Dietary Sources of Melamine Exposure Among Participants in the National Health and Nutrition Examination Survey (2003-2004)

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Abstract

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Background: Melamine is an industrially synthesized commercial chemical present in animal feed, pesticides, and fertilizers. High levels of melamine exposure due to historical food adulteration events have led to acute renal failure. Low level melamine exposure is pervasive in the general population, and chronic low-level exposure may lead to negative health consequences. Melamine has been detected in foods in the US, including meat and dairy products. This study aimed to determine the food sources associated with urinary melamine concentrations and assess how age might modify the relationship between dietary factors and melamine concentrations.

Methods: This analysis used nationally representative data from the National Health and Nutrition Examination Survey (NHANES) 2003-2004 including 10 meat and dairy dietary exposures and 20 non-meat or dairy dietary exposures from 24-hour food recalls, and creatinine-adjusted urinary melamine concentration (n=478). Multivariate linear regression was used to examine the relationship between dietary intake and log-transformed creatinine-adjusted melamine while controlling for sex, age, race, body mass index (BMI) status, family poverty income ratio (PIR), and creatinine. Interaction terms were added to fully adjusted models to examine potential effect modification by age.

Results: In fully adjusted models, each additional ounce of processed meat consumed was associated with a 9.64% (95% CI: 2.03, 17.71) higher melamine concentration ($p<0.05$). Each additional ounce of total meat was associated with 3.74% (-7.29, -0.05) lower melamine ($p<0.05$) and each ounce of red meat was associated with 5.55% (-11.05, 0.21) lower melamine ($p=0.06$). We also observed several positive associations between other food groups and melamine, including fruit 10.85% (-1.89, 25.24), whole grain 21.05% (9.2, 34.18), and soy 7.47% (-0.4, 16.07) ($p<0.10$). The relationships between certain dietary exposures (non-whole grains, white potatoes, starchy vegetables, alcohol ($p<0.05$), and red meat, solid fat ($p<0.10$)) and melamine were modified by age. Increasing age appeared to reduce the association between these dietary exposures and melamine.

Conclusions: This study identified several food groups that are positively and negatively associated with melamine exposure in the US. Results were mixed for meat intake. Positive associations with fruit, whole grains, and soy suggest that the use of pesticides in food production may contribute to melamine exposure. Our results also suggested that younger age groups may have disproportionately higher urinary melamine in association with certain food groups compared with older ages. Further research, including young children, should be conducted to clarify the dietary sources of melamine in the current US food supply and examine their contribution to total melamine exposure and potential adverse health outcomes.

INTRODUCTION

Melamine is an industrially synthesized chemical compound and is a known kidney toxicant (Hau et al., 2009). Exposure to melamine in high concentrations leads to the development of kidney stones and generalized kidney disease (Guan et al., 2009), and recent studies suggest lower concentration exposures in the general population may be associated with early signs of kidney injury (Sathyanarayana et al., 2019). Studies in China and Taiwan have suggested that human exposure to melamine through environmental sources is pervasive (Qin et al., 2010, Wu et al., 2018), but there is little information on the levels and sources of melamine exposure in the United States (US). Widespread commercial use of melamine and its presence in animal feed, pesticides, and fertilizers, may lead to contamination of the human food supply through multiple routes, making diet an important exposure pathway for humans (WHO, 2009).

High-level exposure to melamine during multiple historical contamination events has been shown to lead to kidney injury and fatalities in animals and children (Brown et al., 2007; Thompson et al., 2018; Dobson et al., 2008; Guan et al., 2009). In these events, melamine was added to foods to increase the nitrogen content and falsely inflate protein content. One of the earliest known contamination events occurred in 2004 and involved the addition of melamine to pet foods sold in Asia (Brown et al., 2007). Similarly, in 2007, an outbreak of acute kidney injury in animals exposed to high levels of melamine from contaminated pet food occurred in North America. Wheat flour imported from China was found in pet food, reflecting adulteration with melamine during processing. Exposed pets developed calcium oxalate monohydrate and melamine-containing crystals, leading to renal failure and death (Thompson et al., 2008; Dobson et al., 2008). In 2008, melamine contamination of powdered milk infant formula occurred in China leading to six known fatalities. In addition to these fatalities, children exposed to the contaminated formula had 7 times greater odds (95% CI: 2.1-23.0) of kidney stone development compared to unexposed children (Guan et al., 2009).

In response to the 2008 China infant formula contamination event, the Codex Alimentarius Commission, jointly run by the United Nations (UN) Food and Agriculture Organization (FAO) and World Health Organization (WHO), adopted a worldwide maximum melamine level of 2.5 mg/kg for food and animal feed, and maximum level of 1 mg/kg for powdered infant formula (WHO, 2012). These guidelines were created to prevent kidney disease through adulteration of foods, but low-level contamination of melamine in food products remains difficult to avoid given the widespread industrial use of melamine.

Recent evidence suggests that low-level exposure to melamine and its structural analogue, cyanuric acid, may be associated with early markers of kidney damage (Sathyanarayana et al., 2019) and oxidative stress (Liu et al., 2020). Melamine may also have endocrine disruptive and neurotoxic properties, though further research is needed (Bolden et al., 2017). Because children often have higher exposures to many environmental chemicals than adults, and because melamine exposure is widespread among children (Sathyanarayana et al., 2019), additional research is needed to examine the sources and consequences of melamine exposure among the general public and vulnerable groups such as children.

