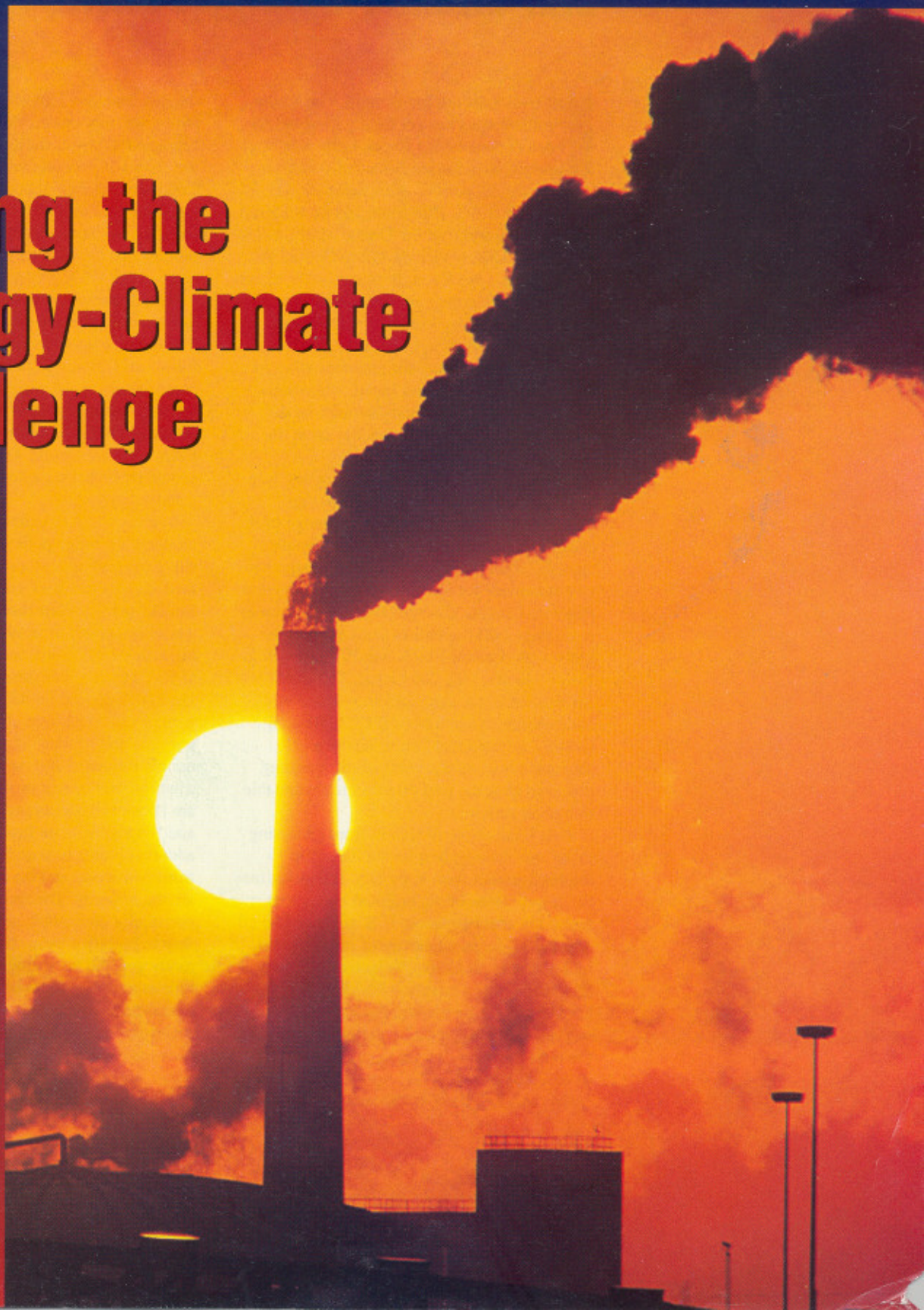
WHERE SCIENCE AND POLICY MEET

ENVIRONMENT®

June 2001
Volume 43 Number 5
$4.95 U.S.
$6.50 Canada

Facing the Energy-Climate Challenge



ALSO . . .

Endocrine disruptors: Research and policy responses

Germany's innovations for managing protected areas

0 74851 64645 8

ENVIRONMENT

VOLUME 43, NUMBER 5 JUNE 2001

ARTICLES

8 THE ENERGY-CLIMATE CHALLENGE: ISSUES FOR THE NEW U.S. ADMINISTRATION

by John P. Holdren

More than 75 percent of the world's energy supply comes from oil, coal, and natural gas. Recent evidence has strengthened our understanding of the link between fossil fuel use and global warming. How can we best address the challenges of climate change, given the importance of energy for economic prosperity?

22 HORMONE DISRUPTORS: A CLUE TO UNDERSTANDING THE ENVIRONMENTAL CAUSES OF DISEASE

by Sheldon Krimsky

Increasing evidence that certain chemicals—called hormone or endocrine disruptors—are the cause of developmental and reproductive abnormalities in humans and animals offers clues about the possible chemical causes of disorders for which the etiologies have been poorly understood. The challenge before scientists and policy makers is to ensure the protection of human health given the best available data, including its uncertainties.

32 RECONCILING OPPOSITION TO PROTECTED AREAS MANAGEMENT IN EUROPE: THE GERMAN EXPERIENCE

by Susanne Stoll-Kleemann

European countries, including Germany, have experienced opposition to the designation of protected areas from local populations, thus thwarting the efforts of nature conservation agencies. Germany and other countries can learn from development cooperation agencies that have successfully implemented biodiversity initiatives in developing countries using participatory or inclusive measures.

ABOUT THE COVER

The combustion of fossil fuels for electricity and transportation drives the world economy. Plans to curb carbon dioxide emissions to slow global warming are complicated by the potential economic impacts.

