



Risk in Perspective

Are Chemicals in the Environment Disrupting Hormonal Control of Growth and Development?

The wide span of opinion on the xenoestrogen issue is typical of the early stages of an emerging scientific question, when possibilities of great concern are raised but existing information (and, perhaps more importantly, scientific consensus about the meaning of that information) is insufficient to resolve whether emerging fears are well founded.

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Alligators in Florida's Lake Apopka are failing to reproduce; many males have reduced genitalia. Female-female pairs of gulls in California are building nests, and some young males in the same population show partially feminized reproductive tracts. Male rainbow trout in Great Britain living near sewer outlets are generating proteins in their tissues normally found only in females' eggs. Meanwhile, several studies suggest that over the last 40 years, human males have suffered a steep, worldwide decline in the numbers and quality of their sperm cells. Incidences of abnormal or incomplete genital development, such as undescended testes and malformed penises, are reported to be increasing in certain Scandinavian countries. And a variety of human cancers known to be affected by sex hormones appear to be on the rise, including breast cancer, testicular cancer, and prostate cancer.

There is increasing concern among some scientists that these phenomena represent the diverse manifestations of a common, emerging environmental problem: accumulation in the environment of certain persistent chemicals that mimic the actions of the body's natural sex hormones. In this issue of **RISK IN PERSPECTIVE**, we examine the biological basis of these concerns as well as the unknowns.

Natural hormones produced within our bodies, including estrogens and androgens (such as testosterone), control the normal processes of development, growth, and control of sexual differentiation, sexual behavior, and reproductive function. Appropriately timed changes in the circulating concentrations of these hormones exert this control through binding of the hormone molecules to certain specific receptor molecules in cells of the tissues to be affected, triggering the appropriate biological effects.

XENOESTROGENS

It is becoming clear that a number of foreign chemicals can bind to hormone receptors as well, although generally they bind more weakly than do the genuine hormone molecules. In the laboratory at least, some of these chemicals in

sufficient concentrations appear to trigger the receptors' biological actions (i.e., they act as "agonists"). Others may block access of genuine hormone molecules to their receptors (i.e., they act as "antagonists"), perhaps preventing needed modulation of biological function by the body's own hormones. Still others affect the metabolism, and hence the concentrations, of the body's natural hormones. A variety of compounds, representing different compositions and chemical classes, appear to have such properties. These include certain chlorinated organic compounds (principally some pesticides such as DDT, kepone, and others, but also certain polychlorinated biphenyls), some plasticizers and breakdown products of polycarbonate plastic, and some pharmaceuticals, such as diethylstilbestrol (DES).

Such compounds are coming to be termed "xenoestrogens," referring to the fact that they are agents foreign to the body's own metabolism yet have properties that mimic those of endogenous sex hormones. (Since androgens as well as estrogens are at issue, and since blocking as well as stimulation is of concern, the broader term "environmental hormone disruptors" is also used.) It is feared that exposure to xenoestrogens, by producing hormonal stimuli that are of inappropriate timing, magnitude, or biological context, may result in unwanted biological effects such as the proliferation of mammary-tissue cells (increasing cancer risk) or the diversion of the normal paths of sexual differentiation of developing embryos. The matter is complicated by the existence of environmental compounds that act as antiestrogens—that is, compounds that tend to reduce the response to sex-hormonal stimuli. Some agents may act as antiestrogens at low doses and as estrogen agonists at high doses.

What is less clear is whether the small concentrations of xenoestrogens usually experienced by most humans are capable of having any significant biological effect. The quantities involved are small; they are typically dwarfed by our intake of naturally occurring estrogenic

compounds that are found in a variety of vegetables in our diet. These plant compounds, often termed phytoestrogens, have been consumed in significant quantities for centuries by some cultures. For instance, soy products, long consumed in the Orient, are a major source of certain estrogenic flavonoids. While phytoestrogens can provide estrogenic stimuli in test tube studies, the effects of low exposures in living organisms can sometimes suppress responses to estrogen.