No known major melamine contamination events have occurred since 2008, yet melamine is still present in the environment. One source of melamine is as a byproduct of cyromazine, a pesticide that can be used in animal feed (Dorne et al., 2013). Experimental studies demonstrate that the majority of dietary melamine in animal feed is excreted in animals' urine. However, low concentrations of melamine have been detected in the animals' edible tissues, milk, and eggs in Asia and may be another potential dietary source of exposure (Sun et al., 2011; Tkachenko et al., 2015; Yang et al., 2011).

There is little known about the sources of melamine in the diet of the US population. One analysis conducted in Albany, New York detected melamine in over 80% of food samples analyzed and observed the highest melamine concentrations among dairy products, cereal products, and meat (Zhu and Kannan, 2019). These data suggest that low-level contamination of foods may be common and that animal products may contribute substantially to total dietary melamine, though not all foods were represented in that study. A study conducted in Shanghai, China found that consumption of fruits, beef and mutton, processed meats, eggs, and rice were positively associated with urinary melamine in adults (Shi et al., 2020). Replication of this study is needed in the US population to expand on these findings.

The purpose of this study is to examine the major dietary sources of melamine in the US population. We hypothesized that meat and dairy intake would be positively associated with urinary melamine concentration. In a secondary analysis, we examined associations of non-meat or dairy intake with melamine exposure.

METHODS

Participants and study design

This cross-sectional study used data from the National Health and Nutrition Examination Survey (NHANES) 2003-2004, the most recent survey year for which melamine data were available, to assess the relationship between dietary intake and urinary melamine concentrations. NHANES is a nationally representative survey that combines interviews and physical examinations to assess the health and nutritional status of non-institutionalized adults and children in the US. NHANES uses a complex, multistage, probability sampling design (CDC, 2003-2004). This analysis included participants with available data on urinary melamine concentration and urinary creatinine concentration. Participants without available dietary data (n = 13) or with urinary melamine concentrations greater than 5 standard deviations above the mean (n = 1) were excluded. In total, 478 participants ages 8 years or older were included in the analysis.

Dietary assessment

NHANES dietary intake data are based on 24-hour recalls, in which participants report foods and beverages consumed during the preceding 24-hour period (midnight to midnight). The first of two dietary recall interviews (Day 1) is conducted by a trained interviewer in the Mobile Examination Center (MEC) at the time of the in-person exam. The second dietary recall is collected over the phone one week later. Estimates of energy, macronutrient, micronutrient intakes are generated by matching reported intake to nutrient data from the USDA Food and Nutrient Database for Dietary Studies, 2.0 (FNDDS 2.0). The MyPyramid Food Guidance System, which was used in the US from 2005 to 2011, translates the Dietary Guidelines for Americans into concrete recommendations for consumers on the amounts of foods and beverages to consume from each group to meet nutrient needs. The MyPyramid Equivalents Database (MPED) 2.0 was developed by translating the foods in the FNDDS 2.0 into the 32 MyPyramid food-group equivalents. We obtained data on estimated intakes in each food group (such as grains, fruits, and vegetables) from the MPED 2.0 for Day 1 dietary recalls, enabling us to account for food components in mixed dishes and accurately assign to the appropriate food group (Bowman et al., 2008). We only examined recent dietary exposure (Day 1 dietary recall) in association with urinary melamine concentration, as melamine has a short half-life (Lin et al., 2013), and spot urine samples represent participants' prior 24 hours of exposure.

In our primary analysis, we considered 10 meat and dairy dietary equivalents derived from the MyPyramid groupings as the exposures of interest. These included total meat (from meat, poultry, and fish); red meat (from beef, pork, veal, lamb, and game); processed meat (from franks, sausages, and luncheon meat); poultry; fish and other seafood high in n-3 fatty acids; fish and other seafood low in n-3 fatty acids; total dairy (milk, yogurt, cheese); milk; cheese; and eggs[1]. Due to small sample size ($n<20$), we did not include organ meats or yogurt as exposures of interest. In secondary analyses, we assessed all remaining 20 non-meat or dairy dietary equivalents.

Assessment of melamine excretion

Our primary outcome was urinary melamine concentration, which was measured for a subsample ($n = 492$) of NHANES 2003-2004 participants. Spot urine samples (5 mL) were collected and

[1] For original naming conventions and definitions of dietary equivalents, refer to MyPyramid Equivalents Database, 2.0 for USDA Survey Foods, 2003-2004, available at: https://www.ars.usda.gov/ARSUserFiles/80400530/pdf/mped/mped2_doc.pdf.

processed in the MEC by certified laboratory professionals, then stored frozen in biorepositories before being sent to laboratories for analysis. Urinary melamine concentrations were measured using liquid chromatography-tandem mass spectrometry (LC-MS/MS). The limit of detection was 0.09 ng/mL. We adjusted urinary melamine for creatinine concentration to account for variable dilution or concentration among spot samples (O'Brien et al., 2016; CDC, 2003-2004).

Assessment of covariates

Covariates were chosen a priori to control for differences in metabolism, demographic factors, and hydration status, which could impact the association between diet and urinary melamine concentration. Participants 16 years of age or older self-reported demographic variables, including age, sex, self-identified race/ethnicity, and income. A proxy respondent provided this information for participants less than 16 years of age or those who were unable to answer questions themselves. Family poverty income ratio (PIR) is the ratio of reported family income to the poverty threshold, calculated based on the Department of Health and Human Services' poverty guidelines. Categorization of family PIR was based on financial eligibility for federal programs including Supplemental Nutrition Assistance Program (SNAP) and Special Supplemental Nutrition Program for Women, Infants, and Children (WIC). We categorized family PIR into low income cutoff for SNAP benefits (range: 0-1.3), low income cutoff for WIC benefits (range: 1.31-1.85), middle income (range: 1.86-3.5), and high income (range: 3.51-5).

