Bisphenol A, Diet and Obesity: Exposure Measurement and the Relationship Between Diet and Bisphenol A Exposure

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Abstract

Diet is considered the primary source of BPA exposure, due to the use of BPA in polycarbonate plastics and epoxy resins used in food packaging. Existing human research has major limitations and the cost of serum and urinary BPA assay remains a challenge in evaluating BPA exposure and chronic disease outcomes. Despite the fact that diet is a vehicle for BPA exposure, few studies have considered whether dietary composition alters the toxicokinetics of BPA. Epidemiological studies have also not addressed diet as a potential confounder or effect modifier even though diet is associated with both disease risk and BPA exposure. The Urinary Biomarkers of Dietary Intake (UB-Diet Study) was developed to evaluate the feasibility of using questions that target intake of known dietary sources of BPA to estimate BPA exposure. Predicted BPA exposure levels from the BPA exposure assessment module (BEAM) were compared to multiple spot urine samples. Food records were also collected on the days that urine samples were collected to further evaluate the relationship between diet and urinary BPA levels. Reported macronutrient and food group servings were compared to urinary BPA levels. The BEAM data was not able to accurately predict participants' urinary BPA levels. Recent canned food intake was associated with urinary BPA levels, but only explained approximately one-fifth of the variability in urinary BPA levels and several participants who reported consuming no canned foods had high urinary BPA levels. The study findings suggest that BPA levels may be positively associated with higher caloric and fiber intake, and intakes of vegetables, refined grains and red meats, and inversely associated with total fat intake. More research is needed to characterize sources of BPA exposure, to evaluate the role of diet in the toxicokinetics of BPA and to determine if chronic low level BPA exposure poses any health risk.

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Chapter 1
History, Usage and Human Exposure to Bisphenol A

First synthesized in 1891, bisphenol A (BPA) is now one of the highest volume chemicals produced (1). Eight billion pounds are produced annually for use in plastics and epoxy resins, resulting in widespread human exposure (2). BPA was tested for potential use as a synthetic estrogen in the 1930s, but was determined to have weak estrogenic activity and was abandoned in favor of diethylstilbestrol (DES) (1, 3). Since the 1940s and 50s, BPA has been used as a component of polycarbonate (PC) plastics and in epoxy resins (1). The list of products currently made with PC plastics or lined with epoxy resins is extensive, and includes food and beverage storage containers and packaging (3).

In the past 20 years it has become apparent that BPA can leach from the plastics and resins in which it is a component (4). The use of BPA in food packaging, along with the ability of BPA to leach into the food, has led many to believe that diet is a major route of human BPA exposure (5-10). BPA has also been found in products made from recycled paper (11), dust particles (12-14), thermal receipt paper (15, 16), soil, tap water and surface water (17-22). This has led to widespread human exposure to BPA, with detectable levels observed in more than 90% of urine samples tested in the United States (3, 23).

The current lowest observed adverse effect level (LOAEL) for BPA of 50 mg/kg body weight/day was established using traditional toxicology studies in animal and *in vitro* models (24). Thus, the US Environmental Protection Agency set the safety standard for human exposure at 50 µg BPA/kg body weight/day. Despite debate about the safety of low level BPA exposure, this remains the current tolerable daily intake level recommendation for human exposure (6, 24-27).

BPA and Human Exposure

Biomonitoring data indicate that BPA exposure is widespread within the U.S. and worldwide (2). The major route of exposure to BPA is assumed to be oral, with limited data on whether inhalation and dermal exposure contribute substantially to overall BPA exposure (3, 16, 28-30). **Table 1** contains data on the observed levels of exposure in the National Health and Nutrition Examination Survey (NHANES) study population.

Table 1 – Observed Levels of Urinary BPA in NHANES Adult Population (20-yrs and older) (ug/g creatinine)(31)

Study Years	*Geometric Mean (95% CI)*	*50th Percentile (95% CI)*	*75th Percentile (95% CI)*	*95th Percentile (95% CI)*
2003-2004	2.41 (2.15 – 2.72)	2.60 (2.30 – 2.80)	5.10 (4.50 – 5.70)	15.2 (12.4 – 18.1)
2005-2006	1.75 (1.62 – 2.81)	1.80 (1.70 – 2.00)	3.40 (3.10 – 3.70)	10.7 (8.80 – 12.1)
2007-2008	1.99 (1.82 – 2.81)	2.00 (1.80 – 2.30)	3.90 (3.40 – 4.60)	13.2 (9.10 – 15.7)

Abbreviations: CI = confidence interval, g = grams, ug = micrograms

A major reason that diet is considered the primary source of human BPA exposure is the use of BPA-containing food packaging and food and beverage storage containers. Polycarbonate plastics have historically been used to make certain types of reusable food and beverage storage containers, while epoxy resins are used to line metal cans and lids to prevent undesirable reactions between metals in the can and the food (32, 33). BPA is also sometimes used as an antioxidant in other plastics, such as certain brands of plastic stretch film (34). In addition to its intended uses, BPA has also been recognized as an unintentional contaminant in paper products made from recycled materials (11, 35-37), due to recycling of receipt paper, which are printed on thermal paper that contains high levels of BPA (11, 38).

At least eighteen studies (from eleven countries) have demonstrated that there are detectable levels of BPA in many food items (9, 32, 33, 39-53). **Table 2** includes BPA levels in selected canned product food groups presented in a World Health

Organization (WHO) and Food and Agriculture Organization of the United Nations (FAO) report (54), and maximum levels observed in currently available studies (9, 32, 33, 39-53). A more detailed summary of studies evaluating levels of BPA in packaged foods are included in **Appendix 1**. Appendix 1, **Table 1** contains a list of foods in which BPA has been detected, and the observed levels. Appendix 1, **Table 2** contains a list of foods that have been tested, and have not been found to have detectable levels of BPA. These studies suggest that canned vegetables, soups, bean dishes (baked, refried) and pastas in sauce tend to have the highest levels of BPA. A BPA exposure risk assessment by von Goetz *et al* indicates that canned vegetables, meats and soups may be the major contributing sources of dietary BPA exposure, however, this assessment used BPA level data from a very limited number of studies (55). It is important to note that canned food items have been tested in far greater numbers than other foods, but the limited data on similar foods that are fresh or packaged in other types of containers indicate that these foods generally have low or non-detectable levels of BPA (9, 40, 56).

Table 2 – Observed BPA Levels in Food Groups(54)

Food Group	***Observed Levels*** (ug/L or ug/kg)		***Number of Samples***
	Average	**Maximum**[1] (Food Item)	
Fruits	9.8	38.0 (mixed fruit) (33)	70
Vegetables	32.4	730.0 (green beans)(41)	305
Meat (not seafood)	69.6	70.0 (corned beef)(33)	70
Soups	49.1	385.0 (meat-based)(46)	66
Seafood	26.6	169.3 (saury)(57)	166
Carbonated Beverage	1.0	8.21 (soda)(46)	710
Non-carbonated Beverage	23.2	3.96 (orange juice)(40)	131

[1]Levels from literature review – See Appendix 1, Table 1
Abbreviations: kg = kilograms, L = liters, ug = micrograms

Differences in analytical approaches make it difficult to compare findings of BPA content in foods across studies. Some studies examine levels only in the liquid portions, some only in the solid portions and some in the entire product, which could result in differences in observed levels. Studies that have analyzed both liquid and solid portions

of a given food item have found different levels depending on the portion (liquid, solid, total content) measured (49, 52). A recent analysis by Noonan *et al* observed that BPA appeared to partition into solid portions of foods, suggesting that BPA levels would be highest in the foods actually consumed, rather than the surrounding liquid, which may be discarded (41). In addition to differences depending on the portion measured, a previous study observed that BPA levels are highly variable in food products, even for the same food item, from the same company, but in different lots (41). This has made it challenging to estimate an average exposure level for any one given food item.

Despite these challenges, most dietary intervention studies clearly demonstrate that consuming packaged foods alters levels of urinary BPA. Three small feeding studies assessed changes in urinary BPA levels in response to diets containing or lacking packaged foods. A randomized, single-blinded 2 x 2 crossover study found consuming canned soup daily resulted in mean urinary BPA levels of 20.8 μg/L (95% CI: 17.9 - 24.1 μg/L) compared to 1.1 μg/L (95% CI: 0.9 - 1.4 μg/L) when soup prepared from fresh ingredients was consumed (58). A second study with 20 volunteers (18 – 54 years) found high intake of packaged foods to be associated with a large increase in urinary BPA levels over 24 hours (59). A third study observed a statistically significantly decrease in urinary BPA levels after providing three days of meals of unpackaged foods to 20 participants who reported typically consuming packaged food items (60). All three studies are small, but collectively indicate that packaged foods can contribute substantially to BPA levels. A recently published study observed significant reductions in measured BPA levels after 48-hours of fasting, but that BPA levels remained above the limit of detection, suggesting diet is the major, but not the only, source of BPA exposure (61). Another recent study did not observe a decrease in urinary BPA levels after an intervention in which participants were either served a diet free of packaged

foods or provided with recommendations for avoiding exposure to BPA (62). In this study, the researchers hypothesized that BPA may have come into contact with foods during processing and preparation instead of being present in food packaging.

While not all food storage containers are labeled, most BPA-containing plastics fall in the number 7 recycling category. Some number 3 (polyvinyl chloride) plastics may contain BPA, which is added as an antioxidant at much lower concentrations than is used for plastics in the number 7 recycling category (63-65). Most household food storage containers, such as Tupperware®, are recycling code 5, and do not contain BPA (66-68).

A number of studies have demonstrated that BPA can leach from BPA-containing bottles into the stored contents (69-73). Studies indicate that personal usage habits can influence levels of BPA that leach into foods, for example, heating contents or prolonged storage may result in increased leaching of BPA (69, 71, 73). One study examined changes in BPA levels in a crossover intervention study comparing BPA-free and BPA-containing plastic bottles (74). Mean urinary BPA levels were 1.2 ug/g creatinine (95% CI: 1.0 -1.4) when participants used stainless steel, BPA-free bottles compared to a statistically significant higher level of 2.0 ug/g creatinine (95% CI: 1.7 – 2.4) when they consumed beverages from a polycarbonate plastic bottle. Many manufacturers have begun to voluntarily phase-out the use of plastics containing BPA for these types of food and beverage containers (68, 74). Given the increasing numbers of products made with BPA-free plastics, plastic storage containers likely currently account for only a small proportion of total BPA exposure in the US population. Cooper *et al* found that beverages stored in containers that claim to be BPA-free did not have detectable levels of BPA (75). Packed foods (canned foods and some frozen and fast food items) are currently considered the primary dietary source of BPA.

