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LETTER TO EDITOR

Report of Very Low Real-World Exposure to Bisphenol A is Unwarranted Based on a Lack of Data and Flawed Assumptions

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The article by Teeguarden *et al.* (2011) contains numerous flawed assumptions, omissions, and misrepresentations of the published literature on bisphenol A (BPA) that demand our rebuttal. We herein raise serious issues regarding the validity of the conclusions reached by the authors. The title itself, "24-h Human Urine and Serum Profiles of Bisphenol A During High Dietary Exposure," clearly states that study participants were exposed to high amounts of BPA. A fatal flaw of this study is the complete absence of the critical and necessary data concerning actual BPA levels in the meals fed to the small number (20) of adult participants isolated in a BPA-free clinical facility during the study. In fact, the results suggest that BPA exposure from many of the different meals was very low, the opposite of what the title states.

Teeguarden *et al.* state: "Very little $_{TOT}$BPA was eliminated after ingestion of all study breakfasts and lunches 1 and 2 evidence that these meals contained very little $_{TOT}$BPA relative to the other meal." This directly contradicts the misleading title and acknowledges that, in fact, an unknown but clearly low exposure to BPA occurred during much of the study. How this translates into "High Dietary Exposure" as used in the title is entirely unclear. The consequence was that all serum samples had no detectable unconjugated (biologically active) BPA, 86% of serum samples had no detectable total BPA, and 51% of urine samples taken between breakfast and lunch were below the level of detection for total BPA. The urine data vary sharply from detection of total BPA in urine from 93% of the U.S. general population, based on the National Health and Nutrition Examination Survey (NHANES) conducted by the U.S. Centers for Disease Control and Prevention (CDC) (Calafat *et al.*, 2008; Stahlhut *et al.*, 2009).

A serious omission in the "Discussion" section by Teeguarden *et al.* is a study showing that removal of known sources of BPA from the diet of five families resulted in a 66% reduction in total urine BPA levels from 3.7 ng/ml (16.2nM) preintervention to 1.2 ng/ml (5.3nM); a return to the diet being consumed before the experiment resulted in a rapid rebound to preintervention urine BPA levels, with 100% of samples containing measurable BPA (Rudel *et al.*, 2011). This finding clearly documents that removal of BPA from the diet reduces measurable BPA, whereas return to using BPA-containing products increases BPA levels—the classic scientific experimental design. This publication directly contradicts the conclusion by Teeguarden *et al.* that in the real world, there is little BPA exposure. This is further supported by over 20 publications reporting measurable serum unconjugated BPA in the general human population (Vandenberg *et al.*, 2010a) at median levels well above those that result in adverse effects in experimental animals (Prins *et al.*, 2011; vom Saal *et al.*, 2007). It is notable that none of the publications showing substantial BPA in human serum and other tissues from multiple experiments using a variety of methods are cited in the Teeguarden *et al.* study.

A likely explanation for the discrepancy between the CDC's NHANES and Teeguarden *et al.* data, and that also negates the exposure estimates cited by Teeguarden *et al.*, is that there are multiple unknown sources and routes of exposure to BPA. Thus, it is highly unlikely that all BPA exposure is due solely to leaching from cans and polycarbonate food and beverage containers. For example, it is known that thermal paper is coated with milligrams of free BPA (Mendum *et al.*, 2011), which could be just one of many nondietary sources of BPA, and cashiers have higher levels of BPA than people in other jobs (Braun *et al.*, 2011). In the Rudel *et al.* (2011) study in the real world, even after limiting BPA exposure via the diet, there remained detectable levels of

BPA in all parents and children. The assumption that all BPA exposure is via the diet, and that BPA is rapidly and completely cleared from the body within 24 h, is also not supported by published data for total urine BPA in the CDC's NHANES study (Stahlhut *et al.*, 2009). Food and Drug Administration (FDA) administrators have stated that under the current laws, they do not have the authority to require reporting of products that contain BPA (FDA, 2010); this makes it impossible to account for the sources of exposure contributing to BPA levels that are detected in people after the few known food packaging sources are eliminated from the diet (Rudel *et al.*, 2011).

It is important to note that the authors of this study do not provide brand identification of the canned foods that were fed to the study participants. This is significant because published data and publicly available information have shown that within a given food type, high BPA levels are found in certain brands but much lower levels are measured in the same canned food from an alternate company. Furthermore, it is known that most cans used for canned fruit—a major portion of the diet in the Teeguarden study—do not use BPA-based epoxy lining on the main wall of the can. Consistent with this, Braun *et al.* (2011) report that consumption of canned fruit is not a predictor of higher BPA exposure. Consequently, in the absence of quantifying the BPA in food given to the study participants, there is no basis for the claim that they had High Dietary Exposure.