DEPARTMENTS

2 CONTRIBUTORS

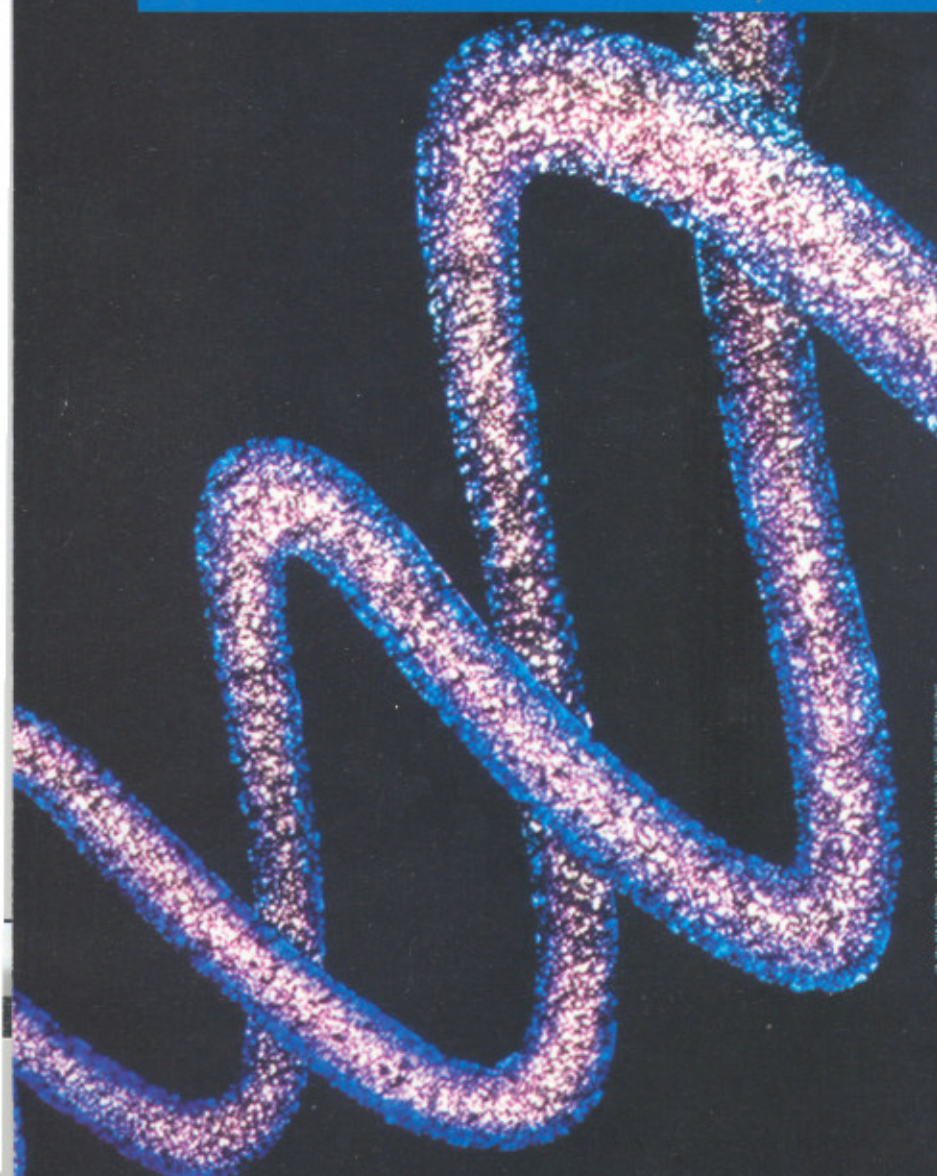
3 BYTES OF NOTE

4 SPECTRUM

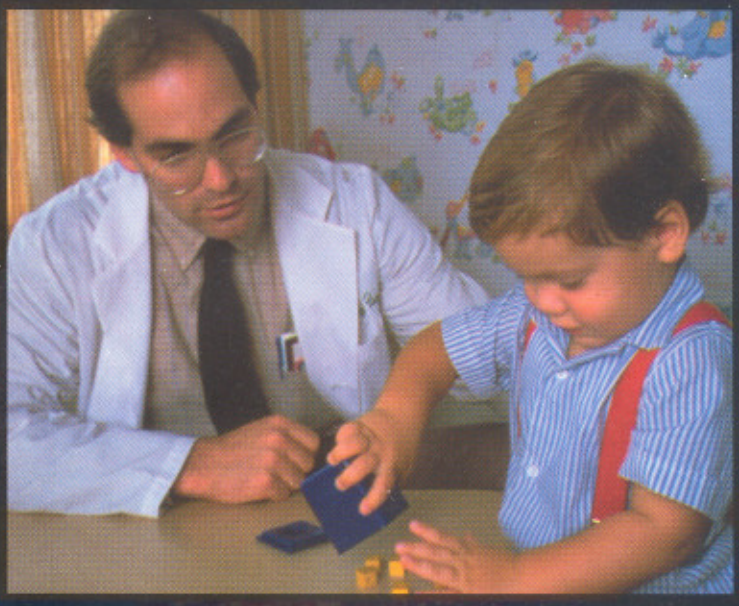
45 BOOKS OF NOTE

Hormone Disruptors
A Clue to Understanding the Environmental Cause

by Sheldon Krimsky



s of Disease



An increasing body of evidence indicates that certain chemicals in the environment—known as hormone or endocrine disruptors—cause developmental and reproductive abnormalities in humans and animals. Studies of wildlife show associations between hormone-disrupting chemicals in the environment and declining populations, thinning eggshells, morphologic abnormalities, and impaired viability of offspring. Scientists also have postulated a relationship between these chemicals and abnormalities and diseases in humans, including declining sperm counts; breast, testicular, and prostate cancers; and neurological disorders, including cognitive and neurobehavioral effects. While continuing to learn about the effects and interactions these chemicals have on humans and wildlife, scientists recently began working with policy makers to develop a testing program and identify chemicals that require further regulation.

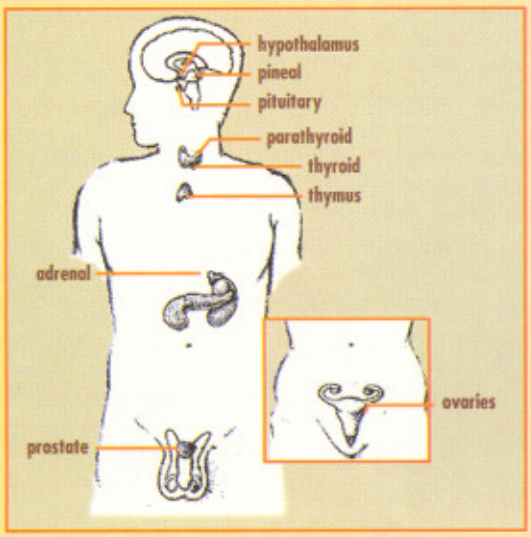
One individual in particular has helped to amass and interpret the scientific evidence on endocrine disruptors, thereby stimulating the interest in and funding for endocrine disruptor research that continues today. Her name is Theo Colborn.