While diet is assumed to be the primary source of BPA exposure, few studies have evaluated dietary BPA intake in relation to urinary levels in free-living populations to determine the extent to which dietary intake predicts observed BPA levels. An analysis of urinary BPA levels before and after BPA was voluntarily removed from packaging in Japan showed markedly lower urinary BPA levels after BPA was removed from food packaging (76). The Children's Total Exposure to Persistent Pesticides and Other Persistent Organic Pollutants (CTEPP) study measured BPA levels in children's environments (including dust and food samples and urine levels) over 48 hours. They found that dietary sources accounted for 99% of BPA present in the children's environment, but explained only 17% of urinary BPA levels (77). Braun *et al* found that BPA levels in single spot urine samples were associated with the frequency of consumption of canned vegetables in pregnant women (78). Casas *et al* observed a statistically significant association between fish intake and BPA levels in a single spot urine sample among pregnant women and their children at age 4 years (79). The authors indicated that fish is often consumed canned in this Spanish study population. Further research is needed to determine which foods are the greatest contributors to dietary BPA intake in the general population with paired data on dietary intake in free-living populations and urinary BPA levels.

In addition to diet, other suggested predictors of higher urinary BPA levels include male gender (80, 81) (except in NHANES data, where observed levels have been found to be higher in women (8)), certain occupations (78), race/ethnicity (23, 82), lower family income (78, 82), lower poverty to income ratios (82), lower food security status (82), increased use of emergency food services (82), higher BMI (80, 83, 84) and being a current smoker (78). Age also tends to be positively associated with urinary BPA levels (81, 85, 86), although some studies have found an inverse association (23, 80). Many of

these factors are likely surrogates for dietary habits associated with increased potential BPA exposure, as diet was not considered a covariate in these analyses. For example, studies have shown that income is an important predictor of diet (82, 87, 88) and male gender and higher BMI are associated with greater food consumption (89-93).

Smoking and occupation are two potential predictors that could contribute to higher BPA exposure independent of diet. Cigarette filters contain BPA (78) and occupations that involve routinely handling receipts (78) have been associated with increased total urinary BPA levels, although, these associations have not been consistently reported (80, 82, 85, 86). Recently, studies evaluating associations between personal product (mouthwash, soaps, fragrances) usage and BPA exposure levels have found associations between some products, such as mouthwash, and spot urinary BPA levels, suggesting other potential sources of BPA exposure (94, 95).

BPA Metabolism and Toxicokinetics

Acute dose toxicokinetic studies in humans, suggest BPA is completely absorbed in the gastrointestinal tract and is excreted in the urine (54). These acute dosing studies also indicate that BPA is rapidly metabolized by first pass metabolism in the liver via conjugation by UDP-glucuronosyltransferases (UGTs) (93, 96). Conjugation of BPA is considered a detoxification process, as only unconjugated BPA has estrogenic activity (97, 98). The primary UGT thought to be involved in BPA metabolism is UGT2B15, and a recent study demonstrated that a genetic variant in UGT2B15 reduced intrinsic clearance of BPA (96, 99). It has generally been accepted that most free and conjugated BPA is eliminated in the urine within 2 to 7 hours after exposure, with complete elimination within 12 to 24 hours. Based on results from the toxicokinetic studies, it is currently assumed that BPA is not stored in the body. Collectively, this

would indicate that internal exposure to unconjugated BPA is low, however, there has been substantial debate about the accuracy of these assumptions (100, 101).

Classic toxicology studies typically evaluate acute dose exposures when evaluating toxicokinetics of chemicals, but this approach does not reflect typical human exposure, which is chronic, low dose, and part of a diverse group of other chemical and food exposures that could change rates of absorption, metabolism and excretion. Additionally, the assumptions that diet is the only source of exposure, that absorption, metabolism and excretion is rapid and complete, and that BPA is not stored in the body have been challenged by recent data. An analysis using NHANES data did not observe the expected inverse relationship between fasting time and urine levels (102). Additionally, a small 48-hour fasting study observed a rapid decline in urinary BPA levels after fasting, but study participants' levels never fell below the limit of detection (61). These findings have led researchers to hypothesize that either the half-life of BPA is longer than previously believed, that BPA is stored in the body, or that ingestion is not the only route of exposure (54, 93).

Data currently support at least two of these hypotheses. Studies have observed measureable levels of BPA in liver and adipose tissues, suggesting potential for BPA storage (102-104). Studies also suggest that BPA can be absorbed sublingually (105, 106), dermally (16, 105, 107), and inhaled (12, 16, 105), however, there is some debate over how much non-oral routes of exposure might contribute to overall BPA exposure in the general population (30, 105, 108, 109). It is also important to note that, even if BPA is rapidly excreted, due to the presence of BPA in food, water and air, exposure to some level of BPA is likely fairly constant (3, 6, 54).

There is also debate regarding the potential for β-glucuronidases to impact internal exposure to unconjugated BPA (110). It has recently been suggested that β-

glucuronidases may reverse the detoxification of BPA after first pass metabolism by UGTs. β-glucuronidases hydrolyze the glucuronide moiety and are present in most tissues, including the liver, kidney, spleen, and endocrine and reproductive organs (111, 112). Deconjugation of BPA at the tissue level could increase internal exposure levels and influence BPA's ability to adversely affect health.

These questions have implications for risk assessment as storage of BPA, non-oral routes of exposure, potential changes in metabolism due to diet composition, and deconjugation of BPA by β-glucuronidases would alter internal exposure to BPA. Some researchers have argued that internal exposure to unconjugated BPA is quite low because of rapid metabolism and excretion of BPA and lack of BPA storage, but if the assumptions regarding BPA absorption, metabolism, distribution and excretion are incorrect, it changes the potential for BPA to impact health.

BPA and Human Health

BPA is an endocrine disrupting chemical (EDC) with estrogenic activity (25). EDCs include any chemicals that interfere in some way with the normal functioning of the endocrine system. EDCs may disrupt normal biological functions through several different mechanisms. These mechanisms include the ability to influence the metabolism of natural hormones (production and/or degradation), alter the transport of hormones (changing the availability of free hormone for binding to receptors), or bind to hormone receptors themselves, triggering various downstream effects. The current debate surrounding EDCs is whether any exposure is safe (4, 10, 25, 26). Endogenous hormones are active at levels at or below the picomolar range, while studies have suggested that environmental chemicals that act as EDCs have activity in the nanomolar to micromolar range (25). In addition to the ability of EDCs to act like hormones, they

can also alter levels of endogenous hormones (25). The low levels needed for endogenous hormones to be active means that even small changes in hormone levels can produce effects. If a chemical has the ability to influence the production, metabolism, or secretion of hormones this can lead to changes in hormone levels, which, even if the change is small, can have health implications (25).

Current research indicates that BPA is not acutely toxic, nor is it genotoxic, and the International Agency for Research on Cancer (IARC) has declared the carcinogenicity of BPA to be not classifiable (113). Variability in methodologies, doses, exposure routes, outcomes, and differences between species and genders has produced conflicting results when evaluating BPA exposure and health outcomes (54). There has also been criticism about the relevance of doses used and outcomes assessed in previous studies (4, 25, 54). A 2006 review of studies that evaluated health effects of low-dose BPA exposure found forty published studies that identified effects below the safety level established by the US EPA and FDA (25).

Accumulating evidence from animal and *in vitro* studies demonstrate the ability of BPA to disrupt multiple hormone pathways at exposure levels below the US EPA's limit and at levels commonly observed in human populations (4, 6, 27). Activity testing performed by the US EPA found that BPA altered 101 different signaling pathways, including those of estrogens, androgens and thyroid hormones (54). The ability of BPA to disrupt signaling pathways means low doses can have much larger effects, because signaling pathways are designed to amplify signals from small amounts of signaling molecules (25). Recent epidemiological data suggest that BPA may be associated with alterations in sex and thyroid hormone levels (80, 86, 114-120), infertility and polycystic ovary syndrome (121-123), obesity (80, 83, 84, 124-129), pre-diabetes/type II diabetes (124, 130-132), and cardiovascular disease (124, 131, 133-135). These studies provide

suggestive evidence, but must also be interpreted with caution since most are cross-sectional analyses with important limitations, such as lack of long-term exposure data, which is more relevant for chronic disease risk (136).

On March 30, 2012 the US Food and Drug Administration (FDA) released their decision not to ban BPA use in food packaging. A statement released by the FDA, stated, "while evidence from some studies have raised questions as to whether BPA may be associated with a variety of health effects, there remain serious questions about these studies, particularly as they relate to humans" (137, 138). This decision closely reflects that of a 2010 panel from the World Health Organization (WHO) and the Food and Agriculture Organization of the United Nations (FAO) (54). The report from the joint WHO and FAO panel concluded that establishing recommendations for BPA exposure levels was hindered by the lack of available research. Human studies are lacking and there remain gaps in our understanding about sources of BPA exposure and toxicokinetics. The remainder of this dissertation will focus on the relationship between diet and BPA exposure, including a systematic review and evaluation of limitations in current human data on the association between BPA exposure and obesity (Chapter 2), an assessment of the feasibility of using a questionnaire as an alternative approach to collecting BPA exposure data in epidemiological studies (Chapter 3), and an evaluation of the relationship between diet and exposure to BPA (Chapter 4).

Chapter 2
Bisphenol A exposure and risk of obesity among adults: The need for human studies evaluating exposure to BPA and chronic disease outcomes

Introduction

Being overweight or obese contributes to an increased risk for many chronic diseases, including cardiovascular disease, Type II diabetes and some cancers (139, 140). In the United States, 69.2% of adults over age 20 years are overweight and 35.9% are obese (141). While excess caloric intake and a sedentary lifestyle are known risk factors for gaining weight, there has been increasing interest in the effects that environmental chemicals may have on the development of obesity (142). Endocrine disrupting chemicals (EDCs) are a class of chemicals that interfere in some way with the normal functioning of the endocrine system, and thus may alter hormonal regulation of body weight. The timing of increases in industrial usage of EDCs coincides with the obesity epidemic in the US (143). Bisphenol A (BPA) is an EDC that is used as an additive in polycarbonate plastics and epoxy resins.

In 2002, Baillie-Hamilton *et al* (143) put forth a hypothesis that EDCs could contribute to weight gain, and that the historical toxicological emphasis on weight loss as an indicator of toxicity could have resulted in weight gain going largely unnoticed as an adverse effect of EDC exposure. These observations, and results from animal and *in vitro* studies, have resulted in increasing interest in evaluating the potential for environmental exposures to act as "obesogens." Obesogens were defined by Grun and Blumberg as "molecules that inappropriately regulate lipid metabolism and apidpogenesis to promote obesity" (144). A 2012 report from the National Institute of Environmental Health Sciences concluded that there is suggestive evidence that BPA may act as an obesogen, but that further research is required (145). Animal and *in vitro*

study findings on the association between BPA exposure and weight gain have been inconsistent (142), which can likely be attributed to variability in methodologies, doses, exposure routes, outcomes, and differences between species and genders (54). Exposure to low levels of BPA perinatally (146-154), and during adolescence (155, 156), has been shown to result in increased weight in rodents.

The majority of research on the association between BPA and weight gain to date has focused on *in utero* and early life exposures, and very few studies have evaluated the risk of obesity associated with BPA exposure in adult animals. However, *in vitro* data suggest that BPA exposure could also influence risk of obesity in adults by altering levels of and/or binding to receptors for thyroid hormones (114-116, 118, 119, 157, 158), sex hormones (80, 115, 117, 119, 120, 159, 160), adiponectin (161, 162) and interfering with regulation of peroxisome proliferator-activated receptor gamma (PPARγ) activated pathways (144, 163, 164).

