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**In Reply:** Dr Weingärtner and colleagues raise an issue regarding elevated plasma plant sterol concentrations and increased risk of coronary heart disease (CHD). However, this assessment did not take into consideration important human epidemiological studies that suggest a reduction in CHD risk with increased plasma plant sterol levels. In a large cross-sectional human study of 2542 middle-aged persons, plant sterol levels were not associated with increased CHD risk or family history of CHD.<sup>1</sup> Results of a cohort study with 1242 individuals aged 65 years or older in the Longitudinal Aging Study Amsterdam (LASA) revealed that moderately increased and high concentrations of plasma sitosterol were associated with reduced CHD risk.<sup>2</sup> The prospective EPIC-Norfolk population study showed no difference in baseline plasma plant sterol concentrations between healthy subjects who developed CHD during the 6-year follow-up compared with those who did not.<sup>3</sup> The wide age range and ethnic diversity of these large studies suggest that their findings will be relevant to the general population.

Treatment with statins lowers plasma cholesterol by inhibiting cholesterol synthesis, which causes a compensatory increase in sterol absorption and may lead to increased plasma sterol concentrations. Nevertheless, statins reduce CHD risk. Plant sterol concentrations are higher in vegetarians, and the human ancestral diet provided more than 1 g of plant sterols per day. Yet vegetarians have a low CHD risk. In epidemiological studies, plasma plant sterol levels reflect cholesterol absorption where plant sterols are not being supplemented. Individuals using plant sterol supplementation or those consuming increased nuts, fruit, and vegetables may also have higher levels of plasma plant sterols, yet nut, fruit, and vegetable consumption is not implicated in increasing CHD risk.

Weingärtner et al showed an atherogenic effect for plant sterol supplementation in mice.<sup>4</sup> However, the dosage used for mice was about 100 times higher than the usual amounts consumed by humans. In addition, studies in animals including apoE-deficient mice, apoE\*3 Leiden transgenic mice, ABCG5/8 knockout mice, rabbits, obese Zucker rats, and hamsters have shown that plant sterols protect against development of atherosclerotic lesions, plaque formation, vascular endothelial damage, and foam cell formation.<sup>5</sup>

In summary, based on evidence from both humans and animal models, we believe that plant sterol levels in plasma are not related to increased CHD risk.

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## RESEARCH LETTER

### Canned Soup Consumption and Urinary Bisphenol A: A Randomized Crossover Trial

**To the Editor:** Human exposure to bisphenol A (BPA) is widespread.<sup>1</sup> In adults, urinary BPA concentrations are positively associated with cardiovascular disease and diabetes.<sup>2</sup> Exposure occurs primarily through the diet.<sup>3</sup> Bisphenol A has been quantified in many canned goods,<sup>4,5</sup> where it is present as a by-product of interior epoxy coatings used to prevent corrosion. We hypothesized that canned soup consumption would increase urinary BPA concentrations relative to fresh soup consumption.

**Methods.** In 2010, we recruited Harvard School of Public Health (HSPH) student and staff volunteers (aged >18 years) via informational fliers and e-mail. The study was approved by the HSPH institutional review board. Written informed consent was obtained.

We used a randomized, single-blinded, 2 × 2 crossover design. For the first 5-day period (October 25-29, 2010), one group consumed a 12-ounce serving of fresh soup (prepared without canned ingredients) daily between 12:15 and 2 PM; the other group consumed a 12-ounce serving of canned soup (from 18.5-ounce Progresso brand) per the same schedule. After a 2-day washout, treatment assignments were reversed (November 1-5, 2010). We used 5 different

varieties of vegetarian soup per treatment and repeated them in the same order the following week. Participants were not restricted in their consumption of other foods.

Donation of spot urine samples took place between 3 and 6 PM on the fourth and fifth days of each phase. Urine was collected in polyethylene containers and stored in polypropylene cryogenic vials. When urine was donated both days, combined urine samples were created to minimize within-person variation. The specific gravity (SG) of the urine was measured using a handheld refractometer; total (free plus conjugated species) urinary BPA concentration was measured at the Centers for Disease Control and Prevention using online solid-phase extraction coupled to isotope dilution high-performance liquid chromatography–tandem mass spectrometry.<sup>6</sup>

Urinary BPA concentrations were adjusted for dilution by multiplying values (in  $\mu\text{g/L}$ ) by  $[(1.014 - 1)/(SG - 1)]$ . In the absence of a period effect, we used a paired *t* test to examine mean absolute change in SG-adjusted untransformed urinary BPA concentrations ( $\text{BPA}_{\text{canned}} - \text{BPA}_{\text{fresh}}$ ) because differences were normally distributed, and we calculated confidence intervals for the mean using SAS version 9.2. Statistical tests were 2-sided and performed at the .05 level of significance.

