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A Crossover Study of Noodle Soup Consumption in Melamine Bowls and Total Melamine Excretion in Urine

Melamine exposure remains common even after the 2008 melamine-tainted baby formula incident, which resulted in 6 deaths and approximately 50 000 hospitalizations.[1] A continuous low-dose melamine exposure has been linked to urolithiasis in both children and adults.[2,3] Another source of melamine exposure is melamine tableware.[4] In a pilot study, we asked 16 healthy volunteers (age range, 20-27 years) to consume 500 mL of hot noodle soup (initial temperature, 90°C) served in melamine bowls in the morning of October 2011. We collected from each participant 1 spot urine sample immediately before and at 2-hour intervals for 12 hours after consuming the noodle soup. This experiment simulated the natural situation; thus, not all participants provided urine samples at every 2-hour interval. However, all urine samples from all participants were collected after consumption for 12 hours. Postconsumption mean urinary melamine concentrations, corrected for urinary creatinine, initially increased sharply, peaked at 4 to 6 hours, and then declined sharply for 2 hours and then less steeply for the remainder of the monitoring period (eFigure 1; http://www.jamainternalmed.com). We therefore investigated if consumption of hot noodle soup served in melamine bowls would increase total urinary melamine excretion.

Methods. In a randomized 2 × 2 crossover study in December 6, 2011, we asked 1 group (3 men and 3 women [group A]) to fast for 8 hours before consuming 500 mL of hot noodle soup (initial temperature, 90°C) served in a melamine bowl as a 30-minute breakfast. The study design was the same as the aforementioned pilot study. We collected spot urine sample before and at 2-hour intervals for 12 hours after consumption. Another group (3 men and 3 women [group B]), following the same procedures, consumed the same soup from ceramic bowls (eFigure 2), in which melamine levels were nondetectable.[4] All subjects were different from those of the pilot study and were advised not to use any melamine tableware 3 days before the experiment. Soft drinks were not restricted. After a 3-week washout period, the assigned treatments were reversed (December 27, 2011). This study had institutional review board approval, and each participant provided written informed consent.

Urinary melamine levels were measured by triple-quadrupole liquid chromatography tandem mass spectrometry. The method of detection limit (MDL) was 0.8 ng/mL (parts per billion) in urine, with any measurement below the MDL treated as 0.4 ng/mL.[3] Total melamine excretion was calculated as melamine concentration of 1-spot urine sample × the amount of that spot urine and the amounts of all the urine samples collected for 12 hours after the participant consumed hot noodle soup were summed. A Wilcoxon signed rank test was used to examine the absolute differences of total melamine excretion between the 2 groups, whereas a Wilcoxon rank sum test was used to compare the differences of total melamine excretion in the 2 melamine or ceramic groups. *P* values were 2-sided, with a significance level of .05.

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Results. Twelve healthy people (6 men and 6 women; age range, 20-27 years) participated. All urine samples from all participants were collected after consumption for 12 hours in both groups. Temporal change in mean urinary melamine concentration corrected for urinary creatinine was similar to the previous pilot study (**Figure**, A; eFigure 1). The mean (range) and total number of postconsumption spot-urine specimens collected from melamine bowl users were 4.3 (1-13) and 52, respectively; all melamine concentrations were detectable. In contrast, the mean (range) and total number of postconsumption spot-urine specimens collected from ceramic bowl users were 4.3 (2-7) and 51, respectively, but melamine concentrations in 17 urine samples (33%) were below the MDL. Total melamine excretion (mean [SE]) in urine for 12 hours was 8.35 (1.91) μg and 1.31 (0.44) μg in melamine bowls and ceramic bowls, respectively (Figure, B). The difference was statistically significant (7.04 [1.62] μg; $P < .001$). In contrast, there was no significant difference in the 2 melamine