This systematic review summarizes the currently available literature evaluating the association between BPA levels and risk of overweight or obesity in adult humans (≥ 18 years). Limitations of current studies and recommendations for future studies will also be addressed.

Methods

The Population, Intervention, Comparison, and Outcome (PICO) method (165) was used to construct a focused research question for this systematic review. For this project, the PICO statement was “What is the risk or prevalence of obesity (outcome) among humans (population) who have higher BPA exposure (intervention/exposure) compared to those who have low BPA exposure (comparison)”.

To be included in the systematic review, a study had to be published in a peer-reviewed journal, written in English, and report data on the association between urine or serum BPA levels and body mass index (BMI) (kg/m^2). BMI was not required to be the primary outcome evaluated in the study. Studies were excluded if they did not present data for the association (with corresponding p-value and/or confidence interval) between BPA exposure and BMI (e.g. correlation, linear regression, logistic regression).

For this review, a systematic search of PubMed through September 30, 2013 was performed using the key words “body size”, “BMI”, “body mass index” or “obesity” and “Bisphenol A” or “BPA”. The search was limited to human studies in adults (≥ 18 years), and resulted in 38 articles. Studies in pregnant women were excluded. Data on associations with other markers of obesity and weight gain, such as waist circumference (WC) and weight, are included in the results presented in this systematic review. However, data on these outcomes were not a requirement for inclusion because very few studies evaluated these outcomes.

Abstracts and articles were then reviewed for relevance to the research question. Eight articles were found to be eligible for inclusion (80, 83, 84, 124-126, 128, 129). A total of nine articles were included after an additional article was identified on a reference list (127). Reasons for exclusion included: not the study population of interest (n = 10), no data on association between BPA and BMI (n = 15), duplicate data (n = 1), animal or *in vitro* study (n = 2), not English (n = 1), and review article (n = 1) (**Figure 1**).

Using the STROBE statement checklist as a guide (166), the following information, if available, was abstracted from each study: First author, year of publication, study location, study design, study population (age, gender, health status), exposure assessment, body composition measurement methods, data analysis approach, and study results related to body composition and BPA levels. Data analysis

approach was included to evaluate consistencies in analysis methods and to evaluate assessments of potential confounders. For exposure assessment methods, article abstraction focused on the type of biospecimens collected, reported materials used in collection, storage and processing and BPA assay methodology.

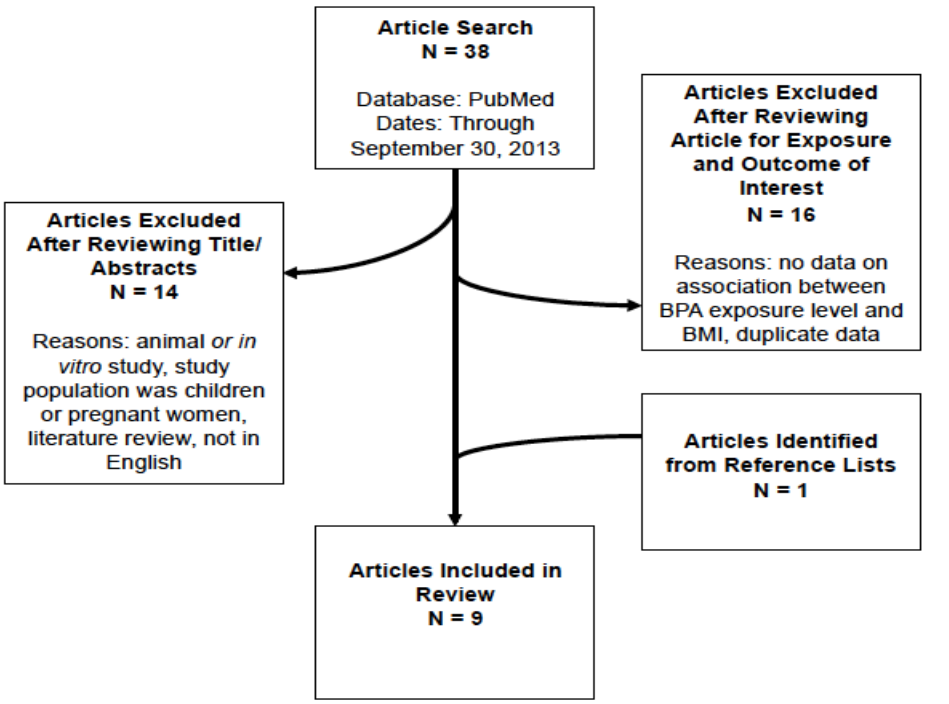

Figure 1 – Article Selection

Results

To date, nine studies have presented data on associations between urinary or serum BPA levels and body composition (80, 83, 84, 124-129). **Table 3** summarizes the studies and their findings. Seven studies were cross-sectional (83, 84, 124-127, 129), one study was a case-control (128) and one was a prospective cohort study, but the data analysis was cross-sectional (80). The studies were conducted in the United States (n = 3) (83, 124, 125), China (n = 2) (84, 129), Italy (n = 2) (80, 128) and Japan (n = 2) (126, 127). All three analyses in the United States used data from the National Health

and Nutrition Examination Survey (NHANES) with differing studies years included (2003 – 2008) (167). For four of the articles, body composition (BMI, WC, and/or weight) was the primary outcome of interest (83, 84, 125, 129). The primary outcomes in the other articles included insulin resistance/glucose homeostasis (124, 128), hepatic steatosis (128), liver enzyme levels (124), lipid levels (124), C-reactive protein levels (124), history of chronic disease (124), hyperandrogenism (128), spleen size (128), and sex hormone levels (80), although the studies also report on the association between urinary or serum BPA levels and body weight/composition. Three studies included only women (127-129), six of the studies were in general adult populations (80, 83, 84, 124, 125, 129), and three studies primarily focused on women with polycystic ovary syndrome (PCOS) (126-128).

All studies evaluated associations using a single cross-sectional measurement of BPA, but study methods varied. Three studies measured serum BPA levels using a competitive enzyme-linked immunosorbent assay (ELISA) kit (126-128), five studies measured total BPA in spot urine samples (83, 84, 124, 125, 129), and one study measured total BPA in a 24-hour urine sample (80). Urinary BPA levels were measured using gas chromatography – mass spectrometry (GC-MS)(125) and/or high performance liquid chromatography – tandem mass spectrometry (HPLC – MS/MS) (80, 83, 84, 124, 125, 129). Data analysis approaches included correlation (126-129), Chi-square tests (128), analysis of variance (ANOVA) (127), linear regression (80, 83, 84, 124) and logistic regression (83, 84, 125), thus limiting the ability to perform meta-analyses.

The three studies that measured serum BPA concentrations observed wide ranges of serum BPA levels across study participants. Tarantino *et al* observed means <0.70 ng/mL (128), while Takeuchi *et al* (2004) (127) observed means ranging from 0.71 ng/mL in healthy women to 1.17 ng/mL in obese women with PCOS, and Takeuchi *et al*

(2002) (126) observed means ranging from 0.64 ng/mL in healthy women to 1.49 ng/mL in women with PCOS.

Four studies reported mean or median urinary BPA levels in spot urine samples, but levels were difficult to compare given that some studies reported means (83, 125, 129), some reported medians (84) and some reported levels unadjusted for concentration (125, 129), while others reported creatinine adjusted concentrations (83, 84). Shankar *et al* observed mean spot urinary BPA levels of 3.97 ng/mL in men and 3.90 ng/mL in women (unadjusted for concentration) (125). The 75th percentile in this population was >4.20 ng/mL. Also in the NHANES population, Carwile *et al* reported a creatinine-adjusted mean urinary BPA concentration of 2.05 ug/g creatinine (83). Mean urinary BPA levels in the study by Zhao *et al* were 2.27 ng/mL (unadjusted for concentration) (129). Wang *et al* observed substantially lower levels in their study population with median levels of 0.81 ng/mL and a 75th percentile level of 1.43 ng/mL (unadjusted for concentration) (84). In a 24-hour urine sample, Galloway *et al* observed a mean urinary BPA level of 3.59 ng/mL (80).

Among the three studies that measured serum BPA, Tarantino *et al* (128) ($r = 0.27$, $p = 0.04$), Takeuchi *et al* (2002) (126) ($r = 0.32$, $p > 0.05$), and Takeuchi *at al* (2004) (127) ($r = 0.50$, $p < 0.001$) observed positive correlations between serum BPA levels and BMI, however, none adjusted for any potential confounders, such as age or health status.

Zhao *et al* (129) observed statistically significant positive correlations (adjusted for age) between urinary BPA levels and BMI ($r = 0.24$, $p < 0.001$), WC ($r = 0.30$, $p < 0.001$), and hip circumference ($r = 0.27$, $p < 0.001$) in premenopausal women. Galloway *et al* (80) did not find BMI to be statistically significantly ($p > 0.30$) associated with urinary BPA levels measured in a 24-hour urine collection. However, WC

(continuous) (p = 0.03) and weight (continuous) (p = 0.003) were statistically significantly positively associated with 24-hour urinary BPA levels. Wang *et al* found a small, but statistically significant, positive trend (p <0.001) between spot urine BPA levels and both BMI (continuous) and WC (continuous) (84). This study observed marginally statistically higher odds of being overweight (24 ≤ BMI < 30, OR = 1.24, 95% CI: 0.97 – 1.59) among participants in the highest BPA quartile (total urinary BPA >1.43 ng/mL) compared to those in the lowest quartile (total urinary BPA ≤ 0.47 ng/mL), and being in the highest BPA quartile was associated with 50% higher odds of being obese (BMI ≥ 30, 95% CI: 1.15 – 1.60) compared to those in the lowest BPA quartile. Wang *et al* also observed higher odds of an elevated WC (≥ 85 cm in women, 90 cm in men) among participants in in the highest BPA quartile (OR = 1.28, 95% CI: 1.03 – 1.60) compared to those in lowest BPA quartile.

There were three analyses using NHANES data. Using NHANES 2003 – 2008 data, Shankar *et al* found higher odds of general obesity (BMI ≥ 30) (OR = 1.69, 95% CI: 1.30 – 2.20, p <0.0001) and central obesity (WC: ≥ 88 cm in women, 102 cm in men) (OR = 1.59, 95% CI: 1.21 – 2.09, p = 0.009) among those in the highest BPA quartile compared to those in the lowest BPA quartile (125). Carwile *et al* performed analyses using NHANES 2003 – 2006 data and results are consistent with the results of Shankar *et al* (83). Those in the highest urinary BPA level quartiles (total urinary BPA >4.20 ng/mL) had higher odds of being overweight (25.0 ≤ BMI <30) (OR = 1.31, 95% CI: 0.80 – 2.14) or obese (BMI ≥ 30) (OR = 1.76, 95% CI: 1.06 – 2.94) and having an elevated WC (≥ 88 cm in women, 102 cm in men) (OR = 1.58, 95% CI: 1.03 – 2.42) compared to participants in the first quartile (total urinary BPA <1.10 ng/mL). While higher urinary BPA levels were associated with general and central obesity in this study, there was not a clear linear pattern to the association. While not the primary outcome of interest, Lang

et al observed non-statistically significant ($p > 0.05$) higher urinary BPA levels among obese (BMI 30 – 34.9: mean = 5.10 ng/mL, 95% CI: 3.97 – 6.24, BMI ≥ 35: mean = 6.93 ng/mL, 95% CI: 4.39 – 9.47) study participants compared to normal weight participants (BMI 18.5 – 24.9: mean = 3.91 ng/mL, 95% CI: 3.34 – 4.48) in the NHANES 2003-2004 study population (124).