Last year, Colborn, a senior scientist at the World Wildlife Fund (WWF) in Washington, DC, received one of the most honored environmental awards—the Blue Planet Prize—an award established by Japan's Asahi Glass Foundation at the 1992 Earth Summit in Rio de Janeiro. The foundation recognized Colborn for her "systematic research that certain types of chemical compounds pose a danger as disruptors of endocrine systems to the development, function, survival, and reproduction of wild organisms and people."[1] Colborn is credited for her synthesis of scientific evidence and her facilitation of multidisciplinary symposia that have focused the attention of many scientists and policy makers worldwide on the potential effects of scores of agricultural and industrial chemicals on the body's endocrine system (see the box below).

Through her careful study of the patterns of wildlife abnormalities in the Great Lakes, Colborn found that some diseases associated with high levels of chemical pollutants, resulting in mortality and gross birth defects, abated after the first generation of pollution controls were established.[2] Furthermore, her astute investigations into the scientific literature revealed patterns of a second category of diseases affecting wildlife offspring. Colborn hypothesized that these diseases arose because certain chemicals interfere with the delicate and intricate signaling pathways of organisms that are particularly vulnerable during fetal development. The brain and reproductive organs, as well as sperm- and egg-producing cells, depend on a proper balance of hormonal signals for their normal development. If the developing fetus is exposed to a cocktail of industrial chemicals which, singly or in combination, interfere with the functions of the body's natural hormones, developmental and reproductive abnormalities can occur. According to some laboratory studies on animals, observable effects of an endocrine-disrupting chemical on fetal development are detectable at concentrations as low as parts per trillion.

The Endocrine System

The endocrine system is one of the two main regulatory systems of animals and humans; the other is the nervous system. In humans, the endocrine system is comprised of a group of glands—the pituitary, thyroid, parathyroid, adrenal, thymus, hypothalamus, pineal, pancreas, ovaries (female), and testes (male)—that secrete hormones through the bloodstream to all parts of the body (see the endocrine system diagram in this box). The hormones act as chemical messengers that control growth, development, and reproduction and maintain the body's delicate energy balance.



SOURCE: Image courtesy of The Why Files (http://www.whyfiles.org). © University of Wisconsin-Madison, Board of Regents.

A Chemical with a Clue

While Colborn was researching the patterns and etiology of disease in wildlife in the Great Lakes during the late 1980s, scientists already had identified a chemical that provided important clues about the way a substance foreign to an organism (a xenobiotic) interferes with the body's natural signaling pathways. The chemical is a drug called diethylstilbestrol, or DES, as it is commonly known. Synthesized in 1938, DES was the first in a new generation of synthetic hormones prescribed to promote healthy pregnancies; slow the growth of tall, pre-adolescent girls; and ameliorate post-menopausal problems. In 1971, medical researchers published evidence that DES administered to seven pregnant women was associated with a rare form of vaginal cancer in their young adult daughters.[3] This synthetic estrogen did not harm the mothers who took the drug, but most likely affected cells in the developing fetus that caused the cancer in their daughters several decades later.

DES was not a typical pharmaceutical. Not only was it widely used in clinical practice, it also was approved for use as a growth promoter in cows and poultry. The cattle industry continued its use of DES until 1979, when the courts finally upheld the regulatory ban of the veterinary drug in animals used for human consumption.[4]


© WORLD WILDLIFE FUND

Theo Colborn received the Blue Planet Prize in 2000 for her research on the effects of endocrine-disrupting chemicals. She is a senior scientist at the World Wildlife Fund in Washington, DC.

As a result of the well-documented cases of human disease caused by DES, funding became available to study how this synthetic estrogen could affect the developing fetus. John McLachlan, then chief of the Laboratory of Reproductive and Developmental Toxicology at the National Institute of Environmental Health Sciences, showed that the effects of DES on mice could be used as a model to explain how other chemicals, such as the insecticide 1,1,1-trichloro-2,2-*bis*-(p-chlorophenyl)ethane (also known as dichlorodiphenyltrichloroethane or DDT), can interfere with the body's normal hormone signaling system. McLachlan organized a series of scientific meetings, beginning in 1979 and continuing through the 1980s and 1990s, that explored the subject of environmental estrogens, particularly the estrogenic properties of selected agricultural and industrial chemicals and the molecular mechanisms through which chemical agents induce hormonal effects.

Bringing It All Together

In 1991, Colborn, in collaboration with John Peterson Myers, director of the W. Alton Jones Foundation, which is based in Charlottesville, Virginia, organized a conference that brought together wildlife biologists, human toxicologists, and endocrinologists to share their knowledge about the hormonal effects of environmental chemicals. They dubbed the meeting the "Wingspread Work Session," named after its location at the Wingspread Conference Center in Racine, Wisconsin. This watershed gathering brought the issues surrounding endocrine-disrupting chemicals to the attention of scientists. Wildlife biologists displayed the data they had amassed on reproductive and developmental abnormalities of birds and marine species and the links to environmental toxicants. McLachlan shared the progress he and his colleagues had made toward understanding the biochemical and genetic mechanisms through which chemicals can interfere with or mimic estrogen in the body. McLachlan recently had returned from a meeting in Europe at which Danish scientists postulated a link between in utero chemical exposure and sperm abnormalities in humans. Therefore, he was able to share with work session participants information on two of the three research paths that eventually converged into a single framework for explaining the hormonal effects of environmental chemicals. These independent research programs include the study of the relationship between fetal exposure to DES and transgenerational carcinogenesis; wildlife reproductive and developmental abnormalities; and male reproductive problems, including sperm count decline, testicular cancer, and hypospadia (abnormal urethral openings in newborn human males).

The 1991 work session—the first of six scientific meetings during the 1990s that focused on endocrine disruptors—resulted in a published proceedings of scientific papers and a consensus statement that outlined the state of knowledge on hormone disruptors as understood by 21 signatories (see the box on this page).

