The precautionary approach: as researchers painstakingly explore the exact mechanism of endocrine disruption, we should consider suspect chemicals guilty until proven innocent.

by Sheldon Krimsky

Research findings on the toxic effects of chemical endocrine disruptors on animals, including humans, suggest that a precautionary approach be taken for industrial chemicals and other environmental pollutants. The traditional principle that a higher dose of a particular chemical would have a greater impact cannot be relied on for endocrine disruptors. Thus, industries must first show that the chemicals they are introducing have no adverse effects before their products are to be allowed to be marketed.

Are synthetic organic chemicals used in pesticides, industrial production, and consumer products putting people and wildlife at risk by interfering with their endocrine systems? This hypothesis has been debated within the scientific community for about 10 years, and many areas of scientific uncertainty still exist. In particular, scientists and policymakers want to know more about human risks from exposure to ambient levels of chemicals found to be hormonally active in laboratory studies.

Undoubtedly, debates over the human effects of endocrine-disrupting chemicals will keep scientists occupied for years. So far, however, discoveries that have helped build the environmental endocrine hypothesis have already sparked a quiet revolution in science and policy by influencing the way we think about chemical risks. In fact, some nations are beginning to take precautionary measures based on the weight of evidence that is mounting from diverse sources.

New Framework Emerges

Scientists widely agree that chemical endocrine disruptors affect some wildlife, including birds, alligators, and fish. Strong but sparser evidence also indicates that endocrine-disrupting chemicals adversely affect humans who are exposed to them.

There are a number of serious human diseases whose causes are not well understood. Among them are breast cancer and diseases of the reproductive system, immune system, and thyroid gland. The knowledge that chemicals can mimic or block the body's own endogenous hormones provides a new conceptual and theoretical approach to investigating the causes of these diseases.

Some of the new hypotheses that implicate endocrine-disrupting chemicals point to fetal exposure to synthetic chemicals as the initiating cause of a disease. The growth of interest in this hypothesis may be traced to the 1991 Wingspread Workshop, organized by Theo Colborn, chief scientist at the World Wildlife Fund and the first person to recognize and publicize the broad implications of endocrine-disrupting chemicals. At that workshop, participants presented laboratory and field data that provided compelling evidence connecting persistent organic chemicals in the environment to abnormal reproductive and developmental effects associated with endocrine disfunction in wildlife.

Historically, the assessment of chemical risk to humans has centered on two types of effects: acute toxicity and carcinogenicity. Recent discoveries that wildlife populations have been adversely affected by synthetic chemicals that mimic or block natural hormones in animals have provided researchers the impetus to look more systematically at other, less straightforward effects of contamination. These include reproductive and developmental abnormalities that may be triggered by exposure of the fetus to chemicals at levels that do not affect the adult animal, and multigenerational effects that may appear in the offspring of adults initially exposed at a prenatal or neonatal stage in their development.

In addition, a significant time gap may separate exposure and observed effects on mature organisms. Abnormal cells produced during early gestation have been implicated in adult-onset diseases. Among the diseases being investigated for connections to endocrine-disrupting chemicals are prostate, testicular, and breast cancers.

Legislative Protection

Two new laws passed by Congress in 1996 - the Food Quality Protection Act and the amendments to the Safe Drinking Water Act - require the U.S. Environmental Protection Agency to develop a screening and testing program for endocrine-disrupting chemicals. The timetable established by Congress stipulates that the screening and testing program should be ready for implementation by August 1998, a schedule that was unduly optimistic. These new laws state that criteria should be developed for assessing the risks of a class of chemicals - such as atrazines and endosulfans used in pesticides and phenols

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used in plastics - whose endocrine effects are new to the scientific community.

Even the definition of endocrine disruptors has been subject to debate. Under the provisions of the new laws, the additive, cumulative, or synergistic effects of endocrine-disrupting chemicals must also be considered. In the main, past chemical regulatory strategies for testing have been based on a chemical-by-chemical approach. While this may be a logical starting point, such a reductionist approach has significant limitations in identifying chemical hazards.

Compounding the Problem

Chemicals tested individually at low doses may elicit no observable adverse effects in some laboratory analyses. Exposure to several chemicals with similar biological action may produce adverse effects in living organisms despite the fact that the doses are considered safe based on single-chemical exposure tests. For example, two distinct estrogenic chemicals may add up to produce twice or even more than twice the estrogenic effect. The search for additive effects and synergism of chemicals in commercial use represents a significant challenge to scientists and regulators.

Testing chemical combinations - even taken two at a time - from an estimated 85,000 chemicals in use in the United States alone can be quite complex and prohibitively expensive. But the recognition that additive effects and synergism are essential to the risk assessment of endocrine-disrupting chemicals has become a hallmark of current policy deliberations.

In addition, the role of chemical metabolites adds another layer of complexity. Chemicals are metabolized differently in different biological systems, where they are exposed to different enzymes. While the parent chemical might prove innocuous or only mildly estrogenic in one system, certain of its longer-lasting metabolites may exhibit potent endocrine-disrupting properties. In the case of the pesticide DDT, for example, the metabolite DDE has been studied extensively for its possible role in breast cancer.

By adding to the list of industrial chemicals the undetermined number of metabolites, the problems of testing grow by orders of magnitude.

Unknown Origins

In their attempts to unravel some of the mysteries of endocrine disruption, scientists have developed animal models to study how a onetime chemical exposure in utero at the appropriate stage of development of the embryo can result in irreversible abnormalities that may not show up for decades or even until the next generation. By following the development of the offspring of a pregnant animal exposed to endocrine-disrupting chemicals during pregnancy, these animal studies provide scientists with a new approach to the study of disease.