Discussion

Overall, six of the nine studies reported that higher blood or urine BPA levels were significantly associated with a higher BMI (83, 84, 125, 127-129). Two of the three studies that did not observe statistically significant associations between urinary BPA levels and BMI did report trends toward a positive association (80, 124, 126). Among the two studies that observed non-significant positive trends, one was a secondary analysis (124) and the other had a small number of study participants (126). Statistically significant associations between higher urinary BPA levels and elevated WC were observed in all four studies that evaluated these associations (80, 83, 84, 125). Together these results support an association between higher BPA levels and central (WC) and general obesity (BMI); however, the results from these studies must be interpreted with caution.

The data presented in all nine studies included in this systematic review were single, cross-sectional measurements of both BPA levels and body composition. Cross-sectional data has an inherent inability to distinguish temporality, so researchers are not able to determine whether differences in observed BPA exposure levels are a cause of current body composition. An additional concern with cross-sectional data is that it only reflects very recent exposures, and for many chronic diseases, long-term exposure is most relevant. This is particularly true for BPA, which is generally considered to be

absorbed, metabolized and excreted within 24-hours of exposure (54, 168, 169), and within-person BPA levels are highly variable over time (170-172). Studies have demonstrated high intra-individual BPA levels in spot samples collected at multiple time points on the same day and across multiple days or years (170, 171). Six of the included studies measured BPA levels either in a single spot urine sample or a 24-hour sample (80, 83, 84, 124, 125, 129).

Biomarkers (urine or serum) are currently the only available method for assessing BPA exposure level. Three studies measured serum BPA levels using an ELISA kit, which is not considered to be the most accurate method for measuring BPA exposure (7, 8, 16, 23, 173, 174). BPA is a non-persistent chemical that is found only at very low levels (nano- to pico-molar concentrations) in serum measurements, which increases the potential for extraneous sample contamination to influence serum measurements (54, 175, 176). With serum measurements of unconjugated BPA it remains a challenge to distinguish actual BPA exposure from BPA contamination of the serum samples. Urinary BPA levels are much higher and largely consist of conjugated BPA, which can only be formed *in vivo*, thus acting as a marker for ruling out contamination by extraneous sources (173). In five of the studies, including all three studies that measured serum BPA levels, the manuscripts were unclear as to whether BPA-free materials were used to collect, process and store biospecimens. Failure to use BPA-free laboratory materials could lead to sample contamination and inaccurate BPA measurements, particularly with serum measurements (84, 126-129, 173). This could result in non-differential misclassification of exposure, which may attenuate observed associations.

Actual results are difficult to compare across studies because of differences in BPA assay methodologies and observed BPA levels. While currently available serum

BPA measurement techniques have their limitations, it is also important to note when measuring serum BPA levels, researchers are able to measure circulating levels of biologically active unconjugated BPA, which is indicative of actual internal exposure level. Conversely, total urinary BPA measures both conjugated and unconjugated BPA and does not directly measure actual internal exposure levels. The conjugation of BPA is a detoxification pathway, in that conjugated (usually glucuronidated) BPA no longer has endocrine disrupting properties and is readily excreted in the urine (3, 54, 97, 98). Internal exposure level is the relevant measure for evaluating health outcomes, however, given the limitations in measuring low-level serum BPA, total urinary BPA is currently considered the preferred approach for measuring BPA exposure (54, 173, 175, 176). Thus, it is important to acknowledge that studies using total urinary BPA levels are using the measurement as a proxy for actual internal exposure to unconjugated BPA.

In addition to differences in measurement approaches, observed BPA levels differed across studies. For example, the highest urinary BPA quartile in the Wang *et al* study was levels >1.43 ng/mL, while in the Shankar *et al* NHANES analysis the urinary BPA level in the highest quartile was >4.20 ng/mL and in the lowest quartile was <1.10 ng/mL, indicating a higher exposure level overall in this population. This highlights the current challenge regarding non-monotonic responses and how “low-level” BPA exposure is defined. Current data suggest that BPA exhibits a non-monotonic dose-response relationship, and is sometimes considered to have a U-shaped curve, where very low levels and very high levels of exposure may adversely affect health (25). This presents challenges in determining cut-points for evaluating associations between BPA exposure and health outcomes (25). It is currently unclear if any exposure level is safe. Adding to the complexity of evaluating BPA exposures and health outcomes in population-based epidemiological studies is that nearly all of the population is exposed

to low levels of BPA. There is generally no “unexposed” group to compare to the “exposed” populations. Prospective population-based studies evaluating different levels of exposure could help elucidate if there are thresholds at which BPA is associated with health outcomes. However, if BPA is unsafe at any level, these studies may observe no association, which could indicate either no real association or a lack of an unexposed participant group.

All of the studies included in this systematic review failed to collect data and/or evaluate important potential covariates, such as dietary habits and correlated chemical exposures. Eating greater quantities of food should theoretically lead to greater potential for BPA exposure, but also higher caloric intake, and an increased risk of being overweight or obese. Additionally, other chemical exposures found in the diet and human environments are also suspected of being endocrine disrupting obesogens. As an example, diet is also thought to be the primary route of exposure to phthalates (113, 177), which are often used in food packaging as plasticizers (added to increase flexibility and resilience) (113, 178-181). Phthalates have also been associated with increased risk of obesity (145, 182, 183). Data indicate that most humans are exposed to both BPA and phthalates, making it difficult to evaluate the individual effects of BPA without considering associations with phthalates (184). Future studies should consider overall energy intake and correlated chemical exposures when evaluating the association between BPA and body weight/composition.

Mechanistic studies provide insight into the biological plausibility of an association between chronic, low dose BPA exposure and body composition changes in adults. *In vitro* studies have shown that BPA has the ability to bind to thyroid hormone receptors (157) and human studies have observed associations between higher BPA levels and altered levels of thyroid hormones (114-116, 118, 119). Thyroid hormones

are a major regulator of metabolism, especially basal metabolism, and the impact of even small alterations to thyroid hormone levels on body composition is evidenced by weight changes in patients with thyroid dysfunction (185-187). Another mechanism by which BPA exposure may lead to weight gain is through activation of PPARγ. PPARγ is highly expressed in adipose tissue and regulates adipocyte differentiation and lipid metabolism (188). *In vitro* data suggest BPA has the ability to bind to PPARγ, which could trigger increased adipocyte differentiation and/or uptake of lipids by adipocytes, thus influencing body composition (163, 189, 190).

While cross-sectional studies have important limitations, there are challenges to evaluating BPA with other study designs. Many of the existing longitudinal, prospective cohort studies have not collected urine samples, or if they have, the samples are single-spot urines and/or the urine samples were not collected with BPA-free materials. Other study designs, such as case-control studies also typically collect single cross-sectional biomarker measurements, which likely do not accurately reflect long-term exposure.

Future studies investigating the association between BPA exposure and changes in body weight or composition should collect and evaluate additional potential confounders or effect modifiers, including dietary intake and concurrent chemical exposures. Advances in BPA measurement assays are needed to lower costs and to allow for measurement of low level BPA in both serum and urine, particularly methods that can evaluate levels of the biologically active unconjugated BPA in serum. The U.S. National Institute of Environmental Health Sciences (NIEHS) has an ongoing round robin to specifically address improvements to serum assay methodologies and standardization of assay protocols, which should improve assessment of BPA exposure levels across studies (191). Reducing the cost of measuring BPA exposure will allow for BPA measurements in large prospective observational studies and for repeated

measurements to evaluate longer-term exposure patterns. Alternatively, better understanding of all of the sources of human BPA exposure, and how exposure levels vary over time, would allow for the development of data collection tools, such as a questionnaire, that could be used to estimate relative BPA exposure in large population-based observational studies. Longitudinal studies that prospectively measure BPA exposures and changes in body weight and composition are needed to establish temporality and causality, and the direction of any observed associations.

Conclusion

Currently available research suggests an association between BPA exposure and risk of obesity in adults, although the limited number of human studies and significant methodological issues limit the ability to draw firm conclusions from these studies. Given the paucity of high quality data on the human health effects of BPA exposure, the World Health Organization (WHO) and Food and Agriculture Organization of the United Nations (FAO) determined they were unable to adjust the current limit for safe BPA exposure (54), and the US Food and Drug Administration (FDA) decided not to ban BPA in food packaging (137, 138). However, the lack of high quality research findings does not mean that there are no health effects. The evidence of widespread human exposure to BPA makes it imperative that the safety of BPA be fully evaluated.

Table 3: Human Studies Evaluating Body Mass Index in Relation to Bisphenol A in Adult Populations (≥ 18 years)						
Serum BPA Measurement Studies						
Study	***Study Objective***	***Population***	***Study Design***	***Exposure Assessment***	***Results***	***Covariates***
Tarantino *et al* (2013) (128)	To evaluate whether serum BPA levels are associated with insulin resistance, hepatic steatosis, hyper-androgenism severity and spleen size in women with polycystic ovary syndrome.	Naples, Italy Women Cases Mean age ± SD: 27.7 ±6.8 years n = 40 women with PCOS Controls: Mean age ± SD: 26.2 ±3.9 years n = 20 age-matched healthy, normal weight women who worked at hospital (with regular menstrual cycles, no hyper-androgenaiemia, hirsutism, or acne)	Case-control	Spot blood sample Serum BPA competitive ELISA LOD: < 2pg/mL (range: 7.8-500pg/mL) Unclear if BPA-free collection, processing and storage materials were used. Compared increased levels (>0.45ng/mL) to lower levels (<0.45ng/mL) Chose cut-off based on 95th percentile in controls	<u>Mean BMI</u> Cases: 28.1 ± 7.7 Controls: 22.1 ±1.8 <u>Median BPA</u> (Range) Cases: 0.7 ng/mL (0.1 – 6.0) Controls: 0.1 ng/mL (0.1 – 0.6) Among women with PCOS BMI did not differ between those with BPA levels <0.45ng/mL vs. those with levels about the cut-point (p = 0.30) BMI was significantly correlated (r = 0.27, p = 0.04) with serum BPA measurements Only one control had BPA level above 0.45ng/mL.	None
Takeuchi *et al* (2004) (127)	To evaluate whether serum BPA levels are associated with serum hormone levels in women with ovarian	Japan Non-obese women with normal menstrual cycles Mean Age (±SEM): 27.5 (± 0.7)	Cross-sectional	Spot blood samples Serum BPA – ELISA kit	<u>Mean BMI by group</u> (± SEM) non-obese women with normal menstrual cycles = 19.7 ± 0.3 obese women with normal menstrual cycles = 28.5 ±1.7	None

	dysfunction and obesity.	n = 19 Obese women with normal menstrual cycles Mean Age (±SEM): 28.8 (± 2.0) n = 7 Women with hyperprolactinemia Mean Age (±SEM): 27.7 (± 2.6) n = 7 Women with hypothalamic amenorrhea Mean Age (±SEM): 25.1 (± 1.0) n = 21 Non-obese with PCOS Mean Age (±SEM): 26.5 (± 1.5) n = 13 Obese with PCOS Mean Age (±SEM): 24.7 (± 1.9) n = 6			patients with hyperprolactinemia = 20.8 ± 1.0 women with hypothalamic amenorrhea = 19.2 ±0.6 non-obese PCOS = 19.1 ± 0.6 obese PCOS = 31.3 ± 3.0 <u>Mean BPA by group</u> (± SEM) normal menstrual cycles = 0.71 ± 0.09 ng/mL obese women with normal menstrual cycles = 1.04 ±0.09 patients with hyperprolactinemia = 0.83 ± 0.12 ng/mL women with hypothalamic amenorrhea = 0.84 ±0.10 ng/mL non-obese PCOS = 1.05 ± 0.10 ng/mL obese PCOS = 1.17 ± 0.16 ng/mL Correlation: r = 0.50, p <0.001 Among normal women serum BPA levels were higher in obese women compared to non-obese women, p <0.05	