The 1991 work session consensus statement,[5] a part of which reads, "We estimate with confidence that . . . experimental results are being seen at the low end of current environmental conditions," has been further supported by recently published research in the March 2001 issue of *Environmental Health Perspectives*.[6] The study indicates that the doses at which arsenic may increase cancer through its endocrine-disrupting effects are lower than the doses found to cause DNA damage and mutation. These findings suggest that the hormone-disrupting effects of chemicals may be a more sensitive indicator of their potential harm to humans and fetuses than traditional animal carcinogen studies and cell mutagen studies.

Defining "Endocrine Disruptor"

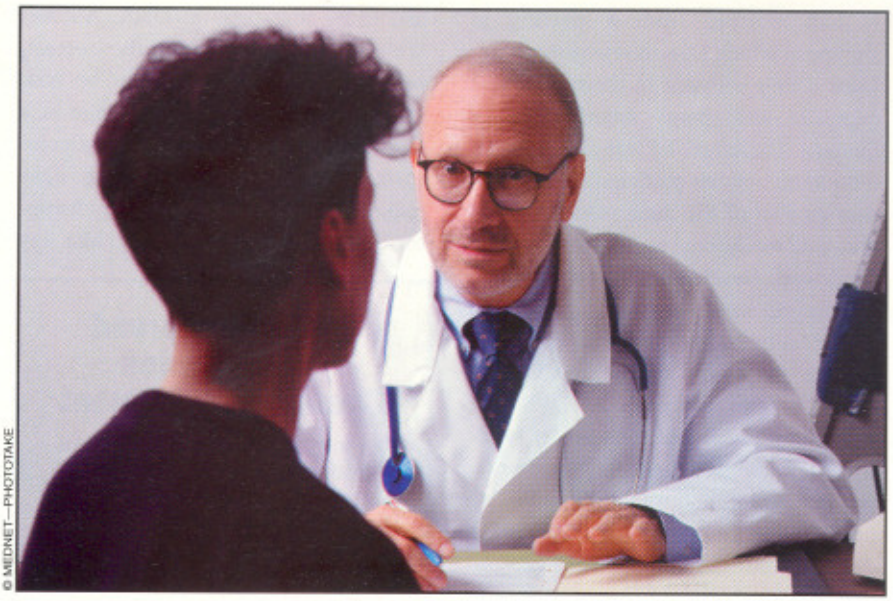
The image that many people have of toxic chemicals is that they destroy cells and organs, impair the immune system, and cause mutations in DNA. Another widely held, and generally correct, belief is that a chemical can be hazardous at a high dose and benign at a low dose, often described by toxicologists with the aphorism, "the dose makes the poison." Endocrine disruptors, however, do not behave like any

1991 Wingspread Work Session Consensus Statement

Twenty-one of the scientists participating in the 1991 Wingspread Work Session drafted and signed a statement that describes what was known about endocrine disruptors at the time. The consensus statement is part of the work session published proceedings, *Chemically-Induced Alterations in Sexual Development: The Wildlife/Human Connection*, which is a compilation of scientific papers presented. The text that follows is taken from the consensus statement.

We are certain of the following: A large number of man-made chemicals that have been released into the environment, as well as a few natural ones, have the potential to disrupt the endocrine system of animals, including humans. Among these are the persistent, bioaccumulative, organohalogen compounds that include some pesticides (fungicides, herbicides, and insecticides) and industrial chemicals, other chemical products, and some metals. . . . (1) The chemicals of concern may have entirely different effects on the embryo, fetus, or perinatal organism than on the adult; (2) the effects are most often manifested in offspring, not in the exposed parent; (3) the timing of exposure in the developing organism is crucial in determining its character and future potential; and (4) although critical exposure occurs during embryonic development, obvious manifestations may not occur until maturity.[1]

1. T. Colborn and C. Clement, eds., *Chemically-Induced Alterations in Sexual and Functional Development: The Wildlife/Human Connection* (Princeton, N.J.: Princeton Scientific Publishing Co., Inc., 1992), 1–8.



© MEDNET—PHOTOTAKE

Last year, the U.S. Centers for Disease Control reported widespread phthalate contamination in the U.S. population, particularly in women of childbearing age. Phthalates, identified as endocrine disruptors, are used in chlorine-based plastics, perfumes, nail polishes, and hair sprays.

garden-variety chemical. These are compounds that can trick the organism's body into believing that they are supposed to play a role in the body's functions. To use an analogy, one can foul up a computer's operation by physically damaging the hardware or by releasing a computer virus that fools the computer's software into thinking the virus belongs there. Endocrine disruptors, like computer viruses, engage with the body's mechanism for regulating growth and development, while sabotaging its normal functions.

For example, the body's natural hormones send chemical messages to cells that result in the production of protein. The surface and inside of cells contain receptor molecules that bind to the body's natural hormones and transmit the hormone's instructions to the cell's DNA. It is now understood that foreign chemicals can bind to the receptor molecules dedicated to one of the body's hormone messengers, either mimicking or obstructing the role of the natural hormones. The foreign chemical and the natural hormone may both bind to the receptor molecules, but they do not function equivalently in the body.

There are also other ways that foreign chemicals can interfere with hormone-signaling pathways that do not involve receptor molecules. As one study notes, "Some [endocrine disruptors] relay molecular messages through a complex array of cellular proteins, hormone and nonhormone response elements that indirectly turn genes on and alter cell growth and division."[7] Thus, no single mechanism can completely describe the patterns of interference of these chemicals, which complicates the effort to discover cause-effect relationships.

Currently, scientists cannot use chemical structure to predict with any degree of certainty which chemicals will interfere with an organism's endocrine system. Therefore, chemicals have to be tested to evaluate their endocrine effects on the organism. To define an endocrine disruptor as "any chemical that may interfere with the normal function of the hormonal systems of humans and animals" is too imprecise for a hazard assessment. A foreign substance may exhibit hormone-like activity in one species, but not in others, and it may affect, but not interfere with, the body's normal function. Further, as stated in a 1999 U.S. National Academy of Sciences (NAS) panel report, "A single chemical can have multiple effects on an organism that act through several mechanisms, not all of which involve hormone receptors."[8]

Because of this uncertainty, defining an "endocrine disruptor" has become a politicized issue. Some scientists object to the terms "hormone disruptor" and "endocrine disruptor," because these terms imply that chemicals that may play a role in hormonal pathways also cause an adverse effect. There are natural plant estrogens (phytoestrogens) that are hormonally active but are not known to cause adverse effects in normal adults. To preserve the distinction between chemicals that interact with hormone receptors or other hormone-mediated pathways and chemicals that cause adverse physiological effects on an organism, NAS chose the term "hormonally active agents" or HAAs. This term refers to substances that interact with the body's hormone systems, regardless of whether they are linked to a disease or abnormality. What evidence exists that HAAs or endocrine disruptors cause adverse effects? The evidence is generally categorized into four types: wildlife, laboratory animals, human cells and tissue, and human epidemiological studies.[9]

Wildlife Evidence

A significant body of field and laboratory studies confirm that wildlife exposure to certain chemicals has produced reproductive and developmental abnormalities. When certain organisms, such as mollusks, were exposed to marine antifouling paints—usually containing tributyl tin (TBT)—the organisms were observed to have a condition called "imposex," in which the females develop male sexual organs. It is believed that TBT interferes with the biosynthesis of sex steroid hormones (hormones produced by the testes and ovaries, such as estrogens, progestins, and androgens).