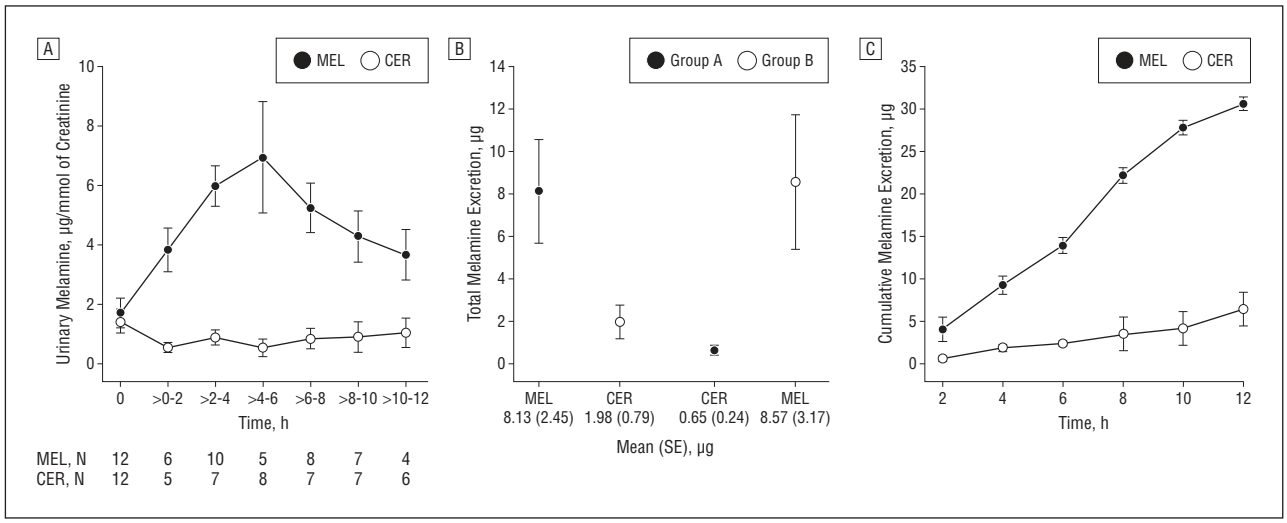

Figure. Consumption of hot noodle soup in melamine (MEL) or ceramic (CER) bowls and excretion of urinary melamine among 12 study subjects. A, Mean (SE) temporal change of urinary melamine levels in the MEL and CER groups. N indicates the number of urine specimens collected in that particular 2-hour interval after consuming hot noodle soup. B, Mean (SE) total melamine excretion in urine 12 hours after consumption by treatment sequence (group A: treatment MEL then CER; group B: treatment CER then MEL). C, Mean (SE) cumulative urinary melamine excretion for 2-hour intervals in the MEL or CER groups.

groups (P=.78), although a significant difference was noted in the 2 ceramic groups (P=.02) (Figure, B). The significance was probably due to the high melamine excretion (carryover effect) in the urine samples prior to consumption in the 2 ceramic groups (eFigure 3). The estimated half-life of urinary melamine elimination was approximately 6 hours (Figure, C).

Comment. Melamine tableware may release large amounts of melamine when used to serve high-temperature foods. The brand of melamine bowls used in this study was chosen from the 5 brands we tested previously.[4] The amount of melamine released into food and beverages from melamine tableware varies by brand, so the results of this study of 1 brand may not be generalized to other brands. The use of nonbreakable melamine tableware is common in our daily life. Although the clinical significance of what levels of urinary melamine concentration has not yet been established, the consequences of long-term melamine exposure still should be of concern.[5]

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INVITED COMMENTARY

New Studies About Everyday Types of Chemical Exposures: What Readers Should Consider

Exposures to chemicals in consumer products and from other sources are an everyday reality and have been a global discussion topic and research interest for many years. For example, setting the stage for much of my awareness and thinking about this was a commentary, published in 1979, titled "Analyzing the Daily Risks of Life," which included extensive mention of chemicals in consumer products.[1] That commentary[1(p41)] began with:

> The world seems a very hazardous place. Every day the newspapers announce that some chemical has been found to be carcinogenic, or some catastrophic accident has occurred in some far-off place.