Takeuchi *et al* (2002) (126)	To evaluate associations between urinary BPA levels and gender and sex-hormone levels.	Japan Healthy women Mean Age (±SEM): 28.7 (± 0.7) n = 14 PCOS women Mean Age (±SEM): 25.7 (± 1.4) n = 16 Healthy men Mean Age (±SEM): 29.4 (± 1.1) n = 11	Cross-sectional	Spot blood sample Serum BPA – ELISA kit	<u>Mean BMI by group</u> (± SEM) Healthy women: 19.4±0.3 PCOS women: 22.4 ±0.9 Healthy men: 21.2 ± 1.1 <u>Mean BPA by group</u> (± SEM) Healthy women: 0.64 ± 0.10 ng/mL PCOS women: 1.49 ± 0.11 ng/mL Healthy men: 1.04 ± 0.10 ng/mL Correlation - women only: r = 0.30, p >0.05 Correlation - all participants, r = 0.32, p >0.05	None
Total Urinary BPA Measurement Studies						
Study	***Study Objective***	***Population***	***Study Design***	***Exposure Assessment***	***Results***	***Covariates***
Shankar *et al* (2012) (125)	To evaluate whether urinary BPA levels were associated with obesity (BMI and WC) by gender and race/ethnicity.	United States NHANES 2003 – 2008 Men and women Ages: ≥ 20 years n = 3,967	Cross-sectional	Spot urine samples Total BPA Analysis method depends on year - GC/MS or HPLC/MS-MS LOD: 0.1 – 2 ng/mL per 100uL urine Urinary BPA levels were evaluated as quartiles	<u>Mean BMI</u> Not provided. <u>Mean WC</u> Not provided. <u>Mean BPA</u> Men: 3.97 ± 0.21 ng/mL Women: 3.90 ± 0.26 ng/mL <u>Overall population BPA vs. BMI ≥ 30kg/m^2</u> Q4 BPA vs. Q1 BPA: OR = 1.69 (95% CI: 1.30-2.20),	Age, sex, race/ethnicity, education, smoking, alcohol intake, physical inactivity, diabetes, hypertension, total serum cholesterol

				BPA Quartiles Q1: < 1.10 ng/mL Q2: 1.10 - 2.10 ng/mL Q3: 2.11-4.20 ng/mL Q4: > 4.20 ng/mL	p <0.0001 Overall population BPA vs. WC ≥ 88cm (women)/102cm (men) Q4 BPA vs. Q1: OR = 1.59 (95% CI: 1.21-2.09), p = 0.0009 Urinary BPA levels were significantly associated with higher odds of obesity (BMI or WC), regardless of race/ethnicity or gender.	*Did not adjust for urine concentration.
Wang *et al* (2012) (84)	To evaluate whether urinary BPA levels were associated with obesity (BMI and WC) or insulin resistance.	Shanghai, China Men and women Ages: ≥40 years N = 3390	Cross-sectional	Spot morning urine sample Total BPA HPLC/MS-MS LOD = 0.30ng/mL (below were assigned value of 0.15) Unclear if BPA-free collection, processing and storage materials were used. Urinary BPA levels were evaluated as quartiles BPA Quartiles Q1: ≤ 0.47 ng/mL Q2: 0.48-0.81 ng/mL Q3: 0.82-1.43 ng/mL Q4: > 1.43 ng/mL	Median BPA (mean not provided) 0.81 ng/mL (interquartile range: 0.47 – 1.43) Mean BMI 24.9 ± 3.6 kg/m^2 (± SD, adjusted for gender) BMI (kg/m^2) definitions: Recommended: BMI < 24 Overweight: 24 ≤ BMI <28 Obese: ≥28 Overweight BMI vs. Recommended BMI Q4 BPA vs. Q1: OR = 1.24 (95% CI: 0.97-1.59) Obese BMI vs. Recommended BMI Q4 BPA vs. Q1 BPA: OR = 1.50 (95% CI: 1.15-1.60)	Age, sex, urinary creatinine, smoking , alcohol consumption, education, systolic blood pressure, HDL-cholesterol, LDL-cholesterol, Total cholesterol, c-reactive protein, fasting plasma glucose, fasting serum insulin, and serum ALT and GTT

					BMI and urinary BPA – continuous Mean BMI by BPA Quartile BMI ± SD Q1 24.6 ± 3.6 Q2 24.9 ± 3.8 Q3 24.8 ± 3.6 Q4 25.1 ± 3.5 (p_{trend} <0.001) WC definitions for elevated: ≥90 cm (men)/ ≥85 cm (women) Elevated WC vs. Normal WC Q4 BPA vs. Q1 BPA : OR = 1.28 (95% CI: 1.03-1.60) WC and urinary BPA – continuous Mean WC (cm) by BPA Quartile WC ± SD Q1: 86.6 ± 9.9 Q2 87.7 ± 9.8 Q3 87.1 ± 9.8 Q4 87.9 ± 9.6 (p_{trend} <0.001)	
Zhao *et al* (2012) (129)	To evaluate whether urinary BPA levels are associated with body composition, serum estrodial, leptin and	Shanghai, China Healthy pre-menopausal women Ages: 20 – 55 years n = 282	Cross-sectional	Spot urine samples Total BPA HPLC/MS-MS LOD not provided. Collection and storage material details were	Mean BPA (± SE) 2.27 ± 0.32 ng/mL Mean BMI 21.2 ± 0.2 kg/m^2 BMI vs. BPA: r = 0.24, p <0.001	Age *Did not adjust for urine concentration.

	osteocalcin levels, and bone mineral density.			not provided.	WC vs. BPA: r = 0.30, p <0.001 Hip circumference vs. BPA: r = 0.27, p <0.001	
Carwile *et al* (2011) (83)	To evaluate whether urinary BPA levels were associated with general (BMI) and central (WC) obesity.	United States NHANES 2003-2004 2005-2006 Men and women Ages: 18 – 74 years Excluded pregnant women, and participants missing urinary BPA or creatinine n = 2747	Cross-sectional	Spot urine sample Total BPA HPLC-MS/MS LOD 03-04 = 0.36ng/mL LOD 05 - 06 = 0.40ng/mL Urinary BPA levels were evaluated as quartiles <u>BPA Quartiles</u> Q1: ≤ 1.1 ng/mL Q2: 1.2-2.3 ng/mL Q3: 2.4-4.6 ng/mL Q4: ≥ 4.7 ng/mL	<u>Mean BPA</u> 2.05ug/g creatinine (interquartile range 1.18-3.33) (creatinine adjusted) <u>Mean BMI</u> Not provided. BMI (kg/m^2) definitions: Recommend: BMI < 25 Overweight: 25.0<BMI ≤29.9 Obese: BMI ≥30 <u>Overweight BMI vs. Recommended BMI</u> Q4 BPA vs. Q1 BPA: OR = 1.31 (95% CI: 0.80-2.14) <u>Obese BMI vs. Recommended BMI</u> Q4 BPA vs. Q1 BPA: OR = 1.76 (95% CI: 1.06-2.94) <u>BMI and urinary BPA – continuous - Change in BMI by BPA Quartile</u> <u>Kg/m^2 (95% CI)</u> Q1 Reference Q2 1.48 (0.46–2.51) Q3 1.69 (0.62–2.76) Q4 1.56 (0.25–2.87) (p_{trend} = 0.18)	Sex, age, race/ethnicity, education, smoking, creatinine

					WC definitions for elevated: ≥102 cm (men)/ ≥88 cm (women) <u>Elevated WC vs. Normal WC</u> Q4 BPA vs. Q1 BPA: OR = 1.58 (95% CI: 1.03-2.42)	
Galloway *et al* (2010) (80)	To evaluated whether urinary BPA levels were associated with serum estrogen and testosterone levels.	Italy InCHIANTI - prospective cohort study Men and women Ages: 20 – 74 years n = 720	Cohort (cross-sectional analysis)	24-hour collection urine sample Total BPA (HPLC/MS-MS) LOD/LOQ - 0.50ug/L Evaluated as covariate, not exposure/outcome association Linear Regression – present geometric means and p-values evaluated at specified cut-offs	<u>Mean BPA</u> 3.59ng/mL (95% CI: 3.42-3.77) <u>Mean BMI</u> Not provided. <u>Mean BPA (ug)/day</u> BMI 18.5-25: 5.67 (95% CI: 5.22-6.16), reference BMI 25-30: 5.84 (95% CI: 5.43-6.27), p = 0.30 BMI 30.1-34.9: 5.66 (95% CI: 5.04-6.34), p = 0.37 BMI ≥ 35: 4.85 (95% CI: 3.94-5.98), p = 0.73 <u>β (95% CI)</u> WC (cm): 0.006 (0.002-0.011), p = 0.013 Wt (kg): 0.006 (0.002-0.010), p = 0.003	Age, sex, study site

Lang *et al* (2008) (124)	To evaluate whether urinary BPA levels were associated with health status (history of chronic disease, C-reactive protein levels, glucose homeostasis, lipid levels, liver enzyme levels).	United States NHANES 2003 – 2004 Men and women Ages: 18 – 74 years n = 1,455	Cross-sectional	Spot urine sample Total BPA HPLC-MS/MS LOD 0.3ng/mL	<u>Mean BPA</u> Not provided. <u>Mean BMI</u> Not provided. <u>Mean BPA (ug/mL) Across BMI Categories</u> BMI 18.5 – 24.9: 3.91 (95% CI: 3.34-4.48) BMI 25.0 – 29.9: 4.18 (95% CI 3.43-4.92) BMI 30 – 34.9: 5.10 (95% CI: 3.97-6.24) BMI 35+: 6.93 (95% CI: 4.39-9.47) (p_{trend} >0.05) Actual p-value not provided.	Age, sex, creatinine

Abbreviations: BPA = bisphenol A, BMI = body mass index, cm = centimeters, ELISA = enzyme-linked immunosorbent assay, kg = kilograms, m = meters, mL = milliliters, ng = nanograms, NHANES = National Health and Nutrition Examination Survey, PCOS = polycystic ovary syndrome, Q = quartile, SD = standard deviation, SEM = standard error of the mean, WC = waist circumference

Chapter 3
Estimating BPA exposure using dietary intake of know sources of BPA: results from the UB-Diet Study

Background

Bisphenol A (BPA), used in the manufacture of polycarbonate (PC) plastics (~75%) and epoxy resins (~20%), is one of the highest volume chemicals produced worldwide (>8 billion pounds) (1, 2). Biomonitoring data from the United States' National Health and Nutrition Survey (NHANES) has detected BPA in the urine of more than 90% of participants, indicating widespread exposure to BPA (1, 3, 23, 174). Current data suggest that the general population is chronically exposed to low levels of BPA, but the health consequences of chronic, low level exposure remains relatively unknown. BPA assays are relatively expensive, and more cost effective methods of BPA exposure assessment are needed to allow researchers to fully evaluate human health effects.