Other cases of imposex were discovered in the United Kingdom among certain river fish living in the vicinity of sewage treatment plants. The effluents

© HOWARD BUFFETT

Scientists are working to determine the normal hormone ratios—the relative levels of testosterone and estrogen—in cougars to help understand why the ratios in the closely related and endangered Florida panther appear to be highly abnormal. Other research indicates that alligator numbers are decreasing in Florida lakes contaminated with hormonally active pesticides.

© STEVEN MORELLO

from the treatment plants suspected of causing these developmental pathologies were found to be comprised of synthetic estrogenic substances, such as nonylphenol (a by-product of detergents) and ethinylestradiol (the main ingredient of the contraceptive pill), as well as natural estradiol from human wastes.

Alligator populations are declining in Florida lakes contaminated with hormonally active pesticides, such as DDT, dicofol, and toxaphene. Genital abnormalities and low egg production have been observed in these alligators. These pesticides or their breakdown products (metabolites) are known to reduce plasma testosterone (a male hormone and one of the androgens) levels in alligators and are considered antiandrogenic. For example, DDT breaks down to a chemical called 1,1-dichloro-2,2-*bis*-(p-chlorophenyl)ethylene or DDE, which has been shown to be a powerful antiandrogen.

Environmental pollutants also have been linked to effects on the reproductive health of several species of birds in the Great Lakes regions and the skewed sex ratios of western gull populations.[10] For more than 40 years, wildlife toxicologists have known that DDT, through its active metabolite DDE, was responsible for eggshell thinning of avian species.

The primary evidence of the effects of endocrine-disrupting chemicals on wildlife is not disputed, although there is still much uncertainty about the mechanisms and dose-responses of the agents in specific species. According to the NAS panel study,

Reported reproductive disorders in wildlife have included morphologic abnormalities, eggshell thinning, population declines, impaired viability of offspring, altered hormone concentrations and changes in sociosexual behavior. . . . Many wildlife studies show associations between reproductive and developmental defects and exposure to environmental contaminants, some of which are HAAs.[11]

The human evidence used in support of the theory that certain chemicals can cause developmental and reproductive abnormalities in organisms has been much more controversial, in regard to the interpretation of evidence and the policy responses to that evidence.

Human Evidence

Many human diseases have unknown etiologies. These include most breast, prostate, and ovarian cancers; infertility; many thyroid-related abnormalities; hypospadia; and abnormal testicular development. Some developmental abnormalities are caused by disruption to the endocrine system or are mediated by hormonal messages. The endocrine disruptor framework, according to which foreign chemicals can interfere with the body's natural hormones, offers a new approach for investigating possible chemical causes or contributing factors of reproductive disorders and developmental abnormalities for which the etiologies remain poorly understood.

Scientists have postulated a link between endocrine-disrupting chemicals and three areas of human abnormalities and diseases in published studies of sperm count declines, cancer (mainly breast, testicular, and prostate), and neurological disorders, including cognitive and neurobehavioral effects.

During the past 50 years, there appears to be an overall downward trend in the density and quality of human sperm within major industrialized regions of the world. Because the patterns are not consistent within each region, some scientists dispute the conclusion that endocrine-disrupting chemicals are the cause of declining sperm counts. Among those who believe this human sperm decline thesis, one of the postulated causes is in utero chemical exposures. Supporting evidence for the

hypothesis can be found in animal studies. For example, the adult offspring of rodents subjected to a single neonatal exposure to traces of dioxins or polychlorinated biphenyls (PCBs) experienced reduced semen quality.[12] In 1996, 19 scientists coauthored a lengthy scientific review titled, "Male Reproductive Health and Xenoestrogens," published in the journal *Environmental Health Perspectives*, in which they stated,

[S]everal aspects of male reproductive health have changed dramatically for the worse over 30–50 years. The most fundamental change has been the striking decline in the ejaculate of normal men. . . . The result is that many otherwise normal men now have sperm counts so low that their fertility is likely to be impaired.[13]

For many reproductive toxicologists, the link between endocrine disruptors and sperm abnormalities in humans remains a working hypothesis with supporting evidence from laboratory studies of animals.

There is ample reason to suspect xenobiotic estrogens as a primary or contributing cause of cancer. Estrogens are known to activate the growth of certain classes of cancer cells. Women with a longer lifetime exposure to estrogens (who experience early menarche and later menopause) are at a higher risk for breast cancer. On the other hand, women who have had their ovaries removed, significantly lowering their production of estrogen, are at a reduced risk of breast cancer, with the lowest risk in those who had the procedure as children.

A series of epidemiological studies conducted on women with breast cancer has not found a consistent link between levels of suspected agents (organochlorines in breast tissue and blood serum, for example) and the risk of breast cancer. One of the largest and best designed of these studies shows no association.[14] Linking endocrine-disrupting chemicals to breast cancer is complicated by many confounding factors. Women who breast-feed their children mobilize the toxic chemicals that have taken residence in their body and transfer them to their infant. This makes it difficult to get an accurate measure of the amount and the timing of a woman's exposure to endocrine disruptors, because measurements of chemical residues taken after breast-feeding may underestimate the woman's actual exposure. The hypothesis that endocrine-disrupting chemicals may cause breast cancer is further complicated because there may be a long latency period between the exposure of cells to endocrine-disrupting chemicals and the development of cancer decades later. Further, many of the studies testing the link between endocrine disruptors and breast cancer have focused on DDE, which is not estrogenic, and PCBs, the most persistent of which are antiestrogenic. Thus, these studies have not examined the link between purely estrogenic compounds and breast cancer, which would provide a more plausible hypothesis. These complex factors in measurement make the link between endocrine disruptors and breast cancer in the human population a difficult hypothesis to test. Ongoing studies in communities with elevated breast cancer rates, such as Cape Cod, Massachusetts, and Long Island, New York, are still exploring the possible connection between environmental estrogens and cancer.

