoint per se, but rather to be a mode or mechanism of action potentially leading to other outcomes, for example carcinogenic, reproductive or developmental effects, routinely considered in reaching regulatory decisions.[7]

The EPA had already established the Endocrine Disrupter Screening and Testing Advisory Committee (EDSTAC) in 1996 to provide advice in developing and implementing new screening and testing procedures for endocrine effects. Such screening and testing were mandated by the U.S. Congress in the Food Quality Protection Act of 1996.

The Endocrine Disrupter Screening Program (EDSP) was developed under the direction of the EPA to screen and test more than 86,000 chemicals. These chemicals include some of those listed in the Toxic Substances Control Act (TSCA) inventory, active pesticide ingredients, chemicals used in consumer products, naturally occurring estrogens, and ingredients in dietary supplements, cosmetics and food additives. The EDSTAC has also recommended that the EPA screen and test representative samples of contaminants in human breast milk, phytoestrogens in soy-based infant formula, mixtures of chemicals commonly found at hazardous waste sites, pesticide/fertilizer mixtures, disinfection by-products, and gasoline for potential estrogenic activity.

While the concerns prompting the initiation of the Endocrine Disrupter Screening Program are relatively new, testing for hormonal activity is not new to the field of toxicology. Traditional toxicology testing

detects adverse outcomes relating to the estrogen activity of given compounds.

The EPA's revised testing guidelines for reproductive and developmental effects of toxic substances and pesticides address potential endocrine effects.[78,79] The EPA has altered some of its risk-assessment guidelines to account for potential effects of endocrine modulation.[80,81,82] Thus, regulatory mechanisms in addition to EDSP are already in place to assess the potential hormonal activity of a substance.

The EDSP process involves the expensive testing of thousands of chemicals. The aims of the EDSP are to determine whether health risks may exist due to "endocrine-active" chemicals and, if it is established that such risks do exist, to ascertain which chemicals, substances, or mixtures are harmful. The role of the EDSP in human health risk assessment should be clearly understood, however.

The screening program administered through the EDSP is a potential hazard–identification step. It is not a human health risk assessment. The EDSP is designed to identify substances with some degree of endocrine-modulating activity. It is not designed to assess whether those substances pose a risk to human health, because the EDSP testing program does not measure human exposure to the substances. Unfortunately, a probable result of the EDSP is that any substance or chemical shown to be "positive" through the various tests administered under the EDSP will be labeled an "endocrine-active substance" and assumed to pose a danger, either to humans or to other organisms. Policymakers must therefore be made aware of the limited utility of the EDSP as they develop public policies relating to endocrine modulators.

Conclusion

Beyond the unique case of DES (formerly used as a drug at high doses during pregnancy), epidemiological data fail to support an association between exposure to environmental endocrine modulators and adverse effects in humans. While a number of pesticides, chlorinated compounds, and other environmental contaminants have been targeted as "endocrine disrupters" in humans, harmful effects have not been consistently observed. Nor, for that matter, have confounding variables been adequately addressed.

Before a causal relationship can be inferred, there must be biological plausibility, a known mechanism of action, and supporting evidence. But, quite simply, studies have not demonstrated that ambient low level exposures to environmental chemicals result in adverse health effects, either in wildlife or in humans.

Policies to protect ecosystems and policies to protect human health must be based on sound science and defensible data. Premature use of testing results or anecdotal case reports that ignore scientific principles may

lead policymakers to make decisions that satisfy the public's anxieties but that fail to address the major factors that potentially affect both wildlife and human populations.

To focus a disproportionate amount of our attention—and a disproportionate share of our often-scarce public health resources—on endocrine modulators, particularly to the exclusion of other potential hazards, does not best serve the public health needs of the United States. Rather, we would do well to remember these words from John Graham, the director of the Harvard Center for Risk Analysis: "Phantom risks and real risks compete not only for our resources but also for our attention. It's a shame when a mother is worried about toxic chemicals and yet her kids are running around unvaccinated and without bicycle helmets."[83]

References

1. Erice. Statement from the work session on environmental endocrine-disrupting chemicals: neural, endocrine, and behavioral effects. *Toxicol Indust Health.* 1998;14:1–8.

