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Compound Interest: Assessing the Effects of Chemical Mixtures *in Vivo*

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Humans are exposed to mixtures of chemicals through food, air, water, dust, and household and personal care products. In most cases, little is known about the combined effects of potentially harmful chemicals. A mouse study in *Environmental Health Perspectives* tested whether one constituent of a chemical mixture might alter tissue levels of the others. If so, the effects of the mixture on the mouse's health might be different from the effects that would be predicted based on the effects of each chemical by itself.[1] Such information is important when assessing the potential health risks of chemical mixtures to which the public may be exposed.

For their experiment, the researchers selected three chemicals to which the public is often exposed: bisphenol A (BPA), triclosan, and tetrabromobisphenol A (TBBPA). BPA is a component of some plastics and epoxy resins that are used to make food and beverage packaging. Triclosan is an antibacterial agent found in multiple personal care products and other items,[2] although it has been removed from over-the-counter soaps sold in the United States.[3] TBBPA, a widely used brominated flame retardant, is often found in house dust.[4]

The scientists chose these particular chemicals because "they are common human exposures that are known to have some estrogenic action," says senior study author Denys deCatanzaro, a toxicologist at McMaster University in Ontario, Canada. Previously, deCatanzaro's team showed that triclosan alone could elevate BPA levels in the reproductive tissues of male and female mice.[5]

Toxicologists have traditionally focused on the effects of one chemical at a time. This approach can be useful for determining the molecular pathways through which a particular chemical may produce an effect, according to lead study author Tyler Pollock, a PhD candidate at McMaster. However, this approach can overlook health effects of that chemical after coexposures, Pollock says.

In a series of three experiments, the researchers subcutaneously injected mice with TBBPA, triclosan, or both; the study used doses much larger than typical human exposures.[1] Then, they fed the mice a radiolabeled form of BPA in a dietary supplement. Although every effort is made to eliminate BPA from the environment of laboratory animals, some may remain in food, bedding, and dust, deCatanzaro says. Using a radioactive tracer helps researchers account for background levels by ensuring that they measure only the doses administered during the experiment.[6]

A new study in mice examined the combined effects of two chemicals on tissue levels of a third chemical. All three chemicals are widely used in personal care and household products, although the mice received much smaller doses than typical human exposures. Image: © nensuria/iStockphoto.

Moreover, deCatanzaro says, using radiolabeled BPA provides a cost-effective and highly sensitive method for quantifying chemical levels in tissues.

In the first experiment, the authors measured the effects of TBBPA on BPA levels in the animals' blood, reproductive organs, heart, lungs, and kidneys. These tissues are particularly rich in estrogen receptors, and there is potential to perturb sexual development and fertility, says deCatanzaro. In the second experiment, the authors measured the combined effects of TBBPA and triclosan on BPA levels. In the third experiment, they examined the effects of TBBPA on levels of the female sex hormone estradiol.

When TBBPA was given alone, BPA concentrations increased in several tissues, but only in females dosed with 3 mg TBBPA and males dosed with 1 mg TBBPA.[1] When triclosan and TBBPA were administered together, the authors used 0.33 mg of triclosan and 0.33 mg of TBBPA, resulting in a combined dose that was slightly higher[1] than the lowest effective dose identified for triclosan alone.[5] Although there were no significant increases in BPA following injections of 0.33 mg of either chemical alone, the combined dose was associated with a significant increase in BPA concentrations in some tissues.[1]

"What we see is that each chemical can significantly alter the other chemical's toxicokinetics [i.e., the rate at which the body metabolizes the chemical]. In the presence of these other chemicals, you get higher BPA exposures in mice," says Pollock. The data are consistent with previous findings that suggest TBBPA and triclosan inhibit enzymes critical for eliminating BPA and estradiol from the body.[7,8]

Although regulatory agencies often base their calculations of tolerable daily intake on the toxicity of individual chemicals, this study demonstrates the limitations of a single-chemical approach in estimating the impact of chemical exposures on public health. "This study … gives the field a new perspective on how to approach the question of adequately and accurately describing how the different chemicals in a mixture can exert biological effects," says Gabriel Knudsen, a toxicologist at the National Cancer Institute, who was not involved in the study.

Knudsen says he hopes that applying this new "mixtures" approach can help inform agencies tasked with setting and enforcing chemical regulations. "More mixtures studies like this one could help shape more well-informed and useful regulations for chemicals that are encountered by people every day," he says.

Lindsey Konkel is a New Jersey–based journalist who reports on science, health, and the environment.

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