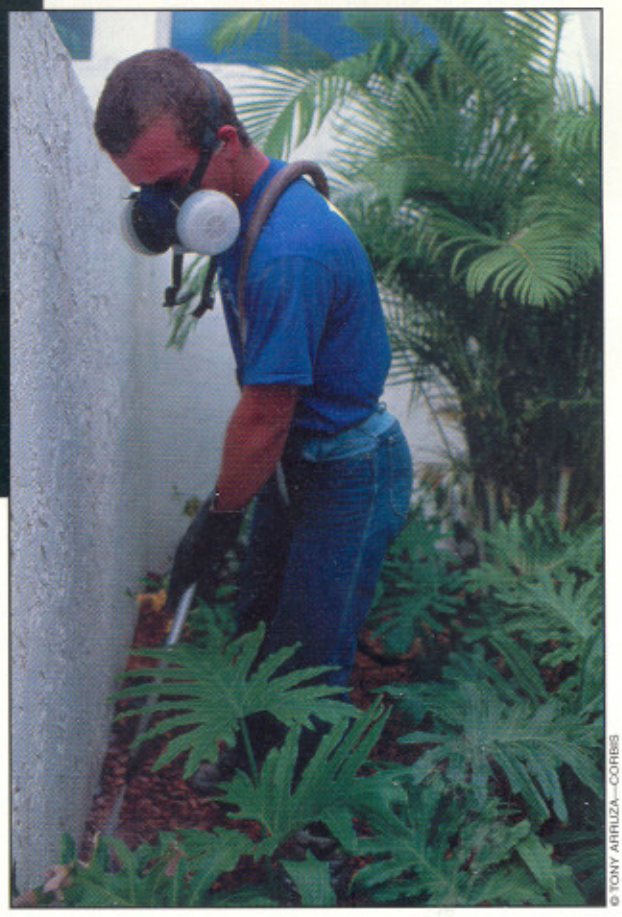
The strongest evidence linking non-occupational exposure of endocrine-disrupting chemicals with adverse human health consequences exists in the areas of neurobehavioral and neurodevelopmental effects. Most of the evidence for these effects comes from studies of three groups of halogenated compounds including PCBs, polychlorinated dibenzo-p-dioxins (PCDDs or dioxins), and polychlorinated dibenzofurans (PCDFs). Several studies included children with high in utero PCB exposure from mothers who ate two to three fish meals a month (26 pounds over 6 years) of Great Lakes fish. These children exhibited a variety of neurological and neurodevelopmental abnormalities, including significantly poorer performances on intelligence tests and delayed neuromuscular development compared to children with lower exposures. Infants breast-fed with milk that contained elevated levels of dioxins and PCBs showed signs of thyroid disturbances. Thyroid hormones play an important role in prenatal brain growth, and even small changes at critical times during the first trimester of pregnancy can result in impairments in cognitive development.

In its 1999 panel report, NAS provided a cautious review of the subject, stating,

In humans, results of cognitive and neurobehavioral studies of mother-infant cohorts accidentally exposed to high concentrations of PCBs and PCDFs and of mother-infant cohorts eating contaminated fish and other food products containing mixtures of PCBs, dioxin, and pesticides, such as DDE, dieldrin, and lindane, provide evidence that prenatal exposure to those HAAs can affect the developing nervous system.[15]

Phthalates, a class of compounds found in many types of chlorine-based plastics, have also been identified as endocrine disruptors. Used as softening agents in plastic, phthalates typically are not tightly bound to the resin and can leach out of food packaging or medical devices. One of the most widely used phthalates, di-(2-ethylhexyl)phthalate (DEHP), has been linked to reproductive abnormalities in women who have been occupationally exposed; it also has been shown to depress hormone levels, including estradiol, in test animals. In September 2000, the U.S. Centers for Disease Control (CDC) reported widespread phthalate contamination among people in the United States, with the highest contamination in women of childbearing age. CDC suggests that perfumes and cosmetics may be the source of contamination. Several phthalate compounds are used as the volatile components of perfumes, nail polishes, and hair sprays.[16]

The published science suggests that there is solid evidence that some chemical agents in sufficient concentrations will affect human reproduction through hormone-mediated mechanisms. The debates over whether there is an observable human effect at lower concentrations center around the substance, dose,



© TONY ARRUZA—CORBIS

Bald eagles that have migrated to the Great Lakes often breed well at first but become less successful as lake contaminants—DDE and PCBs—accumulate in their bodies and impair their fertility. As part of a program to evaluate the hazard potential of endocrine-disrupting chemicals, the U.S. Environmental Protection Agency has targeted 15,000 high-volume chemicals for testing, including commercial chemicals, environmental contaminants, and pesticides, such as those sprayed here in a garden in Palm Beach, Florida.

and age of development at the time of exposure. Because test animals metabolize phthalates differently than humans and most human exposures are from traces in food, cosmetics, and medical devices, some policy makers are hesitant to use animal studies as a basis for regulating most human exposure. A paradox for setting policy exists because the data most relevant to humans at common exposures are weak, and the most definitive data are irrelevant to humans. Human data are obtained directly from unusual cases of high exposures or indirectly from epidemiological studies. The relevance of using the best animal data to evaluate human risks, even at doses approximating human exposure, is questionable because of species dissimilarities. The challenge for policy making is to find a path between the best available data, with their uncertainties, and the protection of human health.

Current Policies and Programs

In 1996, the U.S. Congress passed the Food Quality Protection Act (FQPA), the new pesticide law, which represents a long sought after compromise between business groups and environmentalists.[17] FQPA granted the business community its wish to insure that the 1958 Delaney clause of the Food and Drug Amendments would not apply to pesticide residues on food. The Delaney clause had prohibited the use of any additive in processed food shown to be carcinogenic at any dose in animals or humans. However, it was not applied to carcinogenic pesticide residues in processed foods that came from the pesticides sprayed on crops. In recent years, in response to a lawsuit filed by the Natural Resources Defense Council, the courts overturned the practice of not applying the Delaney clause to carcinogenic pesticide residues from crops in processed foods. That decision threatened pesticide manufacturers, large agricultural businesses, and processed food manufacturers, whose products would be in violation of the Delaney clause even if they contained minute quantities of pesticides carcinogenic in test animals at high doses.

