



Time to Update Environmental Regulations

Should public health standards for endocrine-disrupting compounds be based upon sixteenth century dogma or modern endocrinology?

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Health standards established in the United States for exposure to toxic chemicals rest upon a core assumption: high-dose testing procedures used in regulatory toxicology adequately predict potential low-dose effects. Scientific discoveries over the past decade have profoundly challenged that assumption as information has grown about the commonness of contaminants that behave like hormones.

Endocrinologists long ago discovered that hormones have effects at low serum concentrations that can differ dramatically, and unpredictably, from those caused at high levels (1). Indeed, sometimes they can be diametrically opposed. This endocrinological reality stands in direct conflict with any assumption that high-dose studies predict low-dose impacts. If contaminants with hormonal characteristics, known as endocrine disruptors, behave similarly, then the regulatory tests used to establish safety standards may be blind to important impacts.

A growing body of research now confirms that endocrine disruptors, like hormones, can also contradict the expectations of traditional regulatory testing. This creates the strong likelihood that some health standards currently used to set exposure limits for the American public are too weak.

To the nonendocrinologist, it seems logical that higher doses would lead to greater effects. This assumption has been at the core of toxicology for centuries, beginning with Paracelsus's sixteenth-century observation that "All things are poison and nothing is without poison; only the dose permits something not to be poisonous." His quote has been paraphrased to "the dose makes the poison" and is generally interpreted to mean that the higher the exposure, the greater the impact.

For many contaminants, toxins, poisons, and pharmaceuticals, this assumption has helped protect public health. But substantial evidence is now in hand showing that people are exposed to hundreds (if not more) chemicals that can behave like hormones.

Some endocrine-disrupting chemicals are produced in very high volumes. The compounds of greatest concern include plastic monomers and plasticizers used widely in common consumer goods, leading to virtual ubiquitous exposure in the U.S. and other developed countries. For example, the plastic monomer bisphenol A (BPA) was discovered to be an estrogen in the 1930s, but now it is used as the basic chemical building block for polycarbonate plastic and an epoxy resin used to line most food cans sold in U.S. supermarkets today.

The chemical characteristics of polycarbonate and the epoxy resin guarantee that normal use will contaminate food and water that comes into contact with BPA-based materials, especially if heated. Most plastic baby bottles are made with polycarbonate, and baby formula cans are lined with the resin. This will result in substantial, unavoidable exposures for infants fed warmed formula.

Many studies have shown that BPA is capable of causing a wide range of adverse effects in laboratory studies at serum concentrations beneath the median level found in people throughout the developed world (2). The adverse effects caused by fetal exposure and infant exposure to BPA in animal experiments include breast cancer, prostate cancer, impaired fertility, cystic ovaries, uterine fibroids, hyperactivity, and obesity. The current EPA and FDA health standards for BPA, however, are based upon traditional toxicological testing conducted in the 1980s. Modernizing the BPA standard based on current science would require lowering acceptable exposures by a factor of at least 5,000-fold and would require elimination of BPA from many common products.

Driven by a need to be cost-effective, regulatory toxicology has applied the "dose makes the poison" concept in practice by testing first at high doses and then testing at successively lower doses until no response, or little response, is seen. Often only three or four doses are used, and for the vast majority of chemicals these are rarely, if ever, low enough to be comparable to levels experienced by the general public. The assumption is that this high-dose testing protocol predicts the types of effects that might take place at much lower levels. And because "the dose makes the poison," the expectation is that by working down the dose-response curve from a level that clearly causes an effect to one that does not, this process can identify exposures beneath which there will be no harm.

Endocrinology, however, is replete with cases in which hormone action at low levels differs dramatically from hormone action at high levels. For example, administering newborn mice a high dose (1000 µg/kg/day) of the estrogenic drug diethylstilbestrol (DES) causes weight loss in adult mice. In contrast, a dose of 1 µg/kg/day causes grotesque obesity in adulthood (3).

