Urine Chemical Content May Be a False Measure of Environmental Exposure

This month *Pediatrics* has published 2 articles on environmental chemical exposures that warrant commentary. “Urinary Phthalates and Increased Insulin Resistance in Adolescents” (Trasande et al1) and “Bisphenol A and Chronic Disease Risk Factors in US Children” (Eng et al2). Both of these articles use the urinary content of the chemical as a surrogate for the chemical exposure.

Dr Trasande and his group in the article on phthalates conclude that urine phthalate concentrations (represented by urine di-2-ethylhexylphthalate [DEHP] concentrations) were associated with increased insulin resistance in this cross-sectional study of adolescents. Dr Trasande refers to this as an association and indicated that this study cannot rule out the possibility that insulin-resistant children ingest food with higher phthalate content or that insulin-resistant children excrete more DEHP. Without knowing the tissue or serum concentration of DEHP or referring to primate studies, the authors’ hypotheses are appropriate.

The second article by Eng et al deals with bisphenol A (BPA). It is most important for authors to be familiar with the literature concerning the chemical that they are evaluating. Unfortunately, the BPA article fails to cite important publications dealing with the metabolism of BPA. For example, Daniel Doerge, a well-known authority on the metabolism of BPA, has co-written 5 publications that Eng et al have not cited.3–8 In 2011, in a report entitled, “Twenty-Four Hour Human Urine and Serum Profiles of Bisphenol A during High-Dietary Exposure”3 these investigators found that urinary BPA is not a surrogate of a serum or tissue exposure to BPA, but reflects the intake of BPA in the diet of the individual whose urine has been collected. This study, published in *Toxicological Sciences*, studied 20 adult volunteers who ingested 100% of 1 of 3 specified meals comprising of standard grocery store items for breakfast, lunch, and dinner. They studied the serum concentration of BPA, which was only measurable in the serum of patients with exposure of 1.3 to 3.9 times higher than the 95th percentile of aggregate US exposure. “BPA serum concentrations were primarily less than or equal to the limit of detection…and were on average, 42 times lower than urine concentrations. During these high dietary exposures, BPA concentrations in serum were undetectable in 83% of the 320 samples collected and BPA concentrations were determined to be less than or equal to LOD [limit of detection] in all samples.”

Because there is little BPA in the serum even with large intakes of BPA and the metabolism of BPA in the serum destroys its endocrine receptor affinity, there is little justification to assume that BPA has toxic exposure in the human, even with very high exposure in the diet. Most BPA articles in humans use the urine content of BPA as a surrogate of exposure, when in reality it is a measure of the intake of BPA.
from the diet. The actual serum levels are extremely low and in many instances not detectable. Therefore, the studies that determine the effect of BPA by using urinary BPA levels are unlikely to be valid. Duty et al (2012)\textsuperscript{8} evaluated BPA in neonates in the nursery and found that newborns who were breastfed or formula bottle-fed had similar amounts of BPA in their urine. BPA in nursing bottles has been banned. Yet in reality, the BPA was not derived from the nursing bottle, but from the breast milk and formula milk in the bottle. We are fortunate that there is not an attempt to ban breastfeeding.

Another important article worth citing is the work of Dr Tyl,\textsuperscript{9} which is an excellent animal study evaluating oral effects of BPA entitled, “Three-Generation Reproductive Toxicity Study of Dietary Bisphenol A in CD Sprague Dawley Rats.,” This is almost a perfect study for the following reasons\textsuperscript{10,11}: bisphenol was placed in the diet ad libitum among 7 exposure groups with a range of exposures that were over a 500 000-fold range. Only at the highest dosages were any potential toxic effects of BPA observed. It was not until the animals received 500 mg/kg that any adverse effects were observed, far higher than the highest reported experimental point previously used in animal studies.

Yamada et al\textsuperscript{12} studied maternal serum and amniotic fluid BPA concentrations in the second trimester. The average concentration of BPA was 0.32 nM/mL that is far below the no-effect level that Dr Tyl determined in her animal studies. Although research dealing with the toxicity of BPA has indicated an increase of birth defects, neural behavioral defects, hypospadias, cryptorchidism, growth retardation, and prematurity, actually, it is unlikely that these levels in the serum of animals and humans have any possibility of producing these effects, and that using the urinary concentration of BPA as a surrogate of exposure can lead to serious misleading conclusions. Both of the studies published in this issue combined with the others that I have referenced in this commentary strongly suggest that using urine as a marker of an environmental toxin is not necessarily reflective of a significant exposure. Readers should use caution in interpreting more than the data actually indicate.

REFERENCES

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