Physiological measurements were collected by trained medical personnel in the MEC. Body mass index (BMI) was calculated from measured height and weight. In children less than 20 years of age, BMI status was determined using BMI percentiles for age based on the 2000 CDC

Growth Chart (Kuczmarski, 2002). BMI status among adults ages 20 years and older was determined using CDC classifications (CDC, 2003-2004). Concentrations of creatinine were measured in spot urine samples.

Statistical analyses

Analyses were conducted using STATA/IC version 16.0. All analyses were survey-weighted using the weights assigned in NHANES, including melamine subsample weight, to account for the complex survey design (including oversampling), survey non-response, post-stratification, (CDC, 2003-2004). We calculated mean melamine and creatinine levels according to baseline characteristics of study participants (Table 1).

The distribution of melamine concentrations in our sample of 478 participants was highly positively (right) skewed due to approximately 28.5% of the melamine concentrations below the limit of detection. Results below the limit of detection were imputed to a value equal to the detection limit divided by the square root of two, which is 0.04 ng/mL (CDC, 2003-2004). To approximate a normal distribution in creatinine-adjusted melamine, we log transformed these data.

Multiple linear regression modeling was used to examine the relationships between dietary intakes of select foods and urinary melamine. We examined food group equivalent intakes for association with log-transformed creatinine-adjusted melamine concentration. The minimally adjusted model included sex (male, female) and age (years, continuous). The fully adjusted multivariable model additionally included BMI (underweight, healthy weight, overweight, obese), family PIR category (0 to 1.3, 1.31 to 1.85, 1.86 to 3.5, 3.51 to 5), and urinary creatinine concentration (continuous). The fully adjusted model was a complete cases analysis and included 453 participants. Beta coefficients derived from multivariable regression modeling were back-transformed to represent the expected percentage change in creatinine-adjusted melamine per unit change in the dietary variable. Regression coefficients were considered significant if p <0.05, and we also made note of p-values <0.10 due to the exploratory nature of this study. We included 95% confidence intervals for the back-transformed regression coefficients. Sensitivity analyses were performed excluding participants who used a proxy responder in the fully adjusted model.

We examined the possibility that age may modify the association of diet with melamine because of differing metabolism between children and adults which may alter children's exposures (NRC, 1993). To assess interaction by age, we included an age interaction term (dietary exposure * age) in a fully adjusted model. We estimated percentage change in creatinine-adjusted melamine per unit increase in the interaction term using Wald tests. We also calculated the expected differences in creatinine-adjusted melamine associated with a one-serving increase in dietary exposure across a range of selected ages.

RESULTS

Among the 478 participants included in this analysis, urinary melamine was above the limit of detection in 76% of participants. The mean urinary melamine concentration was 4.05 ng/mL (SE: 0.41) and the median was 2.87 ng/mL (SE: 0.14) (Table 1). Males had lower creatinine-adjusted melamine concentration, with a mean of 36.1 (SE: 4.9) ug/g, compared to 53.1 (SE: 5.9) ug/g among females (p=0.004). Mean creatinine-adjusted melamine concentration differed between age categories (p=0.01), with older age groups having higher concentrations than younger age groups. Participants classified as underweight had higher creatine-adjusted melamine concentration compared to those with higher BMI (p=0.01). We did not observe statistically significant differences in melamine concentrations across race and family PIR categories (Table 1).

The majority of participants (>75%) reported consuming foods from each of the major dietary categories: total meat, total dairy, total grains, total vegetables, and total fruits. Participants' melamine concentrations varied across quartiles of meat and dairy consumption (Table 2a). Participants' consumption of other dietary categories by quartile and melamine concentrations are reported in Table 2b. Quartile ranges are reported in the supplemental table (Table S1).

In our primary analysis, intake of meat or dairy products were not associated with melamine concentrations in minimally adjusted analyses. In fully adjusted models, each additional ounce of total meat was associated with a 3.74% (95% CI: -7.29, -0.05) lower melamine concentration (p=0.05) and each ounce of red meat was associated with 5.55% (-11.05, 0.21) lower melamine concentration (p=0.06). Each additional ounce of processed meat was associated with 9.64% (2.03, 17.71) higher melamine concentration (p=0.02) (Table 3a).

In our secondary analyses of non-meat and non-dairy based dietary intake, we observed positive associations between certain dietary exposures and melamine in the fully adjusted model, including total fruit (10.85% (-1.89, 25.24) p=0.09), whole grains (21.05% (9.2, 34.18) p=0.001), and soy products (7.47% (-0.4, 16.07) p=0.06) (Table 3b).

When examining effect modification by age, we found that the association of specific foods with urinary melamine was reduced in older compared to younger participants. Our data suggested that the relationship between melamine and non-whole grains, white potatoes, other starchy vegetables, and alcohol were significantly modified by age ($p<0.05$). Our data also suggested that the relationship between melamine and both red meat and discretionary solid fat were modified by age ($p<0.10$) (Table 4); increasing age appeared to reduce the association between these dietary exposures and urinary melamine. For example, consumption of one additional serving (two ounces compared to one ounce) of non-whole grains was associated with a 0.10 ug/g higher melamine concentration in people age 10, a 0.20 ug/g higher melamine concentration in people age 40, and a 5.62 ug/g lower melamine concentration in people at age 60 ($p<0.05$) (Table 4).

A sensitivity analysis excluding those who used a proxy responder (n = 87, including 85 who were under the age of 16) resulted in moderate changes from the associations observed in the main analysis. These changes ranged from 1.48% to 35.57% lower melamine concentrations in the sensitivity analysis compared to the main analysis. The direction of associations did not change in the sensitivity analysis. These differences can likely be explained by the interaction of age in the association between dietary exposure and urinary melamine, as all participants under the age of 16 were removed in the sensitivity analysis due to having a proxy dietary recall respondent.

