Environmental Estrogens Stir Debate

In the wake of sensational media coverage, many toxicologists are questioning reports that estrogenlike compounds could be a threat to human reproductive health

Talk about an attention-grabber: "Sperm counts down? Penises shriveled? Hey, Rush, don't blame it on feminists. It may be from chemical pollutants in water and food." So proclaimed *Newsweek*, one of several national publications that earlier this year raised the specter of pollutants possibly damaging the reproductive systems of humans and wildlife. The basis for these news stories was a string of research findings in the past few years linking estrogenlike compounds in the environment to events as diverse as a worldwide drop in human sperm counts, a decline in the number of alligators born in a Florida lake, and feminized suckerfish in Lake Superior. And it's not just males who were said to be at risk. One widely publicized study, for example, found increased rates of breast cancer among women exposed to estrogenlike pesticides such as DDT.

Staying focused. Stephen Safe says risks to humans from environmental estrogens have been greatly exaggerated.

The rash of publicity certainly caught the attention of Texas A and M University toxicologist Stephen Safe. In March, during a keynote speech at the Society of Toxicology's annual meeting in Dallas, Safe blasted the media and his colleagues for hyping the potential risks to humans from dozens of synthetic chemicals that modulate the sex hormones estrogen and testosterone. "This has been blown way out of proportion," fumes Safe, who has spent his career studying dioxins and PCBs—two families of hormone-modulating pollutants.

Safe isn't the only one with doubts. Two widely publicized studies suggesting a link between hormone-modulating pollutants and human health risk have recently wilted under the glare of scientific scrutiny. One of these studies tied a global decline in sperm counts to pollutants that mimic estrogen, but the timing of the decline is being challenged (see box on p. 309). In the other study, a team led by Mary Wolff of Mount Sinai Hospital in New York linked breast cancer to high levels of DDE, a breakdown product of the estrogenic pesticide DDT, but in April, a research team led by Nancy Krieger of the Kaiser Foundation Research Institute in Oakland, California, failed to confirm the finding (*Science*, 22 April, p. 499). "The scare was that these estrogens were so potent that they were causing an increased incidence of breast cancer," says toxicologist Michael Gallo of the Robert Wood Johnson Medical Center at Rutgers University in New Brunswick, New Jersey. "The latest paper quieted down those fears," he says.

Reproductive storms

Welcome to one of toxicology's most contentious issues. Like a towering thundercloud sucking energy from the humid air around it, the debate over hormone-modulating pollutants feeds off two hot topics in environmental science—the relevance of animal studies to human health, and the increased emphasis by the Environmental Protection Agency (EPA) on the noncancer effects of the chemicals it regulates. The first is a revival of a perennial debate, but the second is a fresh concern for EPA, which in the past has crafted regulations based mainly on chemical carcinogenicity.

Evidence of this shift in focus can be seen in the agency's deliberations on dioxin: It recently decided that the compound's effects on reproduction and development should be of greater concern than its ability to cause cancer. It is also planning a major research initiative in 1996 to ferret out the noncancer effects of similar hormonelike pollutants. "We need to address [hormone modulators] in a very significant way," says Lawrence Reiter, director of EPA's health effects research lab in North Carolina. Reiter says the threat of hormone modulators may rival other pressing global environmental concerns. "I believe the problem should be viewed in the context of global warming or stratospheric ozone."

As scientists choose sides in the increasingly sharp debate, there is one point of agreement: Chemicals that can potentially affect hormone levels are everywhere—in the food we eat, in the water we drink, in body fat, and in breast milk. Thus far the discussion has focused on "environmental estrogens," compounds that bind to the receptor for estradiol, the body's main estrogen. But that label covers a range of compounds. Some environmental estrogens are familiar villains, such as the pesticide DDT and bisphenol A, a breakdown product of plastics. Many others, such as coumestrol and the flavanones, occur naturally in plants. Still other chemicals, many of them synthetic, act as "anti-estrogens" by blocking activity of the estrogen receptor or reducing the number of receptors. The last group includes some of the PCBs—compounds being phased out from use as industrial coolants—and benzo[a]pyrene, a combustion byproduct of foods and cigarettes.

Some scientists argue that environmental estrogens and anti-estrogens are just the tip of a hormonal iceberg. They say very little is known about the extent to which many pollutants and naturally occurring substances affect the thyroid, the adrenal glands, or almost any other organ or gland regulated by hormones. Notes EPA reproductive toxicologist Earl Gray, "We are not going to make any progress in understanding the problem until we address what the problem is: There are many manmade and natural chemicals in the environment that have the ability to alter the endocrine system."

