Title: Endocrine Disruptors: Sensationalism or Science?

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The headlines are frightening: Reported incidence of breast and testicular cancers is on the rise. Sperm counts may be plummeting. Children born to women eating toxin-laden fish from the Great Lakes perform less well than other kids on tests of memory, intelligence, and verbal ability. Sexual, neurological, and immune dysfunctions have been reported in wildlife. While the actual extent and causes of these effects remain controversial and undetermined, synthetic chemicals are a prime suspect.

About 50 pesticides, by-products, and classes of industrial chemicals are accused of disrupting the hormonal balance of humans and animals. They have been dubbed "endocrine-disrupting chemicals" (EDCs). Some are familiar bad actors, such as DDT, polychlorinated biphenyls (PCBs), and dioxin, while other alleged EDCs are the pesticides atrazine and Benlate, alkylphenols, certain phthalates, and bisphenol A.

Little scientific consensus exists on the threat and responses have, not surprisingly, been varied. Environmental activists such as Greenpeace view the issue as further fodder for their attack on chlorine chemistry. Specific product bans have been enacted in European countries. But most regulators and legislators are focusing efforts on further research. Congress is poised to authorize a screening program that could net a large number of the industry's products.

Industry is scrambling to respond, funding research on toxic threats to endocrine functions and validating screens they hope will prove both accurate and inexpensive. Chemical companies and trade associations insist that, while it is plausible that certain chemicals could disrupt development in humans and animals, regulation must await the development of a scientific consensus and an evaluation of the risks.

A study on human sperm counts published last week shows how contentious the science is. Niels Shakkebaek of the University of Copenhagen has reported that average human sperm counts dropped by almost 50% between 1938 and 1990; however, the new report, from Columbia Presbyterian Medical Center (New York), sees no decrease. In fact, Columbia Presbyterian researcher Harry Fisch reports an overall increase in sperm counts over the past 25 years.

Paul Foster, a reproductive toxicologist recently recruited to head the Chemical Industry Institute of Toxicology's (CIIT; Research Triangle Park, NC) endocrine research effort, says a lack of data makes it impossible to determine how much concern the issue warrants. "There's precious little evidence that you can actually look at showing any kind of cause and effect relationship between

exposure to a specific chemical and a deficit in human reproductive function," says Foster.

However, he says, research findings in animals are provocative. For example, EPA toxicologist Earl Gray has shown that both a breakdown product of DDT and the fungicide vinclozolin block the receptor for testosterone. Pregnant rats exposed to low doses of either chemical give birth to males bearing female sex characteristics. Research by toxicologist John Sumpter at Brunel University (Uxbridge, U.K.) demonstrates that alkylphenols, the breakdown product of alkylphenol ethoxylate (APE) surfactants, can also give male fish female sex characteristics by mimicking estrogen.

CLEAR EXPOSURE. While the scale of the threat to human health remains to be established, humans are clearly exposed to the hazard. Studies done in the U.K. indicate 30% of drinking water is taken from rivers that are contaminated with APE surfactant-laden sewage effluent. Bisphenol A, a raw material for polycarbonate and certain epoxy resins used to coat the inside of food cans, can leach into foods.

Regulators, particularly in Europe, are beginning to respond, supported by prominent scientists such as University of Missouri endocrinologist Frederick vom Saal, who sits on the National Academy of Sciences' (NAS) panel on EDCs and is on CIIT's technical advisory board. Vom Saal believes regulators should take action against chemicals identified in in vitro tests such as the E-screen, which employs a petri dish of estrogen-sensitive breast cells to detect estrogenicity. "Why not get rid of the clearly bad players that are showing up in these assays?" asks vom Saal.

Vom Saal says low-dose testing of bisphenol A and certain pesticides has led him to believe that standard toxicology tests may not identify EDCs (box). He worries that industry will oppose the use of in vitro testing, thereby limiting the number of chemicals that are ultimately tested.

But other scientists are more conservative. Sumpter, whose research is partly supported by the European Center for the Ecotoxicology and Toxicology of Chemicals (Ecetoc), says there is enough evidence to ban some compounds, such as APE surfactants, but that for most compounds the science is less clear. "We've known for a while that [APEs] are toxic to aquatic life, and now they're known to be estrogenic. There are safer replacements," Sumpter says. But he urges regulators to wait for more science on phthalate plasticizers and other chemicals that have been tagged as EDCs primarly by in vitro tests. He says the science has not advanced far enough to have a sound basis for widespread regulation.

Indeed, many in industry are downplaying the hazard. The Society of the Plastics Industry (SPI) and polycarbonate resin makers, which include Dow Chemical and GE Plastics, are standing behind the safety of bisphenol A. They say leaching of product into food or water happens only in doses too small to have an impact on human health. SPI says it has completed a year-long migration study of polycarbonate that measured no bisphenol A leaching.

CMA's alkylphenols and ethoxylates panel says the fish experiments that Sumpter is citing have not been reproduced in the preliminary results of industry-funded animal tests. Additionally, industry says, preliminary testing shows APE surfactant breakdown products

are quickly metabolized and degrade rapidly in the environment.

Nevertheless, regulation has begun. Denmark has taken the lead in Europe, virtually eliminating the use of APE surfactants (CW, May 1, p. 29). Denmark is also considering a phaseout of polyvinyl chloride (PVC), largely because of the potential toxic and estrogenic effects of some phthalate plasticizers (CW, Feb. 21, p. 17). "The science is just beginning," says a Danish EPA official,"but where we find estrogenic chemicals we will regulate."

The next country to follow the lead may be Sweden, which is considering a phaseout of plasticized PVC. Sweden's minister for environment, Anna Lindh, says, "It's no longer a question if PVC should be phased out, but how it shall be phased out." Sources in the government say this does not guarantee legislation, however.