DISCUSSION

To our knowledge, this is the first study to examine the association between self-reported dietary intake and urinary melamine in a representative sample of children and adults in the US. After controlling for important potential confounders, we found several potential dietary sources of melamine exposure. Consumption of processed meats was positively associated with urinary melamine, but total meat and red meat were negatively associated with melamine. Consumption of fruit, whole grains, and soy was positively associated with melamine. Results suggested that age is an important effect modifier; we observed disproportionately higher urinary melamine in association with intake of specific foods at lower ages. Younger ages may be a greater concern for melamine exposure with these specific foods.

In NHANES 2003-2004, the geometric mean of creatinine-adjusted melamine for US adults and children was 11.17 (95% CI: 9.10, 13.72) ug/g creatinine. This geometric mean was higher than that of a study of 908 adults (≥18 years old) in Shanghai, in which the geometric mean of creatinine-adjusted melamine was 2.977 ug/g creatinine (Shi et al., 2020). The mean (SD) of unadjusted melamine for the NHANES subsample was 4.05 (0.41) ng/mL, which was lower than that of our previous study among younger children (4 months-8 years old), at 27.8 ng/mL (143.23 ng/mL) (Sathyanarayana et al., 2019). Each study suggested widespread exposure to melamine. Differences in geometric mean exposures may be driven by differences in the study populations examined, their dietary patterns, and contamination of food products by region. Additionally, there may be differences in use of melamine in products across time between NHANES from 2003-2004 the sample of adults in Shanghai from 2012, and the sample of children in the US from 2015-2016.

Health implications associated with high doses of melamine include urolithiasis, renal failure, and death (Guan et al., 2009). While there is limited research on health implications associated with to ambient exposure to melamine, studies suggest that the low-level exposure to melamine may be associated with early signs of kidney injury (Sathyanarayana et al., 2019) and with calcium urolithiasis (Liu et al., 2011). Beyond potential kidney injury, low-level exposure to melamine is associated with oxidative stress (Liu et al., 2020) and may have endocrine disruptive and neurotoxic properties (Bolden et al., 2017). These potential health risks associated with melamine exposure highlight the importance of identifying dietary sources of melamine exposure in the general population.

One potential source of melamine accumulation in animals is through animal feed, which has widespread, low-level melamine contamination (Cruywagen et al., 2011; Zhu et al., 2019; Zhu and Kannan, 2019; Rai et al., 2014). In experimental studies, melamine has been detected in edible tissues and byproducts of animals commonly consumed by the general population, such as pigs, cows, and poultry (Tkachenko et al., 2015; Sun et al., 2012; Yang et al., 2011).

Our findings that processed meats are positively associated with urinary melamine is consistent with results from Shanghai (Shi et al., 2020). However, few studies have closely examined the melamine content of processed meats (Zhu and Kannan, 2019) or clarified why these products may contain greater concentrations of melamine than other meats. There is evidence that indicates melamine contamination of food occurs through migration of melamine from food packaging plastics and adhesives and through food processing (Wagner, 2013; WHO, 2009; Zhu and Kannan, 2019, Zhu et al., 2019). It is possible that processed meats may have higher melamine contents due to contamination through food packaging and processing. We also observed that total meat consumption and red meat consumption were negatively associated with melamine, which was inconsistent with the findings of the study in Shanghai. Shi et al. found that beef and mutton (red meats) were positively associated with urinary melamine (Shi et al., 2020). The reasons for these discordant findings are unclear, and further research is necessary to better understand the differences in associations between red meat and melamine.

We found several positive associations between plant-based foods and melamine. One reason that several plant-based foods (whole grains, fruits, and soy products) may be associated with melamine exposure could be related to the widespread use of the pesticide cyromazine. Cyromazine can be applied during the cultivation, processing, and preservation stages of crop production and is metabolized to form melamine through a dealkylation reaction in plants and animals (Shi et al., 2020). Consistent with multiple others, we found that whole grains and fruit were positively associated with melamine exposure (Zhu and Kannan, 2019; Shi et al., 2020). A survey of food products in Albany, New York similarly found that cereal products (including pasta, breakfast cereal, rice, and flour) had higher levels of melamine contamination compared to other food products (Zhu and Kannan, 2019).

A recent study by our research group suggested that melamine exposure is widespread among children (n=109; children 4 months-8 years old) in the US; 78% of children had detectable urinary melamine (>0.5 ng/mL) and melamine exposure was higher among older children compared to younger children (Sathyanarayana et al., 2019). In the present study we could not assess melamine exposures in young children (<8 years old), but we observed higher urinary melamine in association with intake of specific food groups (including non-whole grains, white potatoes, other starchy vegetables, alcohol, red meat, and discretionary solid fat) at younger ages compared to older ages. There are a few possible reasons why we observed age interaction, including that younger ages typically have higher exposure to environmental chemicals compared to older ages due to differences in metabolism, and that children often consume different quantities and types of foods, including more processed foods, compared to adults (NRC, 1993; Zheng et al., 2017).

Our study has several strengths, including that NHANES provides detailed dietary data from a 24-hour recall, which is a well-validated tool that enabled us to examine associations of melamine with a wide variety of specific food groups and subgroups (Bowman et al., 2008). In addition, because 90% of melamine is excreted through urine within 24 hours of consumption (Mast et al., 1983), a 24-hour food recall is an ideal method to examine associations of dietary components with melamine excretion, as the measures are contemporaneous. Finally, the complex survey design of NHANES allowed us to generate nationally representative estimates of melamine exposure in the US and examine the relationships with dietary exposures in the general US population by using the melamine data subsample weighting.