While PC plastics and epoxy resins are used in a variety of projects, it is generally assumed that diet is the major source of BPA exposure in human populations (5-10, 39). In the past, PC plastics were often used to make food and beverage storage containers, however, due to consumer demand and new regulations in several states, PC plastic food storage containers have been largely phased out in the United States and are likely no longer a major source of dietary exposure (192). Epoxy resins are still used in the lining of metal cans and lids (1-3). Measurable levels of BPA have been detected in numerous canned food products (9, 30, 32, 33, 39-53), and in beverages stored in PC plastic containers (71, 74, 75, 193). Very few studies have evaluated the BPA content of non-canned food items, but these studies generally suggest that BPA is typically not present in non-canned food items, or that levels are quite low (9).

Findings from previously published observational and intervention studies support diet as the major route of BPA exposure in humans (58-60, 76-79). An analysis of urinary BPA levels in Japan found that levels decreased significantly after the food industry voluntarily removed BPA from food can linings (76). Another study found that dietary sources accounted for 99% of the BPA present in the children's environment (77). Three intervention studies have demonstrated the ability to alter urinary BPA levels by increasing or decreasing exposure to all packaged foods, including canned foods (58-60). However, a more recent study did not observe the expected decrease in urinary BPA levels when packaged foods were removed from study participants' diet, possibly due to other sources of BPA exposure during food preparation or in the participants' environment (62).

Measuring BPA exposure in the large, prospective human population studies that are typically used to evaluate factors associated with various human health outcomes has been cost-prohibitive. Many of the existing prospective cohort studies were not designed to evaluate BPA exposure. Most collected spot urine or blood samples, which reflect only very recent BPA exposure (24-hours), and may result in misclassification of the long-term exposure patterns, which are likely to be more relevant to human health (93, 96, 168, 169). Additionally, budget considerations often limit study design and size. Case-control studies, by nature of their design, are unable to collect biospecimens during relevant exposure periods. Studies evaluating associations between BPA levels and health conditions using existing surveillance and biomonitoring datasets, such as the National Health and Nutrition Examination Survey (NHANES), are unable to determine causality due to the cross-sectional nature of the data collection.

A less expensive alternative method for ranking individuals by BPA exposure may be to estimate BPA exposure using a set of questions about use of packaged

foods, such as canned and microwaved foods, in conjunction with a standard food frequency questionnaire (FFQ). The goal of this study was to develop and test a BPA exposure assessment module (BEAM). In addition to allowing for larger sample sizes than have previously been possible, a cost-effective questionnaire approach could allow for repeated assessment over time to determine long-term patterns of BPA exposure.

Methods

The Urinary Biomarkers of Dietary Intake Study (UB-Diet Study) was a cross-sectional study of 68 generally healthy adults. The study was conducted at the University of Minnesota's Epidemiological Clinical Research Center (ECRC). The study was approved by the Institutional Review Board at the University of Minnesota, and all study participants provided informed consent to participate in the study.

Study Population

Participant recruitment occurred between August 2012 and January 2013. Advertisements in Minneapolis community newspapers and on Craigslist, and flyers posted on the University of Minnesota campus were used to recruit study participants. Potential participants were instructed to contact the study coordinator by telephone or e-mail. In order to be included in the study, participants had to be: (1) between 20 to 59 years of age; (2) a resident in the seven county Minneapolis-St. Paul metro area in Minnesota (Anoka, Carver, Dakota, Hennepin, Ramsey, Scott and Washington counties); (3) able to give informed consent; (4) available during the study dates; (5) able to speak English; (6) without a history of cancer (excluding non-melanoma skin cancer), heart attack, diabetes or cerebrovascular event; (7) a non-smoker; and (8) without a

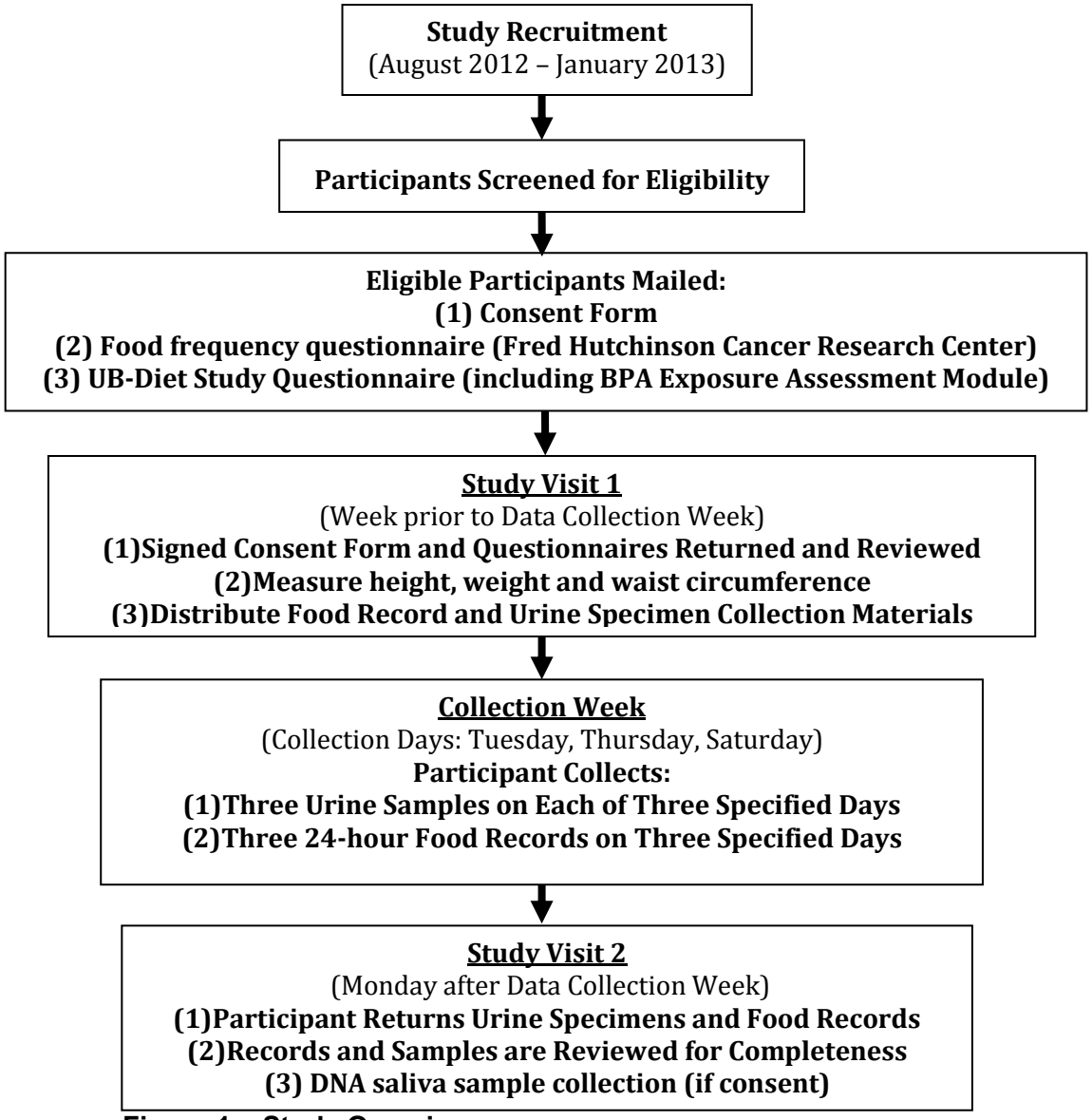

Figure 1 – Study Overview

body weight change of more than 10% in the previous 6 months. Pregnant and lactating women were excluded. Study overviews are presented in **Figures 1** and **2**.

To ensure a range of potential BPA exposure levels, participants were additionally screened to determine typical frequency of canned food consumption with the goal of recruiting participants with a range of potential BPA exposure levels. Potential participants were asked eleven questions about dietary habits, including canned food intake, fruit and vegetable intake and meals eaten away from home (**Appendix 2**). Responses were used to categorize potential participants into four exposure levels: the first group included participants who reported eating canned food < one time per week, the second group who consume ≥ one to < three items per week, the third group who consume ≥ three and < five per week, and the final group were those who reported eating five or more canned items per week (Max per group: 26).

Monday	Reminder call/email No data to collect
Tuesday	24-hour Food Record #1 Urine Collection Day 1 • First morning void (after 5 am) • Mid-day (11 am – 2 pm) • Evening (6 pm – 9 pm)
Wednesday	No data to collect
Thursday	24-hour Food Record #2 Urine Collection Day 2 • First morning void (after 5 am) • Mid-day (11 am – 2 pm) • Evening (6 pm – 9 pm)
Friday	No data to collect
Saturday	24-hour Food Record #3 Urine Collection Day 3 • First morning void (after 5 am) • Mid-day (11 am – 2 pm) • Evening (6 pm – 9 pm)
Sunday	No data to collect

Figure 3 – Data Collection Week Schedule

The most common reason that potential participants were excluded from the study was that their canned food intake patterns placed them in a BPA exposure group that was already full. A total of 182 people were screened for eligibility, with a final number of 68 participants included in the study.

Dietary and Demographic Data Collection

Prior to the first study visit, participants were mailed a consent form, the Fred Hutchinson Cancer Research Center (FHCRC) food frequency questionnaire (FFQ) (194, 195) and a questionnaire designed specifically for use in this study, the Urinary Biomarkers of Dietary Intake Study (UB-Diet Study) Questionnaire. This questionnaire included the BPA Exposure Assessment Module and demographic and lifestyle questions (e.g. age, education, income, race/ethnicity and physical activity), from previously validated questionnaires, including NHANES surveys and the U.S. National Cancer Institute's Diet History Questionnaire (DHQ) (167, 196).