Chemical exposure of the developing fetus or the neonatal animal may come from the ambient environment - water, air, soil, or food supply - or from fat-binding chemicals absorbed by the fetus from the mother during pregnancy or lactation.

One of the most-studied synthetic estrogens is diethylstilbestrol, or DES, a drug given to millions of pregnant women from the 1940s through the 1960s. When abnormalities in the children of these women surfaced, researchers began extensive studies in laboratory animals of the in utero effects of DES on development of the fetus. These studies have revealed much about the mechanism by which foreign agents can bind to hormone receptors and become biologically active.

Researchers have conducted epidemiological studies in the Great Lakes region on pregnant women who ate a diet of fish contaminated with moderate to high levels of PCBs. Adverse effects, including poor motor coordination and reduced tolerance for environmental stress, were observed in the infants of these mothers, while the mothers themselves suffered no such effects. These findings suggest that exposure of the fetus to endocrine-disrupting, foreign chemicals could have lasting effects that go undetected unless the investigator knows what outcomes to study.

Chemical imprinting of the brain from in utero exposure to foreign chemicals may lead to developmental effects later in life that do not leave traditional chemical toxicity biomarkers such as cell death and tumors. Investigators are also learning that measuring residue chemicals in the serum or tissue of organisms and correlating those measurements to endocrine-mediated abnormalities may prove ineffective if the original exposure occurred early in gestation and the effect is not expressed until maturity. In such cases, the damage occurs long after traces of the contaminant have disappeared from the organism.

Reexamining the Canons

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One of the chief canons of toxicology is that the dose makes the poison: the higher the dose of a chemical, the greater the effect. This principle has proven quite effective in accounting for acute toxicity and to some, but lesser extent, for chemical carcinogenicity.

The endocrine system, however, involves a myriad of chemical messengers and feedback loops. Sometimes the endocrine system does not respond to chemicals in accordance with the canons of traditional toxicology. New evidence shows that animals may exhibit observable adverse effects at small doses but not at larger doses. In addition, some doses below the threshold of observed effects on adult animals may induce a significant response to the fetus, which is highly sensitive to hormonal changes during development.

For these reasons, some toxicologists are beginning to reevaluate the standard methods of testing laboratory animals, which test high doses of a chemical on animals and then extrapolate from the results to predict the effects of low doses in humans. Since toxicological experiments other than drug testing on humans are unethical, the new awareness of how endocrine-disrupting chemicals work has increased the need for low-dose animal experiments. Moreover, the mechanisms by which foreign chemicals can disrupt the endocrine system may pass unnoticed if adult animals are studied exclusively. Therefore, it is especially important to examine in utero exposures, which are more complex, more expensive, and more difficult to study.

The Precautionary Approach

During the late 1980s, when Theo Colborn first proposed the general environmental endocrine hypothesis, European nations were discussing a new concept for managing environmental risks. The precautionary principle had its roots in the early 1980s in Germany, where pollution-prevention strategies were being advanced even when risks were not clearly identified. The term precautionary approach was introduced during the 1987 Second International Conference on the Protection of the North Sea to declare an obligation to control the most dangerous substances even before a definitive causal link had been established between chemicals and health or environmental effects.

When this principle is applied to chemical hazards, it suggests that different nations should reexamine the burden of proof they use for managing potential environmental hazards. According to the principle, those who would introduce a new chemical into commerce must demonstrate its safety. In addition, the precautionary principle distinguishes between evidence that justifies a scientific judgment of cause and effect, on the one hand, and strong but inconclusive evidence that justifies policy options based on an assessment of possible consequences if the causal relationship should prove correct.

Laboratory assays suggest that certain environmental chemicals such as bisphenol A and phthalates - compounds commonly found in plastics, resins, and food packaging - can activate hormone receptors. Proponents of the precautionary principle believe sufficient circumstantial evidence exists to justify regulating, substituting, or even banning certain persistent organic chemicals. The issue of endocrine-disrupting chemicals has provided a new forum for examining the application of the precautionary idea to public decisions.

Complex Interactions

Science is in its infancy in understanding the effects chemicals have on humans and the environment. The first generation of laboratory studies of endocrine-disrupting chemicals simply reveals how little is known about the mechanisms of chemical action during the early stages of fetal development.

As biology moves into a more reductionist phase of development, the discoveries about endocrine disruptors are pointing to the importance of a different kind of investigation, namely the investigation of complex feedback systems, multiple chemical pathways, and timing of exposures. This has created new interest in how foreign chemicals become biologically active in an organism.

Another notable outcome of the environmental endocrine hypothesis is its impact on the communicative and organizational structure of science. The problems posed by endocrine-disrupting chemicals cannot be solved by examining a single biological level, such as the cell, the organ, or even the organism. While some questions can be studied at the molecular and cellular level, others can be studied only by examining complex systems operating within the whole organism.

Although the tendency in science is toward specialization, the hypothesis that chemicals ubiquitous in our environment may be masquerading as endogenous hormones has created a new demand for integrative biological studies, multidisciplinary workshops, and

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creative collaborations. Human and animal endocrinologists have more reason to communicate now than ever before. Pediatric epidemiologists and wildlife toxicologists now have shared interests in understanding childhood diseases. If history is any judge, these policy-driven multidisciplinary collaborations will produce breakthroughs in comparative diseases and a better understanding of complex biological systems.

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