One limitation of our study is that our data were gathered in 2003-2004, which may not be reflective of the US population and the food landscape today. Due to stricter regulations, current day human and animal melamine exposure may be lower compared to 2003-2004. In addition, the diets of the general US population may have changed in the past 17 years due to shifts in economic conditions and dietary guidance (Jahns et al., 2018). Further, our study included data from participants ages 8 or older, and we could not assess associations of diet and melamine in younger children.

In conclusion, this study identified several food groups that are positively and negatively associated with melamine exposure in the US population. Our results also suggested that younger age groups may have disproportionately higher urinary melamine in association with certain food groups compared with older ages. Further research, especially studies including young children, should be conducted to clarify the dietary sources of melamine in the current US food supply and examine their contribution to total melamine exposure and potential adverse health outcomes. Future studies should also examine melamine and cyanuric acid in conjunction, as both can be found as contaminants of animal feed and human food products (FDA, 2019; Suchý et al., 2009, Zhu and Kannan, 2019), and can together form harmful crystalline structures that increase risk of kidney injury (Dorne et al., 2013).

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Table 1: Baseline characteristics of participants according to urinary melamine and creatinine excretion in NHANES 2003-2004

	N	Urinary Melamine (ng/mL)		Urinary Creatinine Mean (SE[1]) (mg/dL)	Creatinine-adjusted Melamine Mean (SE[1]) (µg/g)	P-value[2]
		Mean (SE[1])	**Median (SE[1])**			
Total sample	478	4.05 (0.41)	2.87 (0.14)	142.4 (5.2)	44.7 (4.7)	
Sex						**0.004**
Male	227	4.48 (0.69)	2.92 (0.11)	165.7 (7.9)	36.1 (4.9)	
Female	251	3.64 (0.28)	2.57 (0.25)	119.5 (6.0)	53.1 (5.9)	
Age (years)						**0.01**
8-12	23	2.22 (0.21)	1.97 (0.79)	174.9 (16.3)	19.6 (3.5)	
13-19	143	3.34 (0.59)	2.37 (0.19)	162.2 (12.5)	30.7 (4.5)	
20-39	122	3.61 (0.39)	2.71 (0.16)	141.0 (5.3)	40.1 (7.7)	
40-59	86	5.15 (1.2)	3.02 (0.32)	151.4 (8.3)	46.0 (8.9)	
60+	104	4.05 (0.33)	3.17 (0.16)	102.9 (6.5)	69.5 (10.7)	
Race						0.37
Mexican American	106	4.29 (0.73)	3.38 (0.33)	133.2 (7.6)	43.0 (7.8)	
Other Hispanic	20	5.33 (2.09)	3.01 (1.73)	135.6 (3.2)	42.7 (16.2)	
Non-Hispanic White	203	3.99 (0.54)	2.70 (0.12)	136.4 (5.4)	48.4 (6.8)	
Non-Hispanic Black	131	4.00 (0.31)	2.93 (0.26)	190.4 (18.8)	31.1 (3.1)	
Other Race or Multi-Racial	18	2.88 (0.27)	2.46 (0.40)	131.7 (30.4)	31.9 (6.9)	
BMI (kg/m^2)[3]						**0.01**
Underweight (<18.5)	10	5.70 (2.8)	2.21 (1.25)	113.3 (17.8)	121.9 (48.8)	
Healthy weight (18.5-24.9)	193	3.40 (0.36)	2.67 (0.22)	126.4 (4.6)	44.1 (6.2)	
Overweight (25-29.9)	153	4.95 (1.11)	2.94 (0.33)	140.8 (8.1)	51.5 (10.5)	
Obese (>30)	116	3.64 (0.37)	2.91 (0.27)	165.3 (9.7)	30.0 (2.3)	

Family PIR[4]						0.75
0-1.3	169	4.20 (0.37)	2.80 (0.24)	148.6 (9.7)	39.0 (5.0)	
1.31-1.85	65	3.84 (0.36)	3.37 (0.30)	160.3 (13.3)	37.3 (4.7)	
1.86-3.5	104	3.07 (0.27)	2.54 (0.13)	139.7 (13.5)	45.0 (7.1)	
3.51-5	120	4.84 (1.25)	3.11 (0.31)	132.8 (6.16)	53.2 (11.1)	

[1] Standard error of the mean.

[2] P-value for difference of mean creatinine-adjusted melamine concentration among subgroups of demographic categories, calculated using a t-test or ANOVA test.

[3] Body Mass Index (BMI) categorized using CDC definitions based on BMI in adults and BMI percentiles for ages 6 through 20; BMI was missing for 6 participants.

[4] Ratio of Family Income to Poverty (family PIR) was missing for 20 participants.

