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Science 2.0

Does Chemical X Cause Disease Y, And How Do We Know?

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That question is particularly relevant this week in light of numerous media articles reporting that exposure to a common chemical is linked to obesity in children and adolescents. Underlying the articles is a new study on bisphenol A (BPA) published this week in Pediatrics. The key question is that of causation versus statistical association.

The new study is a cross-sectional epidemiology study in which the data analyzed is all collected at the same time. The data are from the NHANES (National Health and Nutrition Examination Survey) database, which collects extensive health and nutrition information on a nationally representative sample of about 5,000 people each and every year. Also collected is biomonitoring data from analysis of blood or urine samples for more than 300 chemicals, including BPA. To be more precise, the analysis measures metabolites of BPA, the significance of which is discussed below.

The availability of the NHANES database has led to a proliferation of cross-sectional studies "linking" exposure to various chemicals with a wide range of disease conditions or other health parameters. While cross-sectional studies do have some legitimate uses, they also have significant limitations.

Image credit: BevNet

An important limitation is that because all of the data is collected at the same time, there is no way to know if the exposure preceded the disease, which is critical to establishing causation, or whether the disease preceded the exposure. Related to this lack of temporal information is the possibility of reverse causation. In the new study, did BPA cause obesity or is it possible, even likely, that obese people are exposed to more BPA by consumption of more food? Extensive testing has shown that diet is the source of most BPA exposure. There is simply no way to know in a cross-sectional study and, thus, no possibility to establish causation.

The lack of temporal information is particularly important for chemicals that have short physiological half-lives. Numerous studies on laboratory animals and humans show that BPA is eliminated in urine

with a half-life of only a few hours. For this reason, BPA levels in urine show high variability not only day-to-day, but even within a day. Although the authors of the new study state that it is "unclear if a single measure of BPA would be indicative of long-term exposure," it is actually quite clear that single measures are not predictive of past or future exposures. Consistent with other studies, one from a group of researchers in Denmark, published a couple weeks ago, concluded: "A consequence of the considerable variability in urinary excretion of BPA may be misclassification of individual BPA exposure level in epidemiological studies."

Other signals that something is amiss are the lack of a clear dose-response and inconsistencies within the study. For example, a statistical association was reported between BPA exposure and body mass index (BMI) greater than the 95th percentile, which was defined as obesity, but not for body mass index greater than the 85th percentile, which was defined as being overweight. Is it really plausible that BPA could cause obesity, but have no effect on being overweight? Other parameters that might be expected to be related to obesity also showed no association with BPA exposure.

The limited results reported in the study might easily be due to confounders that were not considered, or simply chance statistical associations. As discussed by others, "using cross-sectional datasets like NHANES to draw such conclusions about short-lived environmental chemicals and chronic complex diseases is inappropriate."

Finally, although not discussed by the authors, the biological plausibility of the reported statistical associations must be considered. Studies on humans and non-human primates show that BPA is efficiently converted to biologically inactive metabolites during absorption from the gastrointestinal tract and by the liver before entering circulation. Systemic exposure to BPA itself is less than 1% of the amount absorbed. Although BPA is well known to be weakly estrogenic, could this low level be sufficient to activate estrogen receptors in the body and lead to health effects? In a word, the answer is no, according to new research from scientists at the Pacific Northwest National Laboratory and FDA. Using reported urine levels, including values from the NHANES database, the researchers estimated blood levels and compared these with the levels that would be required to activate five different receptors. Even for the highest affinity receptor, the authors conclude "Our results show limited or no potential for estrogenicity in humans."

Based on all we know, it seems extremely unlikely that BPA causes obesity.