As a compromise, FQPA eliminated the Delaney clause for pesticide residues but requires higher safety standards for evaluating pesticide health risks and gives more consideration to exposed children. FQPA requires the U.S. Environmental Protection Agency (EPA) to take into account infants' and children's potentially greater exposure and sensitivity to pesticide residues and provide an additional tenfold safety factor in tolerance limits to ensure levels that are safe for infants and children.

During the debates over FQPA, now former Senator Alphonse D'Amato (R-NY), prompted by Long Island breast cancer activists, introduced a hormone disruptor amendment to the bill, which mandated that EPA test agricultural and industrial chemicals for their potential endocrine-disrupting effects. FQPA required EPA to complete its plan for this testing by 1998 and to begin implementing testing by 1999. Congress also

amended the Safe Drinking Water Act (SDWA) in 1996, giving EPA the authority to conduct testing for estrogenic or other substances found in drinking water for which a "substantial population may be exposed."[18]

Although SDWA and FQPA address the human health aspects of endocrine disruptors, the Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC)—an EPA committee of scientists and stakeholders—recommended, and EPA approved, a policy to consider the human and wildlife effects of endocrine-disrupting chemicals. This policy gave rise to EPA's Endocrine Disruptor Screening Program, which is a program designed to identify and evaluate the hazard potential of endocrine-disrupting chemicals. Beginning with an inventory of about 87,000 chemicals in current use, EDSTAC established a priority target of 15,000 high-volume chemicals for screening and testing, including pesticides, commercial chemicals, and environmental contaminants. After EPA validates the assay and testing protocols, industry will conduct much of the chemical testing.

EPA submitted its screening and testing plan to Congress in August 1998 and a year later reported to Congress that implementation had begun on the development of standardized and validated tests. Many of the tests are still on the drawing boards, and until the in vitro assays and animal tests have been approved by the agency, companies will not begin to test chemical substances or submit data to EPA.

The testing program was recently challenged by People for the Ethical Treatment of Animals (PETA), an animal advocacy group opposed to the use of animals for testing chemicals. Largely in response to the PETA campaign, EPA received more than 50,000 post cards objecting to the use of animals for its endocrine disruptor testing program. The agency, meanwhile, is committed to minimizing the number of animals used in the program and to using alternative methods when available.

PETA's legal challenges and the stringent federal requirements for obligating money and selecting groups of contractees to carry out different components of the screening and testing validation studies have slowed the progress of implementation. In contrast to the broad mandate of EDSTAC, which deliberated from 1996 through 1998 and set the general principles for a screening and testing program, the validation studies will concentrate on focused technical issues such as standardization, consistency, reliability, and replicability of tests in different laboratories, as well as dose-response relationships and measurement protocols.

Challenges to the Testing Program

U.S. legislation on endocrine disruptors is directed solely at developing and implementing this new screening and testing program. If a chemical tests positively as an endocrine disruptor, the legislation offers no mandated responses on the part of a regulatory agency. Further, the battery of tests done under the screening program will be vulnerable to all sorts of criticisms. For example, critics could argue that animal and human endocrine systems will respond differently to xenobiotics. Also, inevitably there will be some inconsistencies in the data. A chemical may test positively for endocrine effects in some tests and negatively in others. A substance also may show up as a weak estrogen mimic in one species and as a stronger one in another. EPA will compare foreign chemicals exhibiting estrogen-like effects to natural human and plant estrogens to examine how the chemicals are metabolized and the physiological responses the chemicals induce. Policy makers will have to decide which tests are most salient for understanding potential human and ecological risks.

Two chemicals in combination may produce twice or more than twice the estrogenic effects of either one, and under FQPA, EPA must take into account the additive, cumulative, and synergistic effects of endocrine disruptors. However, because humans are typically exposed to cocktails of chemicals, it will be a formidable task to test chemicals in combinations. Testing even two at a time from the group of 15,000 may exceed the program's capacity.

EPA has targeted 15 tests for standardization and validation and expects these tests will be operational by 2005, a timetable that some insiders view as overly optimistic. The screening program's tests include the use of rodent assays, for which conducting a single mammalian test can take 2–3 years. Moreover, any regulatory action against the use of a highly profitable chemical likely will be contested by litigation, resulting in long regulatory delays. One study reported that approximately 60 percent of the herbicides (by weight) used in the United States are endocrine disruptors.[19] However, the history of chemical regulations indicates that it may take years before suspect substances are prohibited for commercial use. DDT, lead, mercury, DES, and ethylene dibromide (EDB) are just a few of the chemicals that remained in commercial use years after the evidence of their hazards were known by scientists and after regulatory actions began.

A New Regulatory Approach

When EPA completes the process of standardizing and validating the tests, many political and value judgments will come into play. Among the decisions to be made are the amount of evidence that will trigger a regulatory action against a chemical, how potency factors and species effects will be used to determine acceptable levels, whether chemicals already in use will be subject to weaker regulations, and whether EPA will follow the historical tradition of regulating one chemical at a time.

The snail's pace of pesticide testing was eloquently expressed by former congressman Mike Synar (D-OK) at a 1993 hearing. He said, "Almost 20,000 pesticide products have been under review since 1972 and only 31 have been reregistered. At this rate, it will take us to the year 15,520 AD to complete. I believe in flexibility. I believe in good

science. What I don't believe in is geological time."[20]

Whether our system of production will be weaned from endocrine-disrupting chemicals will depend, in part, on how many such chemicals are discovered, the availability of substitutes at reasonable costs, whether the evidence of human and ecological effects grows and shows consistent patterns, and whether the regulatory bodies are given stronger mandates to act. The regulation of toxic substances has been dominated by the search for cancer-causing chemicals. The endocrine-disruption theory of disease and developmental abnormalities offers a new framework requiring greater subtlety in testing that introduces new challenges in assessing additive and interactive effects of chemicals. Moreover, policymaking is further complicated by the recent scientific consensus that estrogenic chemicals can cause biological effects at very low doses that have long been considered safe. Thus far, the policy requirements have outpaced the science, and the science is outpacing regulatory actions.