2. EHP. Statement from the work session on chemically-induced alterations in the developing immune system: the wildlife/human connection. *Environ Health Perspect.* 1996;104:807–808.

3. Guillette LJ Jr., Gross TS, Masson GR, Matter JM, Percival HF, Woodward AR. Developmental abnormalities of the gonad and abnormal sex hormone concentrations in juvenile alligators from contaminated and control lakes in Florida. *Env Health Perspect.* 1994;102:680–688.

4. Carlsen E, Giwercman A, Keiding N, Skakkebaek NE. Evidence for decreasing quality of semen during the last 50 years. *Brit Med J*. 1992;305:609–613.

5. Sharpe RM, Skakkebaek NE. Are œstrogens involved in falling sperm counts and disorders of the male reproductive tract? *Lancet.* 1993;341:1992.

6. Arnold SF, Klotz DM, Collins BM, Vonier PM, Guillette LJ Jr, McLachlan JA. Synergistic activation of estrogen receptor with combinations of environmental chemicals. *Science.* 1996;272:1489–1492.

7. Environmental Protection Agency. *Special Report on Environmental Endocrine Disruption: An Effects Assessment and Analysis.* 1997;EPA/630/R-96/012.

8. Arcand-Hoy LD, Nimrod AC, Benson WH. Endocrine-modulating substances in the environment: Estrogenic effects of pharmaceutical products. *Int J Toxicol.* 1998;17:139–158.

9. Desbrow C, Routledge EJ, Brighty GC, Sumpter JP, Waldock M. Identification of estrogenic chemicals in STW effluent. 1. Chemical fractionation and in vitro biological screening. *Environ Sci Technol.* 1998;32:1549–1565.

10. Safe SH. Environmental and dietary estrogens and human health—Is there a problem? *Environ Health Perspect.* 1995;103:346.

11. Barnes S, Peterson G, Grubbs C, Setchell K. Potential role of dietary isoflavones in the prevention of cancer. In: Jacobs, MM, ed. *Diet and Cancer: Markers, Prevention and Treatment.* New York: Plenum Press; 1994:135.

12. Barrett J. Phytoestrogens: friends or foes? *Environ Health Perspect.* 1996;104:478.

13. Hu J, Liu Y, Yu Y, Zao T, Liu S. Diet and cancer of the colon and rectum: a case-control study in China. *Int J Epidemiol.* 1991;20:362–367.

14. Kurzer MS, Xu X. Dietary phytoestrogens. *Ann Rev Nutr.* 1997;17:353–381.

15. Messina MJ, Persky V, Setchell KDR, Barnes S. Soy intake and cancer risk: a review of the *in vitro* and *in vivo* data. *Nutr Cancer.* 1994;21:113–131.

16. Murkies A. Phytoestrogens—what is the current knowledge? *Aust Fam Physician.* 1998;27:47–51.

17. Murkies AL, Wilcox G, Davis SR. Phytoestrogens. *J Clin Endocrin Metab.* 1998;83:297–303.

18. Waddell WJ. Epidemiological studies and effects of environmental estrogens. *Int J Toxicol.* 1998;17:173–191.

19. You WC, Blot WJ, Chang YS, Ershow AG, Yang ZT. Diet and high risk of stomach cancer in Shandong, China. *Cancer Res.* 1988;48:3518–3523.

20. Chapin RE, Stevens JT, Hughes CL, Kelce WR, Hess RA, Daston GP. Endocrine modulation of reproduction. *Fund Appl Toxicol.* 1996;29:1–17.

21. Safe SH, Gaido KW. Phytoestrogens and anthropogenic estrogenic compounds. *Env Toxicol Chem.* 1998;17:119–126.

22. Safe SH. Dietary and environmental estrogens and antiestrogens and their possible role in human disease. *Environ Sci Pollut Res.* 1994;1:29–33.

23. Gaido KW, Leonard LS, Lovell S, et al. Evaluation of chemicals with endocrine modulating activity in a yeast-based steroid hormone receptor gene transcription assay. *Toxicol Appl Pharmacol.* 1997b;143:205–212.

