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Low Doses of Hormonelike Chemicals May Have Big Effects

Scientists seek "fundamental changes" in testing and regulation of chemicals that mimic human hormones

- By [Marla Cone](#) and [Environmental Health News](#) | March 15, 2012



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That is a main finding of a [report](#), three years in the making, published Wednesday by a team of 12 scientists who study hormone-altering chemicals.

Dozens of substances that can mimic or block estrogen, testosterone and other hormones are found in the environment, the food supply and consumer products, including plastics, pesticides and cosmetics. One of the biggest, longest-lasting controversies about these chemicals is whether the tiny doses that most people are exposed to are harmful.

In the new report, researchers led by Tufts University's Laura Vandenberg concluded after examining hundreds of studies that **health effects "are remarkably common" when people or animals are exposed to low doses of endocrine-disrupting compounds**. As examples, they provide evidence for several controversial chemicals, including bisphenol A, found in polycarbonate plastic, canned foods and paper receipts, and the pesticide atrazine, used in large volumes mainly on corn.

The scientists concluded that **scientific evidence "clearly indicates that low doses cannot be ignored."** They cited evidence of a wide range of health effects in people – from fetuses to aging adults – **including links to infertility, cardiovascular disease, [obesity](#), [cancer](#) and other disorders**.

"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," they wrote.

In addition, the *scientists took on the issue of whether a decades-old strategy for testing most chemicals – exposing lab rodents to high doses then extrapolating down for real-life human exposures – is adequate to protect people.*

They concluded that it is not, and so they urged reforms. Some hormone-like chemicals have health effects at low doses that do not occur at high doses.

"Current testing paradigms are missing important, sensitive endpoints" for human health, they said. "The effects of low doses cannot be predicted by the effects observed at high doses. Thus, fundamental changes in chemical testing and safety determination are needed to protect human health."

The report was published online Wednesday in the scientific journal *Endocrine Reviews*. Authors include scientists University of Missouri's Frederick vom Saal, who has linked low doses of bisphenol A to a variety of effects, Theo Colborn, who is credited with first spreading the word about hormone-disrupting chemicals in the late 1980s and University of California, Berkeley's Tyrone Hayes, who has documented effects of atrazine on frogs.

The senior author is Pete Myers, the founder of Environmental Health News and chief scientist of Environmental Health Sciences.

Linda Birnbaum, director of the National Institute of Environmental Health Sciences, said the new report is valuable "because it pulls a tremendous amount of information together" about endocrine-disrupting compounds. Her agency is the main one that studies health effects of contaminants in the environment.

Birnbaum said she agrees with their main finding: **All chemicals that can disrupt hormones should be tested in ultra-low doses relevant to real human exposures**, she said.

In many cases, chemical manufacturers still are asking "old questions" when they test the safety of chemicals even though "science has moved on," she said. "Some of the testing paradigms have not advanced with the state of the science." Birnbaum wrote an editorial on Wednesday referencing the new report.

Nevertheless, for most toxicologists, Birnbaum said the report does not offer a big shift from what they are doing. The NIEHS already conducts low-dose testing of chemicals, including looking for multi-generational effects such as adult diseases that are triggered by fetal exposures.

"Some people keep slamming the toxicologists. But you can't paint everyone with the same brush," Birnbaum said.

However, the **scientists who wrote the report said that low-dose science "has been disregarded or considered insignificant by many."** They seemed to aim much of their findings at the National Toxicology Program and the U.S. Food and Drug Administration. **The FDA in 2008 discounted low-dose studies when it concluded that bisphenol A (BPA) in consumer products was safe. Two years later, the agency shifted its opinion**, stating that they now will more closely examine studies showing low-dose effects. The National Toxicology Program in 2008 found that BPA poses "some risks" to human health but rejected other risks because studies were inconsistent.

Several of the report's authors have been criticized by some other scientists and industry representatives because they have become outspoken advocates for testing, regulating and replacing endocrine-disrupting compounds. The *scientists, however, say they feel compelled to speak out because regulatory agencies are slow to act and they are concerned about the health of people*, especially infants and children, and wildlife.

Industry representatives say that just because people are exposed to traces of chemicals capable of altering hormones doesn't mean there are any harmful effects. They say that the studies are often contradictory or inconclusive.

In a statement, the American Chemistry Council, which represents chemical companies, said Wednesday that the industry "has committed substantial resources to advancing science to better understand any potential effects of chemical substances on the endocrine system. While we have not had an opportunity to fully review this paper, Michael Kamrin, emeritus professor of Michigan State University, has concluded 'low dose' effects have not been proven, and therefore should not be applied to real-world conditions and human exposures."

"Based on the evidence, it is concluded that these 'low dose' effects have yet to be established [and] that the studies purported to support these cannot be validly extrapolated to humans," Kamrin, a toxicologist, wrote in the International Journal of Toxicology in 2007.

But vom Saal and other scientists have said that tests that do not find low-dose effects of chemicals such as BPA are often industry-funded, and they often have tested the wrong animals or the wrong doses, or don't expose the animals during the most vulnerable time of fetal growth.

Endocrinologists have long known that infinitesimal amounts of estrogen, testosterone, thyroid hormones and other natural hormones can have big health effects, particularly on fetuses. It comes as no surprise to them that manmade substances with hormonal properties might have big effects, too.

"There truly are no safe doses for chemicals that act like hormones, because the endocrine system is designed to act at very low levels," Vandenberg, a postdoctoral fellow at Tufts University's Levin Lab Center for Regenerative and Developmental Biology, told Environmental Health News.

But many toxicologists subscribe to "the dose makes the poison" conventional wisdom. In other words, it takes a certain size dose of something to be toxic. They also are accustomed to seeing an effect from chemicals called "monotonic," which means the responses of an animal or person go up or down with the dose.

The scientists in the new review said neither of those applies to hormone-like chemicals. "Accepting these phenomena should lead to paradigm shifts in toxicological studies, and will likely also have lasting effects on regulatory science," they wrote.

In the report, the scientists were concerned that government has determined "safe" levels for "a significant number of endocrine-disrupting compounds" that have never been tested at low levels. They urged "greatly expanded and generalized safety testing."

"We suggest setting the lowest dose in the experiment below the range of human exposures, if such a dose is known," they wrote.

Vandenberg said that there may be no effect or a totally different effect at a high dose of a hormonal substance, while a lower dose may trigger a disease.

The breast cancer drug tamoxifen "provides an excellent example for how high-dose testing cannot be used to predict the effects of low doses," according to the report. At low doses, it stimulates breast cancer growth. At higher ones, it inhibits it.

"Imagine taking 100 individuals that are representative of the American population and lining them up in order of exposure to an EDC [endocrine-disrupting compound] so that the person on the far left has the least exposure and the person on the far right has the most. For many toxic chemicals, individuals with the highest levels of exposure, at the right end of the line, have the highest incidence of disease. But for some EDCs, studies suggest that people in the middle of the line have the highest risk," Vandenberg said.

She compared hormones, which bind to receptors in the body to trigger functions such as growth of the brain or reproductive organs, to keys in a lock.

"The more keys that are in the locks, the more of an effect that is seen. But at some point, the locks are overwhelmed and stop responding to the keys. Thus, in the lower range, more keys equals more of an effect, but in the higher range, more keys equals less of an effect," she said.

Vandenberg predicted the report "will start conversations among academic, regulatory and industry scientists about how risk assessments for EDCs can be improved."

"The question is no longer whether these phenomena exist, but how to move forward and deal with them."

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