The high level of global interest within the exposure science, toxicology, risk assessment, and risk management communities about everyday types of chemical exposures has continued, and a recent report from the US National Academy of Sciences Committee on Human and Environmental Exposure Science in the 21st Century[2] begins with:

> We are exposed every day to agents that have the potential to affect our health—through the personal products we use, the water we drink, the food we eat, and the soil and surfaces we touch, and the air we breathe.

In this issue, the Research Letter by Wu et al,[3] titled "A Crossover Study of Noodle Soup Consumption in Melamine Bowls and Total Melamine Excretion in Urine," provides an opportunity to note key considerations when reading about results involving everyday types of chemical exposures. Readers could be asking the following questions for this and other publications:

1. Is the study published in a peer-reviewed journal? In this case, readers have the easy task of looking for this information and finding the peer-review process for this journal (http://archinte.jamanetwork.com/public/About.aspx).

2. Are there other publications that lend or do not lend support to the current research, or is this study possibly the first of its kind that suggests an emerging issue for regulators, chemical companies, consumer product manufacturers, and others to consider? Wu et al[3] cite 1 publication on melamine in tableware; however, there are many others going back to 1986, if searches of the US National Library of Medicine's PubMed (http://www.ncbi.nlm.nih.gov/pubmed) and TOXLINE (http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?TOXLINE) databases are performed (TOXLINE can be used to also search for PubMed content). Additional relevant publications obtained via PubMed and TOXLINE include "Migration of Melamine and Formaldehyde From Tableware Made of Melamine Resin" (1986)[4]; "Comparison of the Migration of Melamine From Melamine-Formaldehyde Plastics ("Melaware") Into Various Food Simulants and Foods Themselves" (2010)[5]; "Analysis of Melamine Migration From Melamine Food Contact Articles" (2011)[6]; and "Survey of Counterfeit Melamine Tableware Available on the Market in Thailand, and Its Migration" (2010).[7]

3. In addition to scientific journal publications, is there information available from government or other websites that provides perspectives about the exposures and potential risks? The answer is a firm "yes." As key examples, a web search found that the German Federal Institute for Risk Assessment (BfR) issued an "opinion" in 2011 on "Release of Melamine and Formaldehyde From Dishes and Kitchen Utensils."[8] Later, in 2011, The BfR followed this with a press release titled "Cooking Spoons and Crockery Made of Melamine Resin Are Not Suited for Microwaves and Cooking."[9] The BfR information is valuable and provides information that is globally relevant to scientists, regulators, and others.

4. How was the study conducted, eg, is it a preliminary or "pilot" study involving a small number of people who were studied, and did the participants represent a narrow or broad, wide range of the types of potentially affected consumers? Considerations relevant to the study by Wu et al[3] include the relatively small number of people involved (6 men and 6 women), all noted as being "healthy."

5. Did the study use bowls and food that some consumers are likely to be exposed to? If yes, are there geographical or other limitations that should be noted by the authors such as the bowls being likely to be sold only in 1 country or region of the world? Also, is the issue likely to be only with 1 or a few manufacturers of the bowls, or is it likely to be a more widespread issue? Wu et al,[3] to their credit, discuss some of this.

6. Did the study try to approach "reasonably foreseeable" consumer exposure conditions? Considerations relevant to the study by Wu et al[3] include the temperatures, exposure durations, type of food being consumed, and other factors. In this study, 500 mL of hot noodle soup with an initial temperature of 90°C was served in a melamine bowl "as a 30-minute breakfast."

7. Is there a known or reasonably foreseeable association between these types of exposures and human adverse effects? For example, if the consumer product-type exposures seem to lead to increased melamine excretion in urine, is the level in urine known to be potentially associated with toxic effects in humans? In this case, Wu et al[3] note 2 publications that they believe provide information that "a continuous low-dose melamine exposure has been linked to urolithiasis in both children and adults." An updated search of PubMed or TOXLINE would have found a recent publication from one of the groups (Liu et al[10]) that continues the discussion.

Readers asking themselves these questions will be in an excellent position to critically evaluate studies about everyday chemical exposures.

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