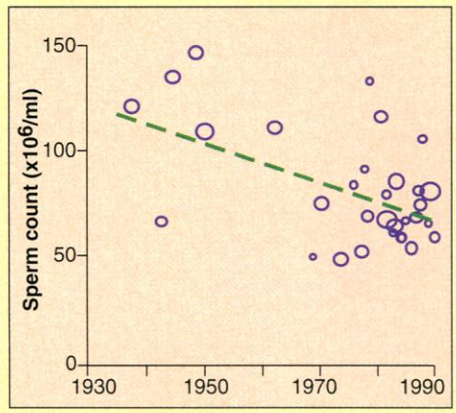
Warnings from the wild

The first evidence that hormone-modulating chemicals could pose a threat to human health came from studies of diethylstilbestrol (DES), a synthetic estrogen that was used to prevent miscarriages for two decades. DES was banned in 1971 after it was linked to a rare vaginal cancer in the daughters of women who took it. The DES experience prompted researchers such as John McLachlan, now scientific director of the National Institute of Environmental Health Studies (NIEHS), to ask as early as 1979 whether similar synthetic chemicals in the environment might disrupt fetal de-

Causes Sought for Sperm-Count Drop

Those who see environmental toxicants as a serious threat to human reproductive systems are quick to cite a *Lancet* article (29 May 1993, p. 1392) that linked a global decline in sperm counts in healthy men over the past 50 years to an accumulation of estrogenlike compounds in the environment. While it makes good copy—at a congressional hearing last fall, University of Florida reproductive physiologist Louis Guillette quipped, "every man in this room is half the man his grandfather was"—many toxicologists say no such link has been established.

The *Lancet* article, by reproductive biologists Niels Skakkebaek of National University Hospital in Copenhagen, Denmark, and Richard Sharpe of the British Medical Research Council Reproductive Biology Unit in Edinburgh, Scotland, discussed a meta-analysis of sperm-count studies published the previous year in the *British Medical Journal* (BMJ) (12 September 1992, p. 609). The *BMJ* study looked at 61 sperm-count studies published between 1938 and 1990. The results of the meta-analysis, carried out by University of Copenhagen statistics professor Niels Keiding and Skakkebaek, found that the mean sperm concentration had declined from 113 million per milliliter in 1940 to 66 million per milliliter in 1990. The *Lancet* paper suggested that environmental estrogens may be a factor in the decline.



SOURCE: *BRITISH MEDICAL JOURNAL*, 1992

Countdown. Sixty-one studies over 52 years suggest declining sperm counts. Circle size reflects relative number of subjects.

One reason to question a relationship between male fertility and environmental estrogens, say critics, is the fact that sperm counts have not dropped steadily throughout the half-century. In a letter to *BMJ* on 12 December 1992, reproductive specialists Anna Brake and Walter Krause of Philipps University in Marburg, Germany, stated that they had reanalyzed the 61 studies and found that in the 48 studies published since 1970—accounting for 88% (13,217) of the men—sperm counts actually increased slightly. The implication is that the decline occurred before 1970. Brake and Krause concluded that "care should be taken when discussing a causal relation with environmental factors."

"These papers have been overinterpreted," asserts Greg Bond, an epidemiologist at Dow Chemical Company. Bond isn't the only scientist urging a more cautious approach to the *Lancet* and *BMJ* papers. Other scientists ask whether the drop in sperm count might be due to increases in venereal diseases such as chlamydia. Untangling such potential confounding factors is a nearly impossible task, says Neil MacLusky, a researcher in reproductive endocrinology at the University of Toronto Medical School.

Indeed, even Skakkebaek warns readers not to get carried away. "We certainly do not claim that there has been a decline in sperm count during the second half of the study period," Skakkebaek says. Still, he says, "there is a big difference between the first part of the [study] period and the last part."

For now, a link between estrogenic pollutants and decreased sperm counts remains speculative. "At this point, I don't think we can say [the sperm-count decline] is caused by environmental estrogens," says EPA toxicologist Linda Birnbaum. "It's just one hypothesis to be tested."

–R.S.

velopment or pose other reproductive threats. Since then, researchers have discovered dozens of chemicals, synthetic and natural, that disturb the endocrine system via the estrogen receptor.