**Results.** Of 84 volunteers, 75 (89%) completed the study. Median age was 27 years and 51 (68%) were female; median treatment adherence was 100% (TABLE). Bisphenol A was detected in 77% ( $n=58$ ) of samples after fresh soup consumption and 100% ( $n=75$ ) of samples after canned soup consumption. The SG-adjusted geometric mean concentration of BPA was 1.1  $\mu\text{g/L}$  (95% CI, 0.9–1.4  $\mu\text{g/L}$ ) after fresh soup consumption (unadjusted: 0.9  $\mu\text{g/L}$ ; 95% CI, 0.7–1.2  $\mu\text{g/L}$ ) and 20.8  $\mu\text{g/L}$  (95% CI, 17.9–24.1  $\mu\text{g/L}$ ) after canned soup consumption (unadjusted: 17.5  $\mu\text{g/L}$ ; 95% CI, 14.1–21.8  $\mu\text{g/L}$ ). Stratification by treatment sequence revealed similar values (FIGURE). Following canned soup consumption, SG-adjusted urinary BPA concentrations were, on average, 22.5  $\mu\text{g/L}$  higher (95% CI, 19.6–25.5  $\mu\text{g/L}$ ) than those measured after a week of fresh soup consumption ( $P < .001$ ), representing a 1221% increase.

**Comment.** Consumption of 1 serving of canned soup daily over 5 days was associated with a more than 1000% increase in urinary BPA. Generalizability is limited due to selection of participants from 1 school and testing of a single soup brand; however, generalizability to canned goods with similar BPA content is expected. The increase in urinary BPA concentrations following canned soup consumption is likely a transient peak of yet uncertain duration. The effect of such intermittent elevations in urinary BPA concentration is unknown. The absolute urinary BPA concentrations observed following canned soup consumption are among the most extreme reported in a nonoccupational setting. For comparison, the 95th percentile unadjusted urinary BPA in the 2007–2008 National Health and Examination Survey was 13.0  $\mu\text{g/L}$  (95% CI, 10.0–15.4  $\mu\text{g/L}$ ).<sup>1</sup> The observed increase in

urinary BPA concentrations following canned soup consumption, even if not sustained, may be important, especially in light of available or proposed alternatives to epoxy resins linings for most canned goods.

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**Author Contributions:** Ms Carwile had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

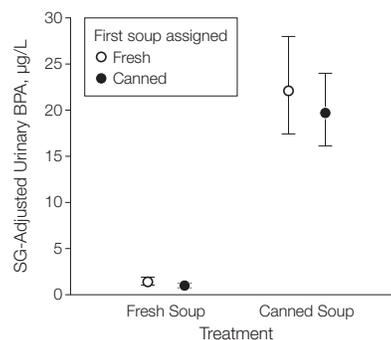
**Table.** Characteristics of 75 Participants in Crossover Study of Changes in Urinary Bisphenol A Concentrations Associated With Daily Consumption of Canned Soup

Characteristic	No. (%)
Sex	
Male	24 (32.0)
Female	51 (68.0)
Race/ethnicity <sup>a</sup>	
White	39 (52.0)
Asian	21 (28.0)
Black	8 (10.7)
Hispanic	6 (8.0)
Other	1 (1.3)
Age, median (range), y	27 (22–56)
Adherence, median (range), % <sup>b</sup>	100 (60–100)

<sup>a</sup>Self-reported race/ethnicity was categorized by the investigators and assessed for the purpose of informing generalizability to other populations.

<sup>b</sup>Adherence was calculated as the percentage of days that a participant consumed assigned soup.

**Figure.** Geometric Mean Specific Gravity–Adjusted Urinary Bisphenol A Concentration After a Week of Soup Consumption by Treatment Sequence



Geometric mean specific gravity (SG)–adjusted urinary bisphenol A (BPA) concentration following a week of daily consumption of fresh or canned soup. For reference, the unadjusted geometric mean for the 2007–2008 National Health and Examination Survey (NHANES) was 2.08  $\mu\text{g/L}$  (95% CI, 1.92–2.26  $\mu\text{g/L}$ ), and the 95th percentile was 13.0  $\mu\text{g/L}$  (95% CI, 10.0–15.4  $\mu\text{g/L}$ ).<sup>1</sup> Error bars indicate 95% CIs.

*Study concept and design:* Carwile, Michels.

*Acquisition of data:* Carwile.

*Analysis and interpretation of data:* Carwile, Michels.

*Drafting of the manuscript:* Carwile.

*Critical revision of the manuscript for important intellectual content:* Carwile, Ye, Zhou, Calafat, Michels.

*Statistical analysis:* Carwile.

*Obtained funding:* Michels.

*Administrative, technical, or material support:* Carwile, Ye, Zhou, Calafat.

*Study supervision:* Michels.

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**Disclaimer:** The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention. The involvement of the Centers for Disease Control and Prevention (CDC) was limited and was determined not to constitute engagement in human subjects research.

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## CORRECTION

**Incorrect Number:** In the Original Contribution entitled "Association Between Smoking and Risk of Bladder Cancer Among Men and Women," published in the August 17, 2011, issue of *JAMA* (2011;306[7]:737-745), an incorrect number was reported in Table 2. Under the column for Women, Person-Years and in the row Former smoker (overall), the number should be 705 925 (not 70 595). This article was corrected online.

Late on the third day, at the very moment when, at sunset, we were making our way [by boat] through a herd of hippopotamuses, there flashed upon my mind, unforeseen and unsought, the phrase, "Reverence for Life." The iron door had yielded: the path in the thicket had become visible. Now I had found my way to the idea in which affirmation of the world and ethics are contained side by side! Now I knew that the ethical acceptance of the world and of life, together with the ideals of civilization contained in this concept, has a foundation in thought.

—Albert Schweitzer (1875-1965)