24. Golden RJ, Noller KL, Titus-Ernstoff L, et al. *Crit Rev Toxicol.* 1998;28:109–227.

25. Gellert RJ. Uterotrophic activity of polychlorinated biphenyls and induction of precocious reproductive aging in neonatally treated female rats. *Environ Res.* 1978;16:123.

26. Sager DB, Giraud DM. Long-term effects on reproductive parameters in female rats after translactational exposure to PCBs. *Environ Res.* 1994;66:52.

27. Cooke PS, Zhao YD, Hansen LG. Neonatal polychlorinated biphenyl treatment increases adult testis size and sperm production in the rat. *Toxicol Appl Pharmacol.* 1996;136:112–117.

28. Biegel LB, Flaws JA, Hirshfield AN, et al. 90-day feeding and one-generation reproduction study in Crl:CD BR rats with 17b-estradiol. *Tox Sciences.* 1998;44:116–142.

29. Cunny HC, Mayers BA, Rosica KA, Trutter JA, Van Miller JP. Subchronic toxicity (90-day) study with para-nonylphenol in rats. *Reg Pharmacol Toxicol.* 1998;26:107–115.

30. Ashby J, Lefevre PA, Odum J, Harris CA, Routledge EJ, Sumpter JP. Synergy between synthetic œstrogens? *Nature*. 1997;385:494.

31. Gaido KW, McDonnell DP, Korach KS, Safe SH. Estrogenic activity of chemical mixtures: Is there synergism. *CIIT Activities*. Vol. 17, No. 2, 1997a.

32. Ramamoorthy K, Wang F, Chen IC, et al. Estrogenic activity of a dieldrin/toxaphene mixture in the mouse uterus, MCF-7 human breast cancer cells, and yeast-based estrogen receptor assays: no apparent

synergism. *Endocrinology.* 1997a;138:1520–1527.

33. Ramamoorthy K, Wang F, Chen IC, et al. Potency of combined estrogenic pesticides. *Science.* 1997b;275:405–406.

34. Weise TE, Lambright CR, Kelce WR. Lack of synergistic estrogen effects of dieldrin and endosulfan mixtures on MCF-7 and MVLN cells. *Fundam Appl Toxicol.* 1997;36:294.

35. McLachlan JA. *Science* 1997;277(5325):462–463.

36. Heinz GH, Percival HF, Jennings ML. Contaminants in American alligator eggs from Lakes Apopka, Griffin, and Okeechobee, Florida. *Environ Monit Assess.* 1991;16:277–285.

37. Fox GA. Epidemiological and pathobiological evidence of contaminant-induced alterations in sexual development in free-living wildlife. In Colborn T, Clement, C, eds. *Chemically-Induced Alterations in Sexual and Functional Development: The Wildlife/Human Connection.* Princeton, NJ: Princeton Scientific Publishing Co., Inc. 1992;147–158.

38. Giesy JP, Newsted JD. Relationship between chlorinated hydrocarbon concentrations and rearing mortality of Chinook salmon (*Onchorhynchus tshawytscha*) eggs from Lake Michigan. *J Great Lakes Res.* 1986;12:82–98.

39. Giesy JP, Ludwig JP, Tillitt DE. Deformities in birds of the Great Lakes region: assigning causality. *Environ Sci Technol.* 1994;28:128A–135A.

40. Hornshaw TC, Aulerich RJ, Johnson HE. Feeding Great Lakes fish to mink: effects on mink and accumulation and elimination of PCBs by mink. *J Toxicol Environ Health.* 1983;11:933–946.

41. Nimi AJ. Biological and toxicological effects of environmental contaminants in fish and their eggs. *Can J Fish Aquat Sci.* 1983;40:306–312.

42. Wilford WA, Bergstedt RA, Berlin WH, et al. Chlorinated hydrocarbons as a factor in the reproduction and survival of lake trout (*Salvelinus namaycush*) in Lake Michigan. U.S. Dept. of the Interior. U.S. Fish and Wildlife Service. 1981; Tech. Paper No. 105.

43. Peakall DP, Fox G. Toxicological investigations of pollutant-related effects in Great Lakes gulls. *Environ Health Perspect.* 1987;71:187–193.

