Scientists Warn of Low-Dose Risks of Chemical Exposure

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> A new study finds that even low doses of hormone-disrupting chemicals — used in everything from plastics to pesticides – can have serious effects on human health. These findings, the researchers say, point to the need for basic changes in how chemical safety testing is conducted.

Since before the publication of Rachel Carson's *Silent Spring* 50 years ago, scientists have known that certain synthetic chemicals can interfere with the hormones that regulate the body's most vital systems. Evidence of the health impacts of so-called endocrine-disrupting chemicals grew from the 1960s to the 1990s. With the 1996 publication of *Our Stolen Future* by Theo Colborn, Dianne Dumanoski, and J. Peterson Myers, many people heard for the first time how such exposures — from industrial pollution, pesticides, and contact with finished consumer products, such as plastics — were affecting people and wildlife. Since then public concern about these impacts has grown.

In 2009, the American Medical Association called for reduced exposure to endocrine- disrupting chemicals. Last year, eight scientific societies, representing some 40,000 researchers, urged federal regulators to incorporate the latest research on endocrine-disrupters into chemical safety testing.

Last week, 12 scientists – including such experts as Colborn and the University of Missouri's Frederick vom Saal — published a paper that they say significantly advances the debate. Their research, based on a review of 800 scientific studies, concludes that it is "remarkably common" for very small amounts of hormone-disrupting chemicals to have profound, adverse effects on human health. Hormone-disrupting chemicals, the paper explains, challenge a fundamental tenet of toxicology — "the dose makes the poison" — which contends that the greater the dose, the greater the effect. Hormone-disrupting chemicals don't necessarily behave like this. Significant health effects, the researchers say, sometimes occur at low rather than high doses.

"Whether low doses of endocrine-disrupting compounds influence human disorders is no longer conjecture, as epidemiological studies show that environmental exposures are associated with human diseases and disabilities," the paper's authors write. The study, published in the journal *Endocrine Reviews*, maintains that the low-dose and special dose-response effects of hormone-disrupting chemicals means that "fundamental changes in chemical testing and safety determination are needed to protect human health."

The study's lead author, Laura Vandenberg, a post-doctoral associate at Tufts University's Department of Developmental and Regenerative Biology, said in an interview said that this low-dose and special dose-response behavior "should be expected of any chemical that acts like a hormone."

Not all experts in biology and toxicology agree with the study's conclusions. Some scientists in academia, industry, and the U.S. Environmental Protection Agency said there is not yet convincing proof that extremely low doses of endocrine-disrupting chemicals have ill health effects or consistently produce low-dose effects that are not predicted by their effects at higher doses.

"There's no question that both natural and synthetic compounds can mimic hormones," said George Gray, director of the Center for Risk Science and Public Health at The George Washington University. But that a chemical produces effects at one level, no effects at another, and different effects at yet another level of exposure, "that's not yet widely accepted in toxicology," said Gray. "It's something toxicologists are not yet convinced of and comfortable with," he added.

Hundreds of such hormone-disrupting chemicals have now been identified, and exposure to these compounds is virtually ubiquitous. Among the chemicals the new paper discusses are bisphenol A, used in plastics, can liners, and receipt papers; common pesticides, including atrazine and chlorpyrifos; methyl paraben, a preservative used in cosmetics and personal care products; triclosan, an antibacterial agent used in soaps and toothpaste; nonylphenol, a detergent ingredient; the flame retardant PBDE-99; perchlorate, a fuel compound; and dioxin, an industrial and incineration by-product. The paper also cites DDT and PCBs — discontinued but very environmentally persistent compounds.

"This is the first time anyone's tried to synthesize this whole field and show that this is not a single chemical issue," Vandenberg said of the new study.

Very small amounts of hormones, including endocrine system hormones — those that regulate many of the body's most important systems, among them development, metabolism, and reproduction — can have significant biological effects. So, it's been discovered, can synthetic compounds with similar chemical compositions. Research indicates that exposure to a small amount of such a chemical at a particular stage of development can prompt effects that can impact not just that particular individual, but, in some cases, several generations.

"It's not just sex hormones but also thyroid hormones, and insulin among others, that are involved," said Vandenberg. "We're really complicated instruments."