Since the investigators failed to directly measure BPA levels in the participants' meals and due to limited data from their study, they were forced to make exposure estimates based on other reports. The Teeguarden *et al.* exposure estimates are flawed in that they are all based on single oral bolus studies, although they examined BPA levels after ingestion in food. This matters for BPA because the assumptions concerning pharmacokinetic parameters from single oral bolus studies (Volkel *et al.*, 2002) have been shown to not be applicable to BPA consumed in the diet, which anyone familiar with differences in pharmacokinetics due to method of drug delivery would predict (Sieli *et al.*, 2011).

Instead of actually measuring BPA in the diet, Teeguarden *et al.* state that they used data from an oral bolus BPA administration study with a small number of people (Volkel *et al.*, 2002) to estimate exposure of participants in the present study. However, the Volkel *et al.* study itself has been criticized due to assay insensitivity and the inability to detect unconjugated BPA in serum owing to high background contamination relative to any other published study that measured BPA in serum or urine (Taylor *et al.*, 2011; Vandenberg *et al.*, 2010a, 2010b). The Volkel *et al.* (2002) study assay insensitivity was actually acknowledged by Teeguarden *et al.*: "The current results obtained using analytical methodology 10–45 times more sensitive than the previous human study by Volkel *et al.* . . ." However, in the process of developing a high-throughput assay for BPA, the sensitivity of the BPA assay reported in the Teeguarden *et al.* study has decreased fourfold from the detection limit reported by the CDC in 2005 (Calafat *et al.*, 2005), and other studies dismissed as flawed were more sensitive than the assay used by Teeguarden *et al.* (Vandenberg *et al.*, 2010a).

Teeguarden *et al.* draw the conclusion that "reported BPA concentrations in human blood of 1.4–19.2nM (Vandenberg *et al.*, 2010a) are highly unlikely in the general population." The idea that estimates of BPA exposure, given without actually measuring BPA intake, would be used to assure the public that there should be little concern about exposure to BPA, even though extensive other data contradict that conclusion, is very disturbing. Teeguarden *et al.* seek to simply dismiss all other studies contradicting their conclusions as flawed and state: "Such BPA blood concentrations would require 'oral exposure' to BPA 2–3 orders of magnitude greater than aggregate exposure levels derived from urinary BPA concentrations." To justify the above statement, Teeguarden *et al.* cite three articles (Dekant and Volkel, 2008; Lakind and Naiman, 2008, 2011) that were funded by The Polycarbonate/BPA Global Group of the American Chemistry Council, although these estimates have been deemed to be flawed by others (Vandenberg *et al.*, 2010a,b; vom Saal *et al.*, 2007).

The statements above by Teeguarden *et al.* indicate that they believe that assumptions based on models that lead to estimates (guesses) about exposure can be used to dismiss data from about 20 peer-reviewed published studies that used a wide variety of techniques and showed serum levels of unconjugated BPA in the 1–19nM range; this is similar to conclusions reached in all industry-funded studies (Vandenberg *et al.*, 2010a,b). This conclusion has been rejected as violating basic principles of science in a consensus report from a meeting on BPA held by the German EPA (Gies *et al.*, 2009). The consensus report identified that when data contradict a model, it is unacceptable to reject the data (based on unsupported allegations of contamination), but instead, scientists are required to change the model to account for the data.

Most disturbing is that Teeguarden *et al.* assure the public that BPA is not a concern for babies: "Taken together, our findings are evidence that on the basis of internal exposures to BPA, the active form of the compound, and the Prins *et al.* (2011) rat model of histological changes from neonatal exposure to BPA, that BPA promotion of PIN (early-stage prostate cancer) would not be expected in the general human population . . ." The Teeguarden *et al.* study did not measure BPA levels in babies, nor did it measure BPA in the general human population. Rather, they measured BPA in adult subjects isolated from the real world in a clinical research facility with controlled diets containing unknown amounts of BPA, although as the authors identify, in the majority of the diets, BPA levels were likely very low. That the public can be assured that babies are safe based on data presented in this study is preposterous, given that both drug and chemical (including BPA) metabolism in fetuses and newborns is known to be limited relative to adults (Taylor *et al.*, 2008, 2011).

There is currently a plethora of data in experimental animal models that low-dose exposures to BPA during development that leads to blood levels of unconjugated BPA found in human fetuses (Vandenberg *et al*., 2010a) increases adult risk for prostate and breast cancer and causes reproductive, immune, neurobehavioral, and metabolic abnormalities throughout life (Richter *et al*., 2007; Vandenberg *et al*., 2009). There are also published human data relating neurobehavioral problems in children to maternal levels of BPA during pregnancy (Braun *et al*., 2009). Furthermore, there is ample evidence in animals and humans that adult low-dose BPA exposures have negative health consequences (Richter *et al*., 2007). This study by Teeguarden *et al*. had the potential to add to our understanding of the contribution of dietary exposure to BPA on human serum and urine levels in a highly controlled environment without other sources of BPA exposure encountered in the real world. However, due to the flaws described above, this study actually has minimal value.

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