Table 2a: Mean urinary melamine concentration by quartile of meat and dairy dietary exposure among consumers (N= 478)

Dietary Exposure (unit)	Percent Consumers	Mean Melamine (ng/mL) (SE[1]) by Quartile			
		Quartile 1	Quartile 2	Quartile 3	Quartile 4
Total meat (meat, poultry, fish) (ounces)	92.3%	4.37 (0.36)	4.20 (0.71)	4.85 (1.44)	3.06 (0.29)
Red meat (beef, pork, veal, lamb, game) (ounces)	65.7%	3.42 (0.32)	7.22 (2.56)	3.27 (0.39)	2.76 (0.40)
Processed meat (franks, sausages, luncheon meat) (ounces)	37.1%	4.79 (1.30)	4.22 (0.43)	2.95 (0.52)	5.12 (0.80)
Chicken, turkey, and other poultry (ounces)	37.9%	3.06 (0.37)	3.12 (0.52)	7.19 (3.65)	2.29 (0.29)
Fish and other seafood high in n-3 fatty acids (ounces)	6.3%	2.90 (0.57)	4.36 (1.19)	4.41 (0.47)	3.95 (0.67)
Fish and other seafood low in n-3 fatty acids (ounces)	13%	3.98 (0.48)	3.19 (0.66)	4.70 (1.13)	4.13 (0.71)
Total dairy (milk, yogurt, cheese) (cups)	95.7%	3.88 (0.29)	4.98 (1.78)	4.00 (0.64)	2.97 (0.26)
Milk (cups)	83.9%	3.86 (0.31)	4.21 (0.52)	4.94 (1.77)	3.23 (0.38)
Cheese (cups)	66.8%	2.77 (0.18)	2.84 (0.36)	3.74 (0.55)	4.03 (0.74)
Eggs (ounces)	58.2%	5.66 (2.40)	3.83 (0.43)	4.33 (0.41)	3.49 (0.40)

[1] Standard error of mean.

Table 2b: Mean urinary melamine concentration by quartile of non-meat and non-dairy dietary exposure among consumers (N= 478)

Dietary Exposure (unit)	Percent Consumers	Mean Melamine (ng/mL) (SE[1]) by Quartile			
		Quartile 1	Quartile 2	Quartile 3	Quartile 4
Total grains (ounces)	99.6%	3.50 (0.26)	3.16 (0.31)	5.22 (1.59)	4.08 (0.65)
Whole grains (ounces)	48.0%	3.30 (0.43)	3.39 (0.47)	3.65 (0.46)	6.95 (2.12)
Non-whole grains (ounces)	99.6%	3.98 (0.26)	4.58 (1.38)	3.30 (0.38)	4.03 (0.65)
Total vegetable, excludes legumes (cups)	94.4%	3.48 (0.25)	3.74 (0.43)	4.79 (1.35)	3.86 (0.49)
Dark-green vegetables (cups)	15.7%	3.71 (9.8)	3.77 (0.68)	2.75 (0.92)	5.36 (0.26)
Orange vegetables (cups)	24.1%	4.17 (0.38)	4.36 (0.94)	3.51 (0.38)	3.03 (0.53)
White potatoes (cups)	44.6%	4.06 (0.43)	4.07 (0.44)	3.57 (0.88)	3.82 (0.75)
Other starchy vegetables (cups)	22.2%	3.67 (0.38)	9.30 (4.96)	4.05 (1.15)	2.70 (0.55)
Tomatoes (cups)	72.4%	3.37 (0.39)	5.20 (1.84)	3.98 (0.67)	3.40 (0.36)
Other vegetables (cups)	86.0%	3.39 (0.25)	3.78 (0.40)	3.89 (0.77)	4.76 (1.39)
Total fruits (cups)	78.3%	3.47 (0.40)	3.29 (0.37)	5.91 (2.05)	3.99 (0.27)
Citrus, melons, and berries (cups)	52.6%	4.36 (0.26)	3.72 (0.57)	3.38 (0.19)	6.30 (2.66)
Other fruits (cups)	62.6%	3.49 (0.45)	6.35 (2.45)	3.63 (0.48)	4.77 (0.49)
Soy products (ounces)	36.2%	3.74 (0.41)	6.98 (3.59)	2.74 (0.36)	3.84 (0.44)
Nuts and seeds (ounces)	30.2%	8.24 (3.80)	3.75 (0.59)	2.59 (0.62)	4.10 (0.83)
Cooked dry beans and peas (cups)	19.3%	5.47 (0.47)	4.20 (0.67)	4.15 (1.24)	5.19 (1.20)
Discretionary oil (grams)	99.0%	3.49 (0.50)	4.25 (0.58)	3.80 (0.34)	4.69 (1.33)
Discretionary solid fat (grams)	93.6%	5.59 (1.64)	3.61 (0.30)	2.90 (0.38)	4.24 (0.59)
Added sugars (teaspoons)	99.4%	4.22 (0.44)	5.96 (1.70)	3.26 (0.54)	2.97 (0.23)
Alcohol, total (drinks)	22.0%	4.72 (1.10)	4.23 (0.90)	9.10 (4.48)	2.77 (0.61)

[1] Standard error of mean.

Table 3a: Estimated percent change (with 95% confidence interval) in creatinine-adjusted melamine concentration per unit increase in meat and dairy dietary exposure[1]

Dietary Exposure (unit)	Minimally adjusted[2] N= 478	Fully adjusted[3] N= 453
Total meat (meat, poultry, fish) (ounces)	-1.79% (-5.36, 2.03)	**-3.74% (-7.29, -0.05)[4]**
Red meat (beef, pork, veal, lamb, game) (ounces)	-1.40% (-7.04, 4.50)	**-5.55% (-11.05, 0.21)[5]**
Processed meat (franks, sausages, luncheon meat) (ounces)	6.72% (-1.69, 15.84)	**9.64% (2.03, 17.71)[4]**
Chicken, turkey, and other poultry (ounces)	-3.73% (-11.49, 4.82)	-2.67% (-10.24, 5.34)
Fish and other seafood high in n-3 fatty acids (ounces)	14.69% (-2.86, 35.40)	5.13% (-7.97, 20.09)
Fish and other seafood low in n-3 fatty acids (ounces)	-1.40% (-18.95, 19.85)	-1.99% (-19.51, 19.37)
Total dairy (milk, yogurt, cheese) (cups)	2.33% (-7.32, 13.09)	-0.30% (-9.07, 9.42)
Milk (cups)	2.43% (-13.33, 21.05)	-2.67% (-15.55, 12.08)
Cheese (cups)	2.84% (-5.17, 11.41)	4.82% (-4.60, 15.15)
Eggs (ounces)	-5.64% (-22.59, 15.15)	-3.93% (-20.15, 15.49)

[1] Percent change based on back-transformed beta coefficients from multivariable regression modeling of log-transformed creatinine-adjusted melamine concentration.