Participants were asked to return the completed questionnaires with their consent form at Study Visit 1. Height, weight and waist circumference (WC) were measured at study visit 1. Height was measured without shoes using a wall-mounted stadiometer (Holtain Ltd., Crymych, Dyfed, UK). Weight was measured in kilograms with the participant wearing street clothes without shoes using an electronic scale (BWB-800, Tanita Corporation, Arlington Heights, IL). Waist circumference was measured just above the iliac crest using a non-stretch, retractable measuring tape with a tensioning device (Gulick II Tape Measure, Country Technology, Gays Mills, WI). BMI was calculated as weight (kg)/[height (meters)]^2. The questionnaires and consent form were reviewed for completeness, and participants were asked to clarify any missing or unclear information on the questionnaires.

Participants were also provided urine collection materials and food records, and instructed on how to complete both, at study visit 1. Food record data was collected to serve as a secondary diet data collection approach to assess whether the questionnaire was able capture intake of food items, such as canned food intake, given that the questions included on the BPA exposure assessment module were not previously validated. Additionally, food record data allowed for a direct evaluation of the food items consumed on the specific days that urine specimens were collected. The food record instructions for this study differed from the instructions that are typically provided in that participants were also asked to provide details about the food packaging and brand names of the foods consumed. For example, participants were asked to indicate whether a food item was canned, fresh or frozen. Participants were asked to record all foods and beverages consumed on two weekdays (Tuesday and Thursday) and one weekend day (Saturday), which is consistent with the minimum number of days needed to ensure an accurate representation of usual intake while minimizing participant burden (197). On each of the data collection days, participants completed a 24-hour food record and collected three urine specimens. At Study Visit 2, the food records and urine samples were reviewed to verify that all nine samples were collected and correctly labeled, and to determine completeness and clarify questions about the food record to help enhance data quality.

Design of BPA Exposure Assessment Module

The goal in developing the BPA Exposure Assessment Module (BEAM) was analogous to the goal of nutrient intake data collected by FFQs, which is to rank participants by levels of exposure rather than determining exact exposure levels. Similar to most FFQs, the BEAM asks the participant to report usual frequency of intake

of foods thought to be significant sources of BPA exposure over the previous year. The entire UB-Diet Study Questionnaire, including the BEAM is provided in **Appendix 3**.

Development of the BEAM began with an extensive review of the scientific literature to identify potentially important dietary sources of BPA, which was determined by reported levels of BPA in the food item (**Appendix 1-Tables 1 and 2**). Current literature indicates that canned foods have much higher BPA levels than fresh and other non-canned food items, although very few fresh and non-canned foods have been tested for BPA content (9, 32, 33, 39-53). Thus, additional questions about whether these food items are typically consumed fresh, frozen or canned was considered useful for determining dietary BPA exposure levels. Conversely, the literature suggests that breads and cereals likely contribute little to overall dietary BPA exposure, so questions about the packaging and sources of these food items were not included in the module. In addition to data on food sources, U.S. food consumption data was used to identify specific canned food items that are commonly consumed in the U.S (41). Given that the questions were designed to be administered in combination with a FFQ, the format for the BEAM was based on the format of the National Cancer Institute's Diet History Questionnaire (NCI DHQ) II (9, 33, 39, 41, 105, 193, 196). The questionnaire was chosen because the format allows for the insertion of additional questions to obtain more details about a food item (such as package type). Participants were additionally asked about the proportion of servings cooked from frozen (e.g. microwave meals) and from pre-packaged mixes (e.g. boxed macaroni and cheese, cake mixes, etc.).

The UB-Diet Study Questionnaire also included questions about demographics and lifestyle, as well as broader dietary habits, such as the frequency of meals eaten away from home, as these could serve as additional sources of BPA unknown to participants. The questionnaire also assessed non-diet sources of BPA exposure, such

as handling receipt paper, which contains BPA and could be a significant source of exposure among participants who frequently handle receipts (e.g. cashiers). These additional sources were hypothesized to also be potentially important predictors of urinary BPA levels, strengthening the ability of the questionnaire to rank participants' exposure levels.

Biospecimen Collection and Processing

Participants were asked to collect a total of nine urine samples: three spot urine samples on each of the two weekdays and one weekend day that corresponded with the days on which 24-hour food records were collected. Single void urine samples and single 24-hour samples have been shown to have high within-person variability (170-172). A recent study found that measuring BPA concentrations from multiple spot urine collections resulted in estimated BPA levels that were close to the mean concentrations observed after multiple 24-hour urine collections (172).

On each day, participants were instructed to collect the first morning void (first void, at or after 5 am), a mid-day sample (between 11 – 2 pm), and an evening sample (between 6 – 9 pm). At the initial study visit, participants were given nine-labeled, sterile, commercial 4-ounce polypropylene containers (which do not contain BPA (65)) and instructions for urine collection. Participants were asked to record the time of sample collection on the specimen cup label, place the filled specimen cup in a re-sealable freezer bag, and to refrigerate urine specimens until the second study visit. Total BPA is stable in urine during short-term storage and does not require immediate processing (198). Participants were given a cooler with ice packs for transporting specimens, and were instructed to bring the specimens to the second study visit.

Immediately following the second study visit, specific gravity of the individual samples and the pooled samples was measured using a digital handheld refractometer (ATAGO PAL-10S, ATAGO U.S.A., Inc., Bellevue, WA), with automatic temperature compensation. The nine individual urine samples for each participant were then pooled, mixed thoroughly, and aliquoted into 5mL polypropylene vials. All samples were stored at -70° C until sent for analysis. Samples were shipped as a single batch on dry ice overnight to NMS Labs (Willow Grove, PA) for the BPA analysis. Blinded replicate samples were included to evaluate data quality.

Total (free and conjugated) urinary BPA was measured by gas chromatography – mass spectrometry (GC-MS) (199). The detection limit was 0.50ng/mL, and blinded replicate coefficient of variation was 14%.

Data Analysis

The completed FFQ forms were scanned and analyzed by the FHCRC Nutrition Assessment Shared Resource group (Seattle, WA). Food record nutrient data was calculated using the Nutrition Data System for Research (NDSR, version 2012) software developed by the Nutrition Coordinating Center (NCC) at the University of Minnesota (200, 201). Data from the UB-Diet Study Questionnaire was manually entered into a REDCap database using the double data entry method (202). All data analyses were performed using SAS 9.2 (SAS Institute Inc., Cary, NC).

Data on canned food intake, beverage from cans or plastic containers, and restaurant meals were manually abstracted from the food records and entered into the study database. Servings of canned food and packaged beverages and the number of restaurant meals were summed for a three-day total. A serving size of canned foods was defined as the proportion of a 4-ounce serving of food and a serving of beverage as

the proportion from a 12-ounce can/bottle. Any meal eaten at a restaurant was counted as one restaurant meal. Excluded from this were baked goods (scones, muffins, cake, etc.) and beverages (including lattes, mochas, smoothies), as these eating episodes did not represent entire meals, and these food items are unlikely to result in differential BPA exposure compared to the same food item prepared in the home. No individual canned food item on the BEAM was consumed by a sufficient number of participants to warrant an individual category for data analysis, so canned food intake was summarized using the following categories: canned vegetables, canned fruit, canned meals, and total canned food intake (**Appendix 4**). Similarly, canned food intake on the food records were evaluated as total canned food intake on all three days, due to a lack of consistency in the types of canned foods.

Urinary BPA concentrations were adjusted for dilution by multiplying values (ug/L) by [1.024 -1)/ (specific gravity -1)] (203, 204). Urinary BPA concentrations <LOD (0.50ug/L) were divided by the square root of 2, which is a standard approach for imputing data for samples below LOD (205). Urinary BPA values were log-transformed to normalize the distribution.

Pearson correlations were used to compare the data on reported long-term intakes of canned food, canned and plastic bottled beverages, and restaurant meals collected via the UB-Diet Study Questionnaire with that reported on the 24-hour food records. Due to two outliers in the urinary BPA data, Spearman correlations were used to evaluate correlations between hypothesized sources of BPA exposure assessed by the BEAM and 24-hour food records and observed urinary BPA levels.

Multivariable linear regression was used to evaluate the degree to which data collected on the UB-Diet Study questionnaire explained variability in urinary BPA levels. A model that included all hypothesized dietary predictors of urinary BPA levels (canned

foods, microwave meals, canned and plastic-packaged beverage intake and restaurant meals) was evaluated first. Subsequent analyses were performed to evaluate individual food groups, such as canned vegetables, that were hypothesized to be a source of BPA exposure. Finally, step-wise regression was used to determine which combination of variables explained the largest amount of variability in urinary BPA levels. Data on canned vegetables, fruits, meals and total canned food intake were evaluated categorically, because canned food intake was not normally distributed.

Age, gender, education, BMI, WC, income, occupation, physical activity, chronic health issues, and frequency of receipt handling were evaluated as potential covariates using linear regression. No individual variables were found to be associated with both urinary BPA levels and packaged food intake (all p-values >0.10), so multivariable adjusted linear regression models included only age and gender. All analyses were replicated using data from the 24-hour food records.

To evaluate the ability of the questionnaire and food record data to rank participants according to urinary BPA levels, a potential BPA exposure score based on dietary sources of BPA reported in the literature was created for both the questionnaire data and the food record data. The UB-Diet Study Questionnaire score included canned foods, microwave meals, canned and plastic bottled beverages, and restaurant meals. The food record score included canned foods, canned and plastic bottle beverages, and restaurant meals. Microwave meals were not included in the food record score since only one participant reported consuming a microwave meal. The score was weighted to account for the variation in BPA content of foods. Canned foods were considered the primary BPA source (i.e. canned food score*1.0), as canned foods are well established as a primary route of dietary BPA exposure. The reported BPA content of canned and plastic bottled beverages, microwave meals and restaurant meals typically are

significantly lower than that of canned food items, and the presence of BPA in these items is inconsistent (i.e. the same food items have been observed to have measurable levels and levels below detection). Thus, beverages from cans or plastic bottles, microwave meals, and restaurant meals were given a lower weight in the overall score (example: score*0.25).

Predicted BPA exposure score from the UB-Diet Study Questionnaire data and food record data were divided into tertiles. Similarly, participants' urinary BPA levels were divided into tertiles. Weighted Kappa (K_w) was used to evaluate agreement between the different tools (206). K_w indicates the number of samples classified into the same tertile by the different tools being compared. Observed urinary BPA levels were compared to both the questionnaire score and food record score. Since beverages from cans or plastic bottles, microwave meals and restaurant meals may not always be a source of BPA exposure, total canned food intake was divided into tertiles and evaluated separately. The questionnaire and food record scores and total canned food intakes were also compared. In general, a K_w between 0.61 – 0.80 is considered good agreement between two methods whereas a K_w less than 0.40 is considered poor (207).

Sensitivity analyses were performed excluding participants with missing urine samples (n=6) and excluding participants who reported food consumption that would result in an implausible caloric intake (>5000 kcal/day or <500kcal/day, n=2) on the BEAM (all food records were >1000 kcal/day and <5000 kcal/day.