44. Gilbertson M, Kubiak T, Ludwig J, Fox G. Great Lakes embryo mortality, edema and deformities syndrome (GLEMEDS) in colonial fish-eating birds: similarity to chick edema disease. *J Toxicol Env Health.* 1991;33:455–520.

45. Daston GP, Gooch JW, Breslin WJ, et al. Environmental estrogens and reproductive health: A discussion of the human and environmental data. *Reprod Toxicol.* 1997;11:465–481.

46. Solomon KR. Endocrine-modulating substances in the environment: The wildlife connection. *Int J Toxicol.* 1998;17:159–172.

47. International Joint Commission. International Joint Commission Great Lakes Science Advisory Board's Workgroup on Ecosystem Health. Workshop on Environmental Results: Monitoring and Trends of Effects Caused by Persistent Toxic Substances, 1996.

48. SOLEC. State of the Great Lakes. Environment Canada/U.S. Environmental Protection Agency, 1995.

49. Health Canada. State of Knowledge Report on Environmental Contaminants and Human Health in the Great Lakes Basin, 1997.

50. Purdom CE, Hardiman PA, Bye VJ, Eno NC, Tyler CR, Sumpter JP. Estrogenic effects of effluents from sewage treatment works. *Chem Ecol.* 1994;8:275–285.

51. Matthiesen P, Desbrow C, Saldock M, et al. The identification of compounds causing endocrine disruption in fish in UK rivers. SETAC Meeting Abstract, Washington, DC. November, 1996.

52. Bortone SA, Davis WP. Fish intersexuality as indicator of environmental stress. *BioScience.* 1994;44:165–172.

53. Larsson A, Andersson T, Forlin L, Hardig J. Physiological disturbances in fish exposed to bleached kraft mill effluents. *Water Sci Technol.* 1988;20:67–76.

54. Munkittrick KR, McMaster ME, Port CB, Van der Kraak GJ, Smith IR, Dixon DG. Changes in maturity, plasma sex steroid levels, hepatic mixed function oxidase activity, and the presence of external lesions in lake whitefish (*Coregonus clupeaformis*) exposed to bleached kraft mill effluent. *Can J Fish Aquat Sci.* 1992;49:1560–1569.

55. Van der Kraak GJ, Munkittrick KR, McMaster ME, Portt CB, Chang

J. Exposure to bleached kraft pulp mill effluent disrupts the pituitary-gonadal axis of White Sucker at multiple sites. *Toxicol Appl Pharmacol.* 1992;115:224–233.

56. Munkittrick KR, Van der Kraak GJ, McMaster ME, Portt CB, Van den Heuval MR, Servos MR. Survey of receiving-water environmental impacts associated with discharges from pulp mills. 2. Gonad size, liver size, hepatic EROD activity, and plasma sex steroid levels in White Sucker. *Environ Toxicol Chem.* 1994;13:1089–1101.

57. Robinson RD, Carey JH, Solomon KR, Smith IR, Servos MR, Munkittrick KR. Survey of receiving water environmental impacts associated with discharge from pulp mills. I. Mill characteristics, receiving water chemical profiles and laboratory toxicity tests. *Environ Toxicol Chem.* 1994;13:1075–1088.

58. Gill WB, Schumacher FB, Bibbo M, Straus FH, Schoenberg HW. Association of diethylstilbesterol exposure *in utero* with cryptorchidism, testicular hypoplasia and semen abnormalities. *J Urol.* 1979;122:36–39.

59. Giusti RM, Iqamoto K, Hatch EE. Diethylstilbestrol revisited: A review of the long-term health effects. *Ann Intern Med.* 1995;122:778.

60. Herbst A, Ulfelder H, Poskanzer DC. Adenocarcinoma of the vagina. Association of maternal stilbesterol therapy with tumor appearance in young women. *N Engl J Med. 1971;284:878–881.*

61. Whitehead ED, Leiter E. Genital abnormalities and abnormal semen analysis in male patients exposed to diethylstilbestrol *in utero*. *J Urol.* 1981;125:47.

62. Fisch H, Goluboff ET. Geographic variations in sperm counts: a potential cause of bias in studies of semen quality. *Fertil Steril.* 1996;65:1044–1046.