Another example with clinical implications comes from the well-known "tamoxifen flare." Tamoxifen is useful clinically because at high doses (administered daily at 20 to 40 mg) it is an antiestrogen, suppressing proliferation of breast cancer cells and producing tumor regression (4). Early during treatment, however, when tissue levels are still rising, tamoxifen administration can cause several estrogenic effects, including a slight increase in tumor size. Research by Wade Welshons at the University of Missouri has explored the molecular mechanisms of the tamoxifen flare and finds that at serum concentrations 10,000 times beneath the level used to suppress breast cancer cell proliferation, tamoxifen acts as an estrogen, actually promoting proliferation (Welshons, pers. comm.). Ironically, his calculations show that if one were to use standard risk assessment procedures with the tamoxifen dose-response curve— identifying the highest exposure with no discernable effect and then applying a series of safety factors that take into account various sources of uncertainty—the concentration with maximum proliferative effect would be identified as a safe level of exposure.

In the tamoxifen flare, the dose-response curve showed inhibition at high levels and proliferation at low—that is, completely opposite effects. This is a special case of what are called nonmonotonic dose-response curves: dose-response relationships in which the slope of the line plotting response as a function of dose changes its sign (positive to negative or the reverse) somewhere over the range of doses used.

Clinicians who treat women and men for hormone-stimulated diseases (uterine fibroids, prostate cancer) advise their patients who take a hormone (Lupron) that some adverse effects occur during the initial phase of treatment. This is due to the fact that as the amount of the drug increases after injection, the low doses of Lupron result in the ovaries producing estrogen or the testes producing testosterone; only after reaching a high dose is the drug's desired effect, inhibition of estrogen or testosterone production, achieved—opposite effects occur at low and high doses. This is not just true for hormonally active drugs but for all hormones and hormone-mimicking chemicals used in products.

As research has progressed in the toxicology of endocrine-disrupting compounds, nonmonotonic curves have been reported regularly (5). One of the earliest examples involved the response of the mouse prostate to exposure to several different estrogenic compounds during fetal development (6). These experiments examined the adult prostate weight following fetal exposure, separately, to estradiol or diethylstilbestrol (DES); analogous nonmonotonic findings now exist for BPA in human prostate cancer cells (7). Each experimental series, conducted over an extremely wide range of doses, showed that the highest exposures did not differ from the controls, but that intermediate doses led to significant increases in prostate weight and also to sensitivity to androgen stimulation. The dose-response curve took the shape of an inverted U, a descriptor now used in the literature to describe this type of nonmonotonic dose-response curve. If the dose range had been extended even higher, the response would have fallen significantly beneath the controls as exposure moved into a concentration at which the compounds were overtly toxic. This was demonstrated at the level of individual genes involved in regulating prostate growth (8).

Other endocrine-disrupting compounds demonstrating nonmonotonic patterns include the phthalate DEHP; the pesticides DDE, dieldrin, endosulfan, and hexachlorobenzene; and arachlor 1242, a PCB (5). Some of the reported effects include strong exacerbation of allergic reactions following exposures well beneath current safety standards.

Extensive evidence is now available on the molecular and physiological mechanisms that are responsible for these findings. At very low doses, hormones can stimulate the receptors in cells that allow the hormone to cause effects in the cells (called "receptor up regulation"), while at higher doses, receptor "down regulation" occurs and the number of receptors available to mediate the action of the hormone is reduced (1, 9). Also, there are myriad hormonal feedback mechanisms between the brain, pituitary gland, and hormone-producing organs (thyroid gland, adrenal glands, ovaries, testes) that contribute to the presence of nonmonotonic dose-response curves.

The chemical risk assessment establishment has been unresponsive to the fact that one of its core assumptions has been invalidated. Hence, no standard for any contaminant has incorporated these well-established findings from endocrinology. Instead, standards continue to be based upon testing procedures that assume high-dose testing can adequately predict low-dose results.

The American public depends upon regulatory agencies to set public health standards that will avoid harmful exposures. It is time that the FDA and EPA move beyond sixteenth-century dogma and begin using twenty-first-century scientific knowledge to accurately determine the safety of the chemicals being used in plastic, toys, food containers, pesticides, cosmetics, building materials, clothes—in other words, countless products and materials we incorrectly assume are safe. Given the wide range of health effects now shown to be caused in animals by exposure to these contaminants, modernizing the standards may reap large benefits for public health.

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