LETTER TO THE EDITOR

Invalid Controls Undermine Conclusions of FDA Studies

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We are writing in response to the recent paper on bisphenol A (BPA) by Delclos et al. (2014) and the related paper by Churchwell et al. (2014). These manuscripts represent some of the first data from an important multi-investigator initiative sponsored jointly by the U.S. Food and Drug Administration (FDA) and two divisions of the National Institute of Environmental Health Sciences, the National Toxicology Program (NTP), and the division of extramural research and training. Through this joint initiative, investigators from the FDA and academic researchers are working together for the first time to address important questions surrounding BPA and the risks to human health. This is a costly but critically important investment that will underpin future decisions to protect the public’s health. Although we applaud both federal agencies for their investment, the Delclos et al. and Churchwell et al. publications raise serious concerns about the wisdom of investing research resources and expertise in this multi-investigator initiative. In the preliminary studies reported in these papers, a concerted effort was made to control for BPA contamination in both animal contact materials and those used in sample collection and analysis. Nevertheless, serum analyses revealed that both sets of negative control animals (naive and vehicle only controls) had experienced significant BPA exposure, with serum BPA levels equivalent to those in the lowest BPA exposure groups. Positive and negative controls are essential for this study: Positive controls demonstrate that the animals are estrogen sensitive, and negative controls provide a point of reference for assessing adverse effects. The stated objective of the study was to examine low-dose effects of BPA (i.e., below the published NOAEL [No observed adverse effect level]), not just effects at very high, acutely toxic doses. Contamination in negative controls renders this control group useless for assessing low-dose effects.

Delclos et al. assessed a wide variety of endpoints and conclude that adverse effects only occur at extremely high BPA doses. This is a remarkable conclusion because in the absence of uncontaminated negative controls, it is impossible to determine if lower doses induced effects, especially because BPA levels in controls were similar to those in the four lowest dose groups (i.e., up to 80 μg/kg/day). Churchwell et al. state that the source of the contaminating BPA could not be identified, “but interpretation of the toxicological effects, observed only at the highest BPA doses, was not compromised.” Essentially, the authors are arguing that they can make meaningful interpretations in the absence of controls. This not only violates basic scientific principles, it is untenable in view of the large body of published data demonstrating adverse effects at low doses and nonmonotonic responses for a variety of BPA-induced effects. In the absence of uncontaminated negative control animals, meaningful conclusions about the effects of low doses of BPA simply cannot be made.

Given the concerns in this field and the controversy already surrounding BPA, it is essential that researchers, reviewers, and editors maintain stringent standards. This is, however, particularly important for large-scale studies conducted using good laboratory practice (GLP) guidelines for toxicology studies, because...
these studies are generally accorded more weight in the regulatory arena. The studies by Delclos et al. and Churchwell et al. are particularly disappointing because they were conducted under the auspices of the FDA and will therefore—despite their significant limitations—be cited extensively. More importantly, the results reported in these manuscripts raise a very real concern: If the contamination problem has not or cannot be resolved, the subsequent large consortium effort seems destined to be a flawed study on an unprecedentedly grand scale.

REFERENCES