63. Fisch H, Goluboff ET, Olson JH, Feldshuh J, Broder SJ, Barad DH. Semen analyses in 1283 men from the United States over a 25-year period: no decline in quality. *Fertil Steril.* 1996;65:1009–1014.

64. Paulsen CA, Berman NG, Wang C. Data from men in greater Seattle area reveals no downward trend in semen quality: further evidence that deterioration of semen quality is not geographically uniform. *Fertil Steril.* 1996;65:1015–1020.

65. Rasmussen PE, Erb K, Westergaard LG, Laursen SB. No evidence for decreasing semen quality in four birth cohorts of 1,055 Danish men born between 1950 and 1970. *Fertil Steril.* 1997;68:1059–1064.

66. Falck F Jr, Ricci A Jr, Wolff MS, Godbold J, Deckers P. Pesticides and polychlorinated biphenyl residues in human breast lipids and their relation to breast cancer. *Arch Environ Health.* 1992;47:143–146.

67. Wolff MS, Toniolo PG, Lee EW, Rivera M, Dubin N. Blood levels of organochlorine residues and risk of breast cancer. *JNCI.* 1993;85:648–652.

68. 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. *JNCI.* 1994;86:589–599.

69. Higginson J. DDT, epidemiological evidence. *IARC Scientific Publications.* 1985;65:107–117.

70. Ahlborg UG, Lipwirth L, Titusernstoff L, et al. Organochlorine compounds in relation to breast cancer, endometrial cancer, and endometriosis: as assessment of the biological and epidemiological evidence. *Crit Rev Toxicol.* 1995;25:463–531.

71. Hunter DJ, Hankinson SE, Laden F, et al. Plasma organochlorine levels and the risk of breast cancer. *N Engl J Med.* 1997;337:1253–1258.

72. Miller BA, Ries LAG, Hankey BF, et al., eds. Surveillance Epidemiology and End Results. *SEER Cancer Statistics Review: 1973–1990.* NIH Publication Number 93-2789. Bethesda, MD: National Cancer Institute, National Institutes of Health; 1993.

73. Swerdlow AJ. The epidemiology of testicular cancer. *Eur Urol Suppl.* 1993;23:35.

74. Kosary CL, Ries LAG, Miller BA, Hankey BF, Harras A, Edwards BK, eds. *SEER Cancer Statistics Review, 1973–1992: Tables and Graphs, National Cancer Institute.* NIH Publication Number 96-2789. Bethesda, MD: National Cancer Institute, National Institutes of Health; 1995.

75. American Cancer Society. Cancer Facts & Figures–1999. American Cancer Society; 1999.

76. Nomura AMY, Kalonel LN. Prostate cancer. A current perspective.

Epidemiol Rev. 1991;13:200–227.

77. Potosky AL, Miller BA, Albertsen PC, Kramer BS. The role of increasing detection in the rising incidence of prostate cancer. *JAMA.* 1995;273:548–552.

78. Environmental Protection Agency. Health Effects Test Guidelines; Preliminary Developmental Toxicity Screen. OPPTS870.3500 (40 CFR 798.4420). Washington, DC Office of Pollution Prevention Pesticides and Toxic Substances, 1996a.

79. Environmental Protection Agency. Health Effects Test Guidelines; Reproduction and Fertility Effects. OPTS870.3800 (40 CFR 791.4700). Washington, DC Office of Pollution Prevention Pesticides and Toxic Substances, 1996b.

80. Environmental Protection Agency. Guidelines for neurotoxicity toxicity risk assessment. *Fed Reg.* 1995;60:52032–52056.

81. Environmental Protection Agency. Proposed guidelines for carcinogen risk assessment. *Fed Reg.* 1996c;61:17959–18011.

82. Environmental Protection Agency. Guidelines for reproductive toxicity risk assessment. *Fed Reg.* 1996d;61:56271–56322.

83. Not So Fertile Ground. *Time*; September 19, 1994.

AMERICAN COUNCIL
ON SCIENCE AND HEALTH
1995 BROADWAY, 2ND FLOOR
NEW YORK, NY 10023-5860 USA