A precautionary approach (also known as the precautionary principle) requires that society take bold steps to accelerate the identification of problematic endocrine-disrupting chemicals and to remove them from the environment, even while scientists and policy makers are filling in the knowledge gaps. This approach was highlighted in a recent report issued by the Royal Society of the United Kingdom, which states, "Regulation cannot be put on hold until all the evidence has been collected."[21] The precautionary approach was framed during the Second International Conference on the Protection of the North Sea in 1987, where agreement was reached to control a group of suspect chemicals even before a definitive causal link had been established between the chemicals and human health or environmental effects.

According to this principle, strong circumstantial, but scientifically inconclusive, evidence can justify policy responses if the consequences of not acting represent unacceptable risks: the mistake of overregulating a "safe chemical" is of secondary moral significance to the mistake of approving or continuing the use of a potentially dangerous chemical. EPA's current response to endocrine-disrupting chemicals is a first step toward a precautionary approach.

In her commemorative lecture for the Blue Planet Prize, Theo Colborn called for a change in the way nations of the world manage industrial chemicals, imploring, "Are we going to wait until every child is affected? . . . The individual costs and societal costs are just too high not to change the system."[22]

Sheldon Krimsky is professor of urban and environmental policy at Tufts University and author of *Hormonal Chaos: The Scientific and Social Origins of the Environmental Endocrine Hypothesis* (Baltimore, Md.: Johns Hopkins University Press, 2000). His research focuses on the science behind and social management of endocrine disruptors. Krimsky can be contacted at sheldon.krimsky@tufts.edu.

NOTES

1. The Asahi Glass Foundation, "2000 Blue Planet Prize: Announcement of Award Winners," accessed via http://www.af-info.or.jp/eng/whatnew/hot/enr20001.html on 8 February 2001.

2. T. Colborn et al., *Great Lakes, Great Legacy?* (Washington, D.C.: Conservation Foundation, 1990), xxii.

3. A. L. Herbst, H. Ulfelder, and D. C. Poskanzer, "Adenocarcinoma of the Vagina: Association of Maternal Stilbestrol Therapy with Tumor Appearance in Young Women," *New England Journal of Medicine* 284 (1971): 878–81.

4. D. Cottrell, "The Price of Beef," *Environment* 13 (1971): 44–51.

5. T. Colborn and C. Clement, eds., *Chemically-Induced Alterations in Sexual and Functional Development: The Wildlife/Human Connection* (Princeton, N.J.: Princeton Scientific Publishing Co., Inc., 1992), 1–8.

6. R. C. Kaltreider, A. M. Davis, J. P. Lariviere, and J. W. Hamilton, "Arsenic Alters the Function of the Glucocorticoid Receptor as a Transcription Factor," *Environmental Health Perspectives* 109, no. 3 (2001): 245–51.

7. S. C. Sikka and R. K. Naz, "Endocrine Disruptors and Sexual Dysfunction," in R. K. Naz, ed., *Endocrine Disruptors: Effects on Male and Female Reproductive Systems* (Boca Raton, Fla.: CRC Press, 1999), 301.

8. Committee on Hormonally Active Agents in the Environment, National Research Council, National Academy of Sciences (NAS), *Hormonally Active Agents in the Environment* (Washington, D.C.: National Academy Press, 1999), 21.

9. Extensive reports containing information on the wildlife and human epidemiological evidence of endocrine disruptors include T. E. Colborn, D. Dumanoski, and J. P. Meyers, *Our Stolen Future* (New York: Dutton, 1996); Sikka and Naz, note 7 above; NAS, note 8 above; T. Schettler, G. Solomon, M. Valenti, and A. Huddle, *Generations at Risk* (Cambridge, Mass.: The MIT Press, 1999); and R. Rolland, M. Gilbertson, and R. B. Peterson, eds., *Chemically Induced Alterations in the Development and Reproduction of Fishes* (Pensacola, Fla.: SETAC Press, 1997).

10. Colborn et al., note 2 above; and D. M. Fry, C. K. Toone, S. M. Speich, and R. J. Peard, "Sex Ratio Skew and Breeding Patterns of Gulls: Demographic and Toxicological Considerations," *Studies in Avian Biology* 10 (1987): 26–43.

11. NAS, note 8 above, pages 119 and 168.

12. C. Rönnbäck, "Effects of 3,3',4,4'-Tetrachlorobiphenyl (TCB) on Ovaries of Foetal Mice," *Pharmacology and Toxicology* 69 (1991): 340–5; and L. E. Gray Jr. and J. S. Ostby, "In Utero 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) Alters Reproductive Morphology and Function in Female Rat Offspring," *Toxicology and Applied Pharmacology* 133 (1987): 285–94.

13. J. Toppari et al., "Male Reproductive Health and Environmental Xenoestrogens," *Environmental Health Perspectives* 104, suppl. 4 (1996): 741–76.

14. D. J. Hunter et al., "Plasma Organochlorine Levels and the Risk of Breast Cancer," *New England Journal of Medicine* 337 (1997): 1253–8.

15. NAS, note 8 above, page 5.

16. B. C. Blount et al., "Levels of Seven Urinary Phthalate Metabolites in a Human Reference Population," *Environmental Health Perspectives* 108, no. 10 (2000): 979–82.

17. *Food Quality Protection Act of 1996*. H.R. 1627, P.L. 104–70.

18. *Amendments to the Safe Drinking Water Act of 1996*. S. 1316, P.L. 104–82.

19. P. Short and T. Colborn, "Pesticide Use in the U.S. and Policy Implications: A Focus on Herbicides," *Toxicology and Industrial Health* 15 (1999): 240–75.

20. S. Krimsky, *Hormonal Chaos* (Baltimore, Md.: Johns Hopkins University Press, 2000), 61.

21. The Royal Society, *Endocrine Disrupting Chemicals* (June 2000), iii, accessed via http://www.royalsoc.ac.uk/policy/index.html on 29 December 2000 (see "Reports and Statements").

22. The Asahi Glass Foundation, "Blue Planet Prize 2000 Commemorative Lectures," accessed via http://www.af-info.or.jp/eng/honor/2000lect/2000lect-e.html on 8 February 2001.

For more information on endocrine disruptors, visit the following web sites:

http://www.ourstolenfuture.org
http://www.som.tulane.edu/ecme/eehome
http://www.epa.gov/scipoly/oscpendo
http://www.worldwildlife.org/toxics/progareas/ed/index.htm