[2] Minimal model adjusted for sex (male, female) and age (continuous).

[3] Full model adjusted for sex (male, female), age (continuous), race (Mexican American, other Hispanic, Non-Hispanic White, Non-Hispanic Black, other race or multiracial), BMI status (underweight, healthy weight, overweight, obese), family PIR category (0 to 1.3, 1.31 to 1.85, 1.86 to 3.5, 3.51 to 5), and creatinine (continuous).

[4] P-value <0.05.

[5] P-value <0.10; noted due to exploratory nature of study.

Table 3b: Estimated percent change (with 95% confidence interval) in creatinine-adjusted melamine concentration per unit increase in non-meat and non-dairy dietary exposure[1]

Dietary Exposure (unit)	Minimally adjusted[2] N= 478	Fully adjusted[3] N= 453
Total grains (ounces)	4.82% (-1.20, 11.30)	2.74% (-1.40, 6.93)
Whole grains (ounces)	**29.83% (15.72, 45.65)[4]**	**21.05% (9.2, 34.18)[4]**
Non-whole grains (ounces)	3.57% (-27.46, 10.85)	1.82% (-2.57, 6.40)
Total vegetable, excludes legumes (cups)	3.98% (-14.88, 26.88)	3.46% (-10.15, 19.13)
Dark-green vegetables (cups)	8.23% (-24.28, 54.81)	-15.98% (-47.96, 35.67)
Orange vegetables (cups)	-7.23% (-56.01, 95.62)	-31.28% (-68.66, 50.69)
White potatoes (cups)	-10.15% (-32.91, 20.33)	5.55% (-15.89, 32.58)
Other starchy vegetables (cups)	3.46% (-65.7, 212.37)	-8.98% (-65.01, 136.79)
Tomatoes (cups)	16.42% (-33.37, 103.61)	11.97% (-20.39, 57.31)
Other vegetables (cups)	10.97% (-14.79, 44.34)	6.93% (-14.79, 34.32)
Total fruits (cups)	**15.61% (4.71, 27.77)[4]**	**10.85% (-1.89, 25.24)[5]**
Citrus, melons, and berries (cups)	**15.26% (1.82, 30.61)[4]**	**17.83% (-1.00, 40.36)[5]**
Other fruits (cups)	**17.83% (-0.5, 39.66)[5]**	6.93% (-6.77, 23.00)
Soy products (ounces)	**10.30% (1.41, 20.09)[4]**	**7.47% (-0.4, 16.07)[4]**
Nuts and seeds (ounces)	-3.64% (-12.90, 6.72)	-4.21% (-12.02, 4.40)
Cooked dry beans and peas (cups)	21.17% (-35.54, 127.74)	24.99% (-29.75, 122.34)
Discretionary oil (grams)	-0.60% (-1.59, 0.31)	-0.20% (-0.90, 0.41)
Discretionary solid fat (grams)	-0.02% (-0.83, 0.80)	-0.17% (-0.91, 0.58)
Added sugars (teaspoons)	-0.10% (-1.49, 1.31)	-0.05% (-1.28, 1.20)
Alcohol, total (drinks)	-0.90% (-5.17, 3.67)	-0.90% (-6.67, 5.13)

[1] Percent change based on back-transformed beta coefficients from multivariable regression modeling of log transformed creatinine-adjusted melamine concentration.

[2] Minimal model adjusted for sex (male, female) and age (continuous).

[3] Full model adjusted for sex (male, female), age (continuous), race (Mexican American, other Hispanic, Non-Hispanic White, Non-Hispanic Black, other race or multiracial), BMI status (underweight, healthy weight, overweight, obese), family PIR category (0 to 1.3, 1.31 to 1.85, 1.86 to 3.5, 3.51 to 5), and creatinine (continuous).

[4] P-value <0.05.

[5] P-value <0.10; noted due to exploratory nature of study.

Table 4: Expected age interaction percent change and expected age-specific difference in creatinine-adjusted melamine concentration by increase in dietary exposure[1]

Interaction Term: Dietary Exposure (unit) * Age (years)	Age Interaction[2]		Difference in Melamine (µg/g) Per 1 Serving Higher in Dietary Exposure by Age[4,5,6]		
	% Change (95% CI)[3]	P-value	Age 10	Age 40	Age 60
Red meat (beef, pork, veal, lamb, game) (ounces) * age	-0.22% (-0.46, 0.02)	0.064	0.10	-2.96	-5.62
Non-whole grains (ounces) * age	-0.20% (-0.39, -0.01)	0.049	0.61	0.20	-0.69
White potatoes (cups) * age	-1.27% (-2.4, -0.12)	0.034	7.70	0.16	-4.31
Other starchy vegetables (cups) * age	-4.26% (-7.66, -0.74)	0.022	170.50	4.31	-6.40
Discretionary solid fat (grams) * age	-0.04% (-0.07, 0.01)	0.071	0.34	-0.20	-1.31
Alcohol, total (drinks) * age	-0.14% (-0.28, -0.01)	0.043	0.16	-0.53	-1.30

[1] Full model with age interaction adjusted for sex (male, female), age (continuous), race (Mexican American, other Hispanic, Non-Hispanic White, Non-Hispanic Black, other race or multiracial), BMI status (underweight, healthy weight, overweight, obese), family PIR category (0 to 1.3, 1.31 to 1.85, 1.86 to 3.5, 3.51 to 5), creatinine (continuous), and dietary predictor (continuous) * age (continuous).