The evidence for this biological activity has come from animal studies involving high levels of exposure to estrogenic pollutants. For instance, female rodents exposed to DDT are more likely to develop mammary tumors, while male rodents tend to develop testicular cancer and other reproductive disorders. "But are lab exposures relevant to anything we see in the real world?" cautions John Gierthy, a toxicologist at the New York State Department of Health's Wadsworth Center in Albany, who has devised an in vitro assay for estrogens using a human breast-cancer cell line. Many compounds at high concentrations increase proliferation of these breast-cancer cells, Gierthy says, but that doesn't necessarily mean they will induce such an effect in vivo at background levels.

More persuasive to some researchers are wildlife studies. Some of the strongest evidence from the field comes from research at Florida's Lake Apopka. There, a team led by University of Florida reproductive physiologist Louis Guillette has linked a DDT spill in 1980 to a 90% decline in the birthrate of alligators and possibly to reduced penis size in many of the lake's young alligators. Guillette's work bolsters a case first argued at a Wisconsin conference in 1991, when wildlife toxicologist Theo Colborn, a senior fellow at the World Wildlife Fund, and others reported on the effects of hormone-modulating pollutants on a range of wildlife, from fewer turtle hatchlings to feminized male birds. Many of the studies have focused on the Great Lakes, which until recently had high levels of DDT, PCBs, and dioxins.

Researchers have found, for instance, poor reproductive success for bald eagles that consume pollutant-tainted fish from the Great Lakes. In addition, some researchers link PCBs and similar compounds to "Great Lakes embryo mortality, edema, and deformities syndrome" in herring gulls, terns, and other Great Lakes marine birds (*Science*, 14 February 1992, p. 798). "I walked out of the [Wisconsin] meeting absolutely stunned by what was clearly a very serious problem," says Frederick vom Saal, a developmental biologist at the University of Missouri.

Vom Saal, Colborn, and others contend that because the reproductive biology of many of these animals is similar to that of humans, these findings suggest that people exposed to low levels of hormone modulators may be at risk for fertility problems or even cancer. Openly challenging Safe, vom Saal says: "Let anybody argue with me and say these [wildlife] studies aren't relevant to humans." NIEHS reproductive endocrinologist Kenneth Korach, who co-chaired the third NIEHS symposium on environmental estrogens in Washington, D.C., in January, is a bit more cautious. "I don't want to be an alarmist," says Korach, "but the wildlife exposures might be a tip-off to [the hazards] humans are being exposed to."

Defense mechanisms

Not so, argues Safe. He and others don't question the Apopka data on animals, but he draws a distinction between an environment heavily contaminated by a single source of pollution and the one found in the Great

One Cancer Warrants Closer Look

Despite sharp disagreements over the potential threat to human health from environmental estrogens and other hormone-modulating pollutants (see main text), the combatants agree on at least one point: More research is needed on a possible link between estrogens and a disturbing global increase in testicular cancers.

The incidence of this disease has risen by a factor of two to four in industrialized countries in the past 50 years. It now strikes about 1 in 20,000 men, typically when they are in their 20s and 30s, so its increase can't be due to a burgeoning elderly population. And, as with low sperm counts, it is linked to poorly functioning testes. "Testicular cancer and estrogenic compounds is the thing we need to look at most closely," agrees Rutgers toxicologist Michael Gallo. One reason to suspect estrogens is that an increase in testicular cancer has been observed in the male offspring of pregnant mice exposed to high doses of estradiol, an estrogen produced in the body.

To some scientists, the evidence against environmental estrogens is strong enough for an indictment. "Cumulative lifetime estrogens is the common link that unites these findings," says Public Health Service cancer statistician Devra Lee Davis. But Danish reproductive biologist Niels Skakkebaek and others say they want to see stronger evidence before leaping to any conclusions. In either case, says Gallo, "there's a lot more work to be done."

–R.S.

Lakes, which is rapidly recovering from a range of environmental insults of varying duration and levels. He also draws the line at finding implications for humans. Safe first articulated his views in the January issue of *Environmental Science and Pollution Research*, and expanded on the theme in his address to the toxicology society. "I think the result of Steve's efforts is that many people who are knowledgeable in the field don't think there's much to it," says University of California, Berkeley, toxicologist Bruce Ames, a noted skeptic of the risks to humans from pollutants who shares Safe's concerns.