The health effects documented in the studies the paper reviews have been observed in live animal and cell culture studies and in human epidemiological studies. Their effects include adverse impacts on reproductive and sexual development and fertility; cognition and neurological systems; immune system function; and metabolic effects, including diabetes and obesity. "The weight of the available evidence suggests that EDCs (endocrine-disrupting chemicals) affect a wide range of human health endpoints that manifest at different stages of life, from neonatal and infant periods to the aging adult," write the authors.

Hormones interact with cellular receptors like locks and keys, explained Vandenberg. The hormone or hormone-like chemical is the key, and the receptor, the lock. "Touch the receptor and it starts to produce a response," said Vandenberg. Too much chemical stimulus (the wrong-size key), however, can overwhelm the receptor, causing it to shut down and produce no response.

A key concept of the paper is that endocrine-disrupting chemicals are non-monotonic, meaning that the responses of animals or people to the chemicals do not necessarily intensify or diminish based on

the dose. To illustrate this concept, Vandenberg said, “Picture a line of people, where those on the left have no exposure and those on the right have the most exposure. For endocrine-disrupting chemicals, where the greatest effects occur may not follow that line of increasing exposure level from left to right."

While complex and challenging, the studies gathered in this paper demonstrate that this phenomenon is now well documented, say the authors. “I hope that this paper opens the door to the realization that the endocrine system is the overarching control system of all other body systems,” said Theo Colborn, president of the Endocrine Disruption Exchange, whose work has been instrumental in popularizing knowledge of endocrine-disrupting chemicals. “It controls how we develop, function, and reproduce from the moment we are conceived — in other words, the quality of our lives and our existence."

While epidemiological studies show environmental exposure to EDCs are associated with human diseases, linking a specific environmental chemical exposure to an individual’s health disorder remains difficult, particularly given the many variables that contribute to health outcomes — life stage, genetics, and other environmental factors.

"There are different susceptibilities in different populations that may cause very minute amounts of a hormone to prompt effects in some people but not others,” said Linda Birnbaum, director of the National Institute of Environmental Health Sciences, who was one of the paper’s reviewers. This literature, she said, points to the importance of investigating low doses and timing of exposure when assessing chemicals for endocrine and other hormonal health outcomes, she explained in an interview.

Some scientists think more research is needed to confirm how endocrine disrupting chemicals behave. L. Earl Gray, Jr., a research biologist at the EPA’s Reproductive Toxicology Branch, said these low-dose effects are “certainly biologically plausible.” But he questioned whether there is sufficient evidence to firmly establish the non-monotonic responses of endocrine-disrupting chemicals.

The American Chemistry Council (ACC), which represents chemical manufacturers, issued a statement saying that it “has committed substantial resources” to better understanding the potential effects of chemicals on the endocrine system, and cited a Michigan State University professor emeritus of toxicology who concluded that “low-dose effects have not been proven, and therefore should not be applied to real-world conditions and human exposures.”

To verify these effects, studies must prove the mechanism of these responses and be replicable, said Lorenz Rhomberg, principal at the Gradient Corporation, a private environmental and risk analysis consultancy. “In my experience that’s been lacking,” said Rhomberg, co-author of an ACC-funded study that found low doses of BPA to be without adverse human reproductive and developmental health effects.

But, said Vandenberg, that’s exactly what the new paper shows. “We don't just know that these effects occur, we know how they occur,” she said, noting that for some chemicals like BPA, non-monotonic responses are reported by dozens of labs.

Thomas Zoeller, a University of Massachusetts biologist and paper co-author, said that regulatory testing of chemicals for endocrine-disrupting impacts lags behind the growing evidence of the compounds’ health effects, particularly at levels to which people are routinely exposed. “There is a very large disconnect between regulatory toxicology and the modern science of endocrinology that is defining these issues,” said Zoeller.

How much will testing chemicals at low, environmentally relevant levels improve human health, the paper authors ask? While it's not currently possible to quantify in dollars, current evidence "linking low-dose EDC exposures to a myriad of health problems, diseases, and disorders suggests that the costs of current low-dose exposures are likely to be substantial," they conclude.

"People can easily get overwhelmed by this issue," said Laura Vandenberg. "But from a public health perspective, we can't see this problem as too big to deal with. We wouldn't do that with any other medical problem."

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