[2] Percent change based on back-transformed beta coefficients from multivariable regression modeling of log-transformed creatinine-adjusted melamine concentration.

[3] Estimated modified percent change (with 95% confidence interval) in creatinine-adjusted melamine concentration per unit increase in the interaction term, dietary exposure times age, in fully adjusted model.

[4] Serving sizes are considered 1 unit for each dietary exposure, except for beef, pork, veal, lamb, and game at 3 ounces, and discretionary solid fat at 5 grams.

[5] Difference in back-transformed interaction margins for selected units of dietary exposure at chosen ages from multivariable regression modeling of log-transformed creatinine-adjusted melamine concentration.

[6] Estimated difference in creatinine-adjusted melamine concentration (µg/g) between consumption of one serving and two servings of dietary exposure for given age examples, in fully adjusted model.

Supplemental Table S1: Range of dietary intake by dietary predictor quartile among consumers (N= 478)

Dietary Predictor (units)	Percent Consumers	Range of Dietary Intake by Quartile			
		Q1 (min, max)	Q2 (min, max)	Q3 (min, max)	Q4 (min, max)
Total meat (meat, poultry, fish) (ounces)	92.3%	0.09, 2.23	2.25, 3.93	3.94, 6.42	6.43, 37.41
Red meat (beef, pork, veal, lamb, game) (ounces)	65.7%	<0.01, 1.06	1.08, 2.33	2.33, 3.93	3.94, 36.07
Processed meat (franks, sausages, luncheon meat) (ounces)	37.1%	0.09, 0.71	0.71, 1.54	1.56, 2.89	2.94, 7.22
Chicken, turkey, and other poultry (ounces)	37.9%	0.01, 1.59	1.60, 2.65	2.70, 4.34	4.35, 17.63
Fish and other seafood high in n-3 fatty acids (ounces)	6.3%	<0.01, 0.38	0.41, 0.53	0.78,1.41	1.50, 5.29
Fish and other seafood low in n-3 fatty acids (ounces)	13%	0.19, 1.30	1.39, 2.02	2.02, 3.97	4.25, 9.30
Total dairy (milk, yogurt, cheese) (cups)	95.7%	<0.01, 0.67	0.68, 1.44	1.46, 2.52	2.53, 12.01
Milk (cups)	83.9%	<0.01, 0.21	0.213, 0.81	0.82, 1.66	1.67, 12.01
Cheese (cups)	66.8%	<0.01, 0.38	0.385, 0.80	0.83, 1.54	1.54, 7.07
Eggs (ounces)	58.2%	<0.01, 0.03	0.03, 0.22	0.22, 1.31	1.32, 4.74
Total grains (ounces)	99.6%	0.01, 4.30	4.28, 6.37	6.38, 9.46	9.47, 26.93
Whole grains (ounces)	48.0%	<0.01, 0.43	0.428, 0.81	0.82, 1.65	1.67, 5.25
Non-whole grains (ounces)	99.6%	0.01, 3.87	3.88, 5.89	5.95, 8.74	8.78, 26.93
Total vegetable, excludes legumes (cups)	94.4%	<0.01, 0.66	0.66, 1.22	1.22, 2.01	2.01, 9.58
Dark-green vegetables (cups)	15.7%	<0.01, 0.02	0.03, 0.16	0.17, 0.52	0.56, 2.97
Orange vegetables (cups)	24.1%	<0.01, 0.06	0.06, 0.15	0.15, 0.30	0.30, 1.31
White potatoes (cups)	44.6%	0.04, 0.37	0.38, 0.70	0.72, 1.00	1.02, 3.33
Other starchy vegetables (cups)	22.2%	<0.01, 0.07	0.07, 0.15	0.16, 0.39	0.45, 1.71
Tomatoes (cups)	72.4%	<0.01, 0.16	0.16, 0.36	0.36, 0.66	0.66, 3.49
Other vegetables (cups)	86.0%	<0.01, 0.13	0.13, 0.38	0.38, 0.83	0.83, 4.47
Total fruits (cups)	78.3%	<0.01, 0.32	0.33, 0.94	0.96, 1.86	1.87, 12.10
Citrus, melons, and berries	52.6%	<0.01, 0.14	0.15, 0.50	0.51, 1.19	1.25, 6.70
Other fruits (cups)	62.6%	<0.01, 0.22	0.23, 0.69	0.70, 1.33	1.35, 12.10

Soy products (ounces)	36.2%	<0.01, <0.01	0.01, 0.02	0.02, 0.06	0.06, 13.20
Nuts and seeds (ounces)	30.2%	<0.01, 0.21	0.23, 0.70	0.77, 2.26	2.29, 15.45
Cooked dry beans and peas (ounces)	19.3%	0.02, 0.25	0.25, 0.50	0.51, 0.81	0.86, 1.81
Discretionary oil (grams)	99.0%	<0.01, 4.73	4.78, 13.06	13.08, 27.23	27.52, 138.02
Discretionary solid fat (grams)	93.6%	0.13, 27.99	28.24, 42.75	43.05, 63.56	63.61, 202.21
Added sugars (teaspoons)	99.4%	0.20, 9.03	9.03, 18.01	18.04, 31.25	31.29, 129.45
Alcohol, total (drinks)	22.0%	0.01, 1.00	1.02, 2.00	2.01, 4.00	4.67, 43.01