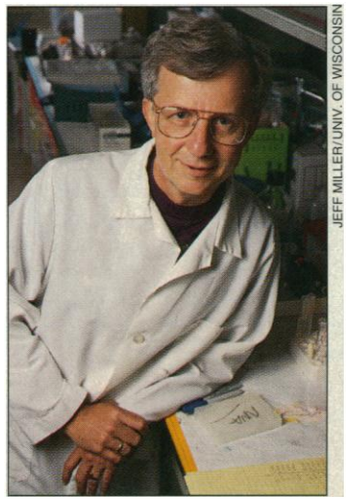
Safe and others make two points in arguing against a demonstrable link between hormone-modulating pollutants and human health effects. For one thing, they say the basic pharmacology doesn't add up. "Most pesticides and other environmental estrogens are only very weak estrogens," says EPA dioxin researcher Linda Birnbaum. Known environmental estrogens bind to the estrogen receptor hundreds to thousands of times more weakly than does estradiol. That's true even for men, who convert androgens such as testosterone to estradiol.

Since background levels of synthetic estrogens are swamped by the body's own estradiol, says Rutgers' Gallo, there's little chance they would be able to exert an effect. The exception, he suggests, might be cases in which people or wildlife are exposed to massive doses of the estrogens, as occurs with lab animals or the Lake Apopka alligators. Humans and other primates also have a mechanism for protecting themselves from estrogens that differs from other mammals, says Neil MacLusky, a researcher in reproductive endocrinology at the University of Toronto Medical School. In humans, the body tacks on a sulfate group or other conjugate to disarm circulating estrogens, whereas rats and mice have a protein that specifically binds estradiol. Such differences could explain why estrogens might affect humans and wildlife differently, MacLusky says. It could also account for some of the variation among wildlife in reacting to different environmental estrogens.

A second reason to doubt that environmental estrogens and other hormone modulators pose a threat to humans, say Safe and others, is the acid-base argument. Individually, a strong acid and a strong base might be corrosive. But when mixed the pair often form a benign compound. Similarly, Safe and others argue that a sea of natural and synthetic anti-estrogens may negate any effects of environmental estrogens. "The net effect may be zero," he says.

The strongest evidence for that comes from the ability of anti-estrogens to inhibit the formation of breast tumors. One such group of compounds are the indole-3-carbinol conjugates (I3C), found in broccoli and other Brassica vegetables. Animals given I3C are less likely to develop breast tumors than control animals, probably because these compounds bind to the arylhydrocarbon (Ah) receptor, which triggers the release of compounds that block estrogen activity.

Some scientists, however, disagree with Safe's theory. Their reason: Anti-estrogens can be potent hormone modulators themselves. "I don't think you can...say these chemicals are anti-estrogenic and therefore will have a balancing effect," says University of Wisconsin toxicologist Richard Peterson, an expert on dioxin, a hormone-modulating byproduct of industrial processes such as wood-pulp bleaching.



JEFF MILLER/UNIV. OF WISCONSIN

Search for answers. Dioxin findings in rats make Richard Peterson wonder about effects on humans.

Double-edged sword

One reason Peterson is skeptical of Safe's claims is that dioxin, depending on its location in the body, can either heighten or mute the body's response to estrogen. Dioxin inhibits breast tumors in rats and mice; however, it also increases liver tumors, an effect that seems to require estrogen. Furthermore, the male offspring of pregnant rats exposed to dioxin exhibit delayed sexual maturation, smaller sex organs, reduced sperm counts, and demasculinized sexual behavior. "These effects are not going to cancel out," says EPA's Gray.

Perhaps most disturbing, Peterson says, is that the lowest dose of dioxin in the pregnant rat necessary to cause reproductive problems in the offspring (64 nanograms per kilogram) is not far from the current average background dose of dioxin and related chemicals that has accumulated in humans (5 to 10 nanograms of dioxin equivalents per kilogram). The fact that dioxin produces adverse developmental and reproductive effects in fish, birds, and mammals suggests that it could do so in humans, says Peterson. Safe agrees that any response to a single, low dose warrants further study, but he points out that the finding relates to rats in utero and that no mechanism has been proposed.

Despite their disagreements, both sides say the issue needs further study. "We have to admit that we don't know how environmental estrogens affect people, that we're speculating about the effects," says Iowa State historian Alan Marcus, who has written a history of the politics of DES. Adds Jonathan Li, a reproductive toxicologist at the University of Kansas Medical Center, "A lot more research needs to be done before you can say there's a relationship" between hormone modulators and disease. In the meantime, most scientists agree with NIEHS's McLachlan: The threat to humans from hormone modulators remains a "theoretical" one.

–Richard Stone