Exposure to phytoestrogens is in turn dwarfed by the doses of estrogens that many humans (at least female humans) receive in birth control pills or post-menopausal hormone replacement therapy. Modern birth control pills have not been associated with elevated cancer risks, although older formulations and post-menopausal hormone replacement therapy have shown some increase in breast-cancer risk in epidemiological studies. Some scientists have questioned whether the low levels of man-made xenoestrogens in the environment can plausibly be thought to affect the risks of hormonally influenced cancers when the exposure levels are over a hundredfold less than exposures to naturally occurring phytoestrogens—and millions of times smaller than exposures to estrogens in birth control pills. These critics point out that natural variation in estrogen concentrations from one individual woman to another—variation that appears to have little if any bearing on health—is much larger than the increase that could come from environmental xenoestrogens; and that hormonal control is biologically designed to produce correct response in spite of these differences. They state that, aside from specific instances of high, local contamination (such as the spill of the pesticide dicofol thought to be responsible for the Lake Apopka alligator problem), there is little indication of any widespread health problems associated with exposure to xenoestrogenic chemicals.

UTTER CATASTROPHE OR UTTER NONSENSE?

The wide span of opinion on the xenoestrogen issue is typical of the early stages of an emerging scientific question, when possibilities of great concern are raised, but existing information (and, perhaps more importantly, scientific consensus about the meaning of that information) is insufficient to resolve whether or not emerging fears are well founded. If the environment is indeed accumulating compounds that can have widespread and serious effects on the health, development, and fertility of wildlife and humans, then we face a great problem; such compounds will be difficult to control and even more difficult to remove from the environment. On the other hand, if low exposure levels pose little real risk, then a crash program of xenoestrogen control and cleanup will divert precious resources from other pressing environmental problems. This could divert regulatory and research attention

away from other, true causes of breast cancer, birth defects, and wildlife toxicity.

KEY UNANSWERED QUESTIONS

Research efforts on xenoestrogens and related issues of environmental-hormone disruption have increased markedly during the last few years in government, industry, and academic laboratories, with further increases likely. The National Academy of Sciences has convened a Committee on Hormone-Related Toxicants in the Environment which will prepare a report (expected about a year and a half from now) assessing the known and suspected mechanisms and impacts on wildlife and humans. This report will identify the significant uncertainties, and recommend a scientific framework with which to approach the problem. There will also be much discussion at meetings of professional societies and specially convened colloquia.

In our opinion, answers to the following questions are sorely needed: (1) How good is the evidence for changes over time in human male sperm counts and the incidence of genital abnormalities? What is the basis for linking any such trends with environmental chemicals? (2) Should hormonally acting agents be presumed to have exposure thresholds for their toxic effects, and if so, how can such thresholds be experimentally characterized? (3) Are phytoestrogens at the levels typically encountered exerting significant endocrine effects? If so, do they act primarily as agonists or antagonists? (4) Since male organisms typically have much less natural estrogen, are they particularly sensitive to xenoestrogens in comparison to females? (4) If so, why are they not affected by phytoestrogens? (5) Are there key times during development of the embryo when even small, inappropriate exposures to estrogenic stimuli can divert normal sexual development pathways or affect future fertility?

If the xenoestrogen problems are real, they have taken some time to develop and will take a good deal more time to cure. Policy makers face a great challenge, given the complexity of hormonal action and the unanswered questions regarding exposure thresholds for biological effect, the relation of test tube studies to effects in living organisms, the unknown net effect of low levels of estrogenic and antiestrogenic agents experienced in combination, and the role of natural and artificial sources. It is likely to be difficult to design policies that are reasonably assured of improving rather than worsening the situation, much less policies that will solve the problem. There is a clear need for research to illuminate these questions and for vigorous scientific debate and examination of the issues to discern the appropriate interpretation of the information we now have. We urge government and industry, separately or in concert, to fund the long-term research programs that will be necessary to obtain answers to these key questions.

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FURTHER READING:

Theo Colborn, John Peterson Myers, and Dianne Dumanoski. *Our Stolen Future: How We Are Threatening Our Fertility, Intelligence and Survival—A Scientific Detective Story*. New York: Dutton/Signet, 1996.

Steven Safe. Environmental and dietary estrogens and human health: Is there a problem? *Environmental Health Perspectives*. 103(4): 346-351 (1995).

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