Work is moving forward on negotiating a treaty on chemicals that are bioaccumulative--so-called persistent organic pollutants (POPs). Many of the 12 priority POPs identified for action, such as dioxin and PCBs, also appear to be EDCs. The Intergovernmental Forum on Chemical Safety, working with the United Nations Environment Program, has set up a working group on POPs that is studying their movement through the global environment, their potential replacements, and mechanisms to restrict them.

National regulators are duplicating this fact-finding effort. Germany, the U.K., and the U.S. are setting research strategies through meetings with industry, academic, and agency scientists. The U.K.'s Institute for Environment and Health, working with international specialists, established broad research priorities on EDCs last July. In the U.S., strategic planning is under way within EPA's Office of Research & Development. The NAS panel on EDCs is scheduled to report next year.

EPA assistant administrator Lynn Goldman, who directs the offices of pesticides, pollution prevention, and toxic substances, says responding to the threat of endocrine disruption posed by new chemicals will be relatively easy in the U.S. because of recently revised guidelines for developmental and reproductive toxicity testing. The revisions recommend testing for sensitive endocrine endpoints, such as sperm count, quality, and activity; and hormonal fluctuations in the female reproductive cycle.

Finding EDCs among the thousands of chemicals now in use will be more challenging, says Goldman, who has formed an agency task force to develop a screening strategy. Congress may add some momentum by mandating the rapid development and implementation of an EDC screening program. Last December, the Senate unanimously passed a revision of the Safe Drinking Water Act that calls for EPA to have a program in place within one year of the bill's signing and to implement screening within two.

Industry representatives are alarmed by the rush to screen, because, they say, existing screens detect chemicals that mimic hormones in the test tube but may pose little threat to humans. Goldman agrees that a positive E-screen does not explain why the chemical is estrogenic, which makes it difficult to determine if the chemical will cause harm in humans. "If you have a chemical with a positive E-screen," she says, "I'll have to say I'm not sure what to do with it right now."

Goldman says she hopes the agency will get voluntary cooperation from industry to arrive at a valid framework for screening. "If we have to do this through rule-making processes it will take an inordinate amount of time and effort. Obviously reaching an agreement on the framework and which tests are going to be used is going to be absolutely key."

Industry in the U.S. and Europe also stress the need for cooperation, and trade associations and industry-supported toxicology labs are boosting research spending. Much of the funding is aimed at developing a better mechanistic understanding of how EDCs function in animals. "The existing in vitro methods are useful but limited," says Geoff Randall, a Zeneca toxicologist who heads the endocrine task force at Ecetoc. "They do not help us understand in vivo mechanisms," he says. "The next step is to develop functional assays involving animals." Foster agrees: "What we're looking to do is get good in vivo data and then see how well some of these in vitro systems predict that effect."

A CMA-organized task group on testing is still at the information-gathering stage, but work is getting under way at CIIT and DuPont. CIIT is assembling a 20-person research team and has dedicated about $1.5 million this year toward its endocrine research program; the lab expects to spend about $5 million on EDCs over the next three years. Ecetoc's endocrine task force has a budget of $100,000-$200,00/year and draws scientists from almost 20 companies.

The ultimate challenge the industry faces is to identify a test that balances accuracy and cost. Widespread screening demands an assay that costs no more than a few dollars. Otherwise, according to industry's worst-case estimates, endocrine screening could boost total testing costs by as much as 50%.

As the work progresses on both sides of the Atlantic, the Organization for Economic Cooperation and Development (OECD; Paris) will try to coordinate efforts. Herman Koeter, OECD's principal administrator and head of the chemical screening program, says an international consensus on new testing rules could be reached within one to three years. Given current knowledge, he estimates hundreds of chemicals should be screened based on their structures or properties. However, he adds that "nobody really knows yet how big the problem is."

Industry is also funding research, seeking to characterize what risk EDCs pose to human health and wildlife through epidemiology and exposure assessment. "Everyone is talking about potential hazard, without considering exposure," says Andre Lecloux, who heads the European Chemical Industry Council's (Cefic) Endocrine Modulating Steering Group (EMSG). "We need to thoroughly study both to better understand risk," says Lecloux.

EMSG has $3.5 million-$4 million/year for research for the next three years. "This is by far the largest research budget in Cefic," says Lecloux. EMSG's likely priorities will be defining the extent to which observed health effects like declining sperm counts may be due to lifestyle factors, such as diet, rather than chemicals. In addition, the group will research the potential effects of phytoestrogens--naturally occurring EDCs found in soybeans and nuts.

In the U.S., the Chlorine Chemistry Council (CCC; Washington) says it has spent about $5 million over the past two years--most of it

supporting academic research on the link between breast cancer and DDT, human sperm quality, and wildlife effects of EDCs. In addition, CCC established a research foundation last fall offering matching funding for research on EDCs and other issues. CCC hoped that $1 million in seed funds from the foundation would attract research dollars from other industry groups or foundations, but no projects have been approved.

STARTING POINT. Some environmental groups view the flurry of industry research as a tactic to head off regulation while public concern runs high. "We call it cigarette science," says Greenpeace Washington legislative director Rick Hind. Greenpeace argues that the risk to human reproduction demands action against EDCs and proposes an immediate phaseout of PVC as a start. The group says PVC production is a major source of dioxin.

While opposing Greenpeace's call for a chlorine ban, the World Wildlife Fund (WWF) is working to convince regulators to move now to reduce human exposure to all known EDCs. "We will never have enough proof of exact cause and effect for every compound," says U.K. WWF pollution consultant Gwynne Lyons. "There is enough proof to start reducing all exposures now."