Results

Complete FFQs and UB-Diet Study Questionnaires were obtained from all participants. Sixty-seven of the sixty-eight participants provided complete food records. Sixty-two participants completed all nine urine sample collections, five participants

completed eight collections and one participant completed seven collections. The two missing samples for this participant were from two different days and at two different time points on each day. All but one participant had measurable levels of BPA in their urine. Excluding participants with missing urine samples did not alter the observed associations, so the presented results include these participants. Specific gravity-adjusted and unadjusted geometric means and 25^{th} – 95^{th} percentile ranges are presented in **Table 4,** along with levels from the NHANES 2003-2004 study population for comparison. The levels among the UB-Diet Study participants were comparable to the levels in the NHANES population, with similar 25^{th} percentiles and means, but slightly lower levels on the upper range of exposure.

Population characteristics and associations with mean urinary BPA levels are presented in **Table 5**. Study participants ranged in age from 20 to 55 years, however, the majority of participants were between 20 – 29 years old. Participants were more likely to have a normal BMI (18 – <25), and more likely to be white, female and have a college degree. The population was generally healthy and reported high levels of physical activity. Urinary BPA levels were not associated with any demographic or lifestyle characteristics.

Table 4 – Geometric Mean Urinary BPA Levels in the UB-Diet and NHANES 2003 – 2004 Study Populations

	Geometric Mean	25^{th} – 95^{th} Percentile
UB-Diet Study: unadjusted, 20-55 years	2.3 ug/L	1.5 – 7.5 ug/L
UB-Diet Study: SG-adjusted, 20-55 years	3.3 ug/L	2.1 – 9.5 ug/L
NHANES 03-04: unadjusted, 20-59 years	2.4 ug/L	1.2 – 15.5 ug/L
NHANES 03-04: per gram creatinine, 20-59 years	2.6 ug/g	1.2 – 15.5 ug/g

Table 5 - Population Characteristics and SG-Adjusted Mean Urinary BPA Levels (ug/L)[1]

		Unadjusted		Age and Gender Adjusted	
Characteristic	**N**	**Mean (95% CI)[2]**	**P-value[2]**	**Mean (95% CI)[2]**	**P-value[2]**
Age			0.70		0.63
20 – 29 years	37	3.38 (2.65 - 4.32)		3.23 (2.48 - 4.21)	
30 – 39 years	13	3.65 (2.42 - 5.51)		3.73 (2.46 - 5.64)	
40 – 55 years	18	2.94 (2.07 - 4.18)		3.86 (2.00 - 4.08)	
Race/Ethnicity			0.84		0.84
White (non-Hispanic)	54	3.29 (2.68 - 4.03)		3.20 (2.58 - 3.97)	
Black (non-Hispanic)	4	3.58 (1.70 - 7.56)		3.90 (1.72 - 8.86)	
Asian/Asian American	6	3.93 (2.14 - 7.24)		3.82 (2.06 - 7.09)	
Other[3]	4	2.55 (1.21 - 5.38)		2.61 (1.22 - 5.55)	
BMI			0.23		0.37
<25 kg/m^2	44	3.49 (2.80 - 4.35)		3.40 (2.62 - 4.42)	
25 - <30 kg/m^2	15	2.51 (1.72 - 3.67)		2.59 (1.70 - 3.95)	
≥ 30 kg/m^2	9	3.87 (2.44 - 6.42)		4.00 (2.39 - 6.68)	
Gender			0.45		0.49
Male	23	3.01 (2.21 - 4.09)		3.03 (2.22 -4.13)	
Female	45	2.47 (2.79 - 4.32)		3.46 (2.78 -4.32)	
Education			0.91		0.72
<College Graduate	27	3.37 (2.53 - 4.49)		3.31 (2.62 - 4.42)	
College Graduate	26	3.16 (2.36 - 4.23)		2.94 (2.14 - 4.04)	
Advanced Degree	15	3.47 (2.36 - 5.09)		3.61 (2.42 - 5.38)	
Income			0.72		0.66
$0 – 19,999	17	3.10 (2.16 - 4.45)		2.99 (2.05 - 4.34)	
$20,000 – 44,999	16	2.79 (1.92 - 4.06)		2.80 (1.92 - 4.08)	
$45,000 – 74,999	13	3.91 (2.59 - 5.92)		3.93 (2.55 - 6.06)	
$75,000 +	11	3.83 (2.44 - 6.04)		3.96 (2.47 - 6.36)	
Other[4]	10	3.08 (1.92 - 4.94)		2.93 (1.80 - 4.75)	
Current Health			0.37		0.36
Excellent	17	3.16 (2.21 - 4.51)		3.17 (2.21 - 4.57)	
Very Good	27	2.84 (2.14 - 3.77)		2.82 (2.12 - 3.76)	
Good	20	4.08 (2.93 - 5.67)		4.13 (2.96 - 5.76)	
Poor	2	4.47 (1.58 - 12.6)		4.15 (1.44 - 12.0)	
Chronic Health Issue			0.10		0.11
Yes	13	4.41 (2.95 - 6.59)		4.38 (2.85 - 6.72)	
No	54	3.04 (2.50 - 3.71)		3.02 (2.46 - 3.70)	
Physical Activity			0.40		0.49
High	40	3.14 (2.49 - 3.92)		3.08 (2.42 - 3.92)	
Moderate	18	4.02 (2.84 - 5.69)		3.91 (2.69 - 5.69)	
Low	10	2.85 (1.79 - 4.54)		2.85 (1.78 - 4.90)	

[1] Geometric means
[2] Linear Regression. Gender model-age adjusted only. Age model - gender adjusted only.
[3] Hispanic/Latino (n = 1), Hawaiian/Pacific Islander (n = 1), Other (n = 2).
[4] Don't know or prefer not to answer.
Abbreviations: BMI = body mass index, CI = confidence interval, kg = kilograms, L = liters, m = meters, ug = micrograms.

Table 6 - Mean Urinary BPA Levels (ug/L)[1] and UB-Diet Questionnaire Packaged Food Intake					
		Unadjusted		Age and Gender Adjusted	
Source	N	Mean (95% CI)[1,2]	P-value[2]	Mean (95% CI)[1,3]	P-value[3]
Canned Food Total			0.55		0.56
≤ 1 time/month	11	3.28 (2.10 – 5.12)		3.25 (2.07 – 5.11)	
2 – 4 times/month	11	3.67 (2.35 – 5.73)		3.53 (2.23 – 5.58)	
2 – 4 times/week	29	2.89 (2.19 – 3.80)		2.83 (2.12 – 3.77)	
≥ 5 times/week	17	3.93 (2.75 – 5.63)		3.87 (2.67 – 5.61)	
Canned Fruit Total			0.96		0.98
Never	20	3.39 (2.64 – 4.34)		3.30 (2.54 – 4.27)	
Monthly	40	3.23 (2.34 – 4.48)		3.16 (2.26 – 4.42)	
≥ Weekly	18	3.20 (2.04 – 5.01)		3.20 (2.02 – 5.06)	
Canned Vegetables			0.33		0.32
Total	18	3.52 (2.49 – 4.97)		3.41 (2.40 – 4.85)	
Never	12	2.61 (1.71 – 3.99)		2.58 (1.68 – 3.95)	
Monthly	20	2.95 (2.13 – 4.09)		2.88 (2.04 – 4.07)	
1 time/week	18	4.14 (2.93 – 5.84)		4.10 (2.86 – 5.90)	
≥ 2 times/week			0.35		0.39
Canned Meals Total	24	2.77 (2.05 – 3.74)		2.74 (2.02 – 3.72)	
Never	28	3.65 (2.77 – 4.82)		3.58 (2.64 – 4.84)	
Monthly	16	3.64 (2.52 – 5.25)		3.57 (2.46 – 5.18)	
≥ Weekly			0.37		0.34
Packaged Food	9	4.02 (2.47 – 6.56)		3.99 (2.42 – 6.56)	
Never/Rarely	11	2.61 (1.68 – 4.07)		2.46 (1.53 – 3.95)	
Monthly	33	3.09 (2.40 – 4.00)		3.06 (2.36 – 3.96)	
Weekly	15	4.05 (2.77 – 5.92)		3.91 (2.64 – 5.78)	
Daily			0.73		0.58
Microwave Meals	40	3.09 (2.45 – 3.92)		2.94 (2.28 – 3.78)	
≤ 1 time/month	13	4.03 (2.66 – 6.08)		4.13 (2.73 – 6.27)	
2 – 3 times/month	12	3.24 (2.11 – 4.99)		3.11 (1.99 – 4.84)	
1 – 2 times/week	3	3.72 (1.57 – 8.79)		3.65 (1.54 – 8.69	
3 – 4 times/week					

[1] Specific gravity adjusted geometric means.
[2] Specific gravity adjusted BPA only.
[3] Additionally, adjusted for age and gender.

Table 6 describes intake of canned food, pre-packaged food items, and microwave meals reported via the study questionnaire. The majority of participants (n=48, 70.6%) reported eating packaged food (any type of packaged food: canned, microwave meals, boxed mixes, such as macaroni and cheese) at least weekly. A total of 11 participants reported rarely or never eating canned foods, while 17 reported eating canned food items at least five times per week. Participants who consumed canned foods were most likely to report eating canned vegetables, with 18 reporting eating canned vegetables two or more times per week. Eighteen participants reported eating

canned fruit weekly, and 16 reported eating canned meals (e.g. soup, chili, ravioli, etc.) weekly. Participants were also asked about microwave meals, which more than half of the participants reported consuming less than once per month (n = 40, 59%). A majority of participants (n=47, 69.1%) reported eating one to two meals away from home per week, and these meals were typically consumed at either fast food or sit down restaurants, rather than in cafeterias (**Table 7**). Very few participants (n = 3) reported rarely/never eating at restaurants.

Table 7 - Mean Urinary BPA Levels (ug/L)[1] and Questionnaire Meals Away from Home

		Unadjusted		Age and Gender Adjusted	
Source	**N**	**Mean (95% CI)[1, 3]**	**P-value[3]**	**Mean (95% CI)[1, 4]**	**P-value[4]**
Meals Away From Home			0.46		0.44
None	3	2.19 (0.94 – 5.14)		2.07 (0.85 – 5.00)	
1 – 2 days/week	47	3.15 (2.54 – 3.91)		3.06 (2.45 – 3.83)	
3 – 4 days/week	10	4.35 (2.73 – 6.94)		4.12 (2.54 – 6.68)	
5 – 6 days/week	5	2.96 (1.53 – 5.73)		3.01 (1.54 – 5.89)	
Everyday	3	5.10 (2.18 – 12.1)		5.39 (2.27 – 12.8)	
Fast Food Restaurants			0.69		0.58
Never	16	2.90 (2.00 – 4.20)		2.72 (1.84 – 4.03)	
1 – 2 times/week	46	3.48 (2.80 – 4.33)		3.43 (2.74 – 4.28)	
≥ 3 times/week	6	3.17 (1.73 – 5.82)		3.13 (1.69 – 5.78)	
Sit Down Restaurants			0.51		0.45
Never	10	3.33 (2.09 – 5.31)		3.26 (2.02 – 5.24)	
1 – 2 times/week	54	3.20 (2.62 – 3.92)		3.13 (2.54 – 3.75)	
≥ 3 times/week	4	5.02 (2.40 – 10.5)		5.17 (2.43 – 11.1)	
Cafeteria			0.79		0.70
Never	53	3.32 (2.70 – 4.07)		3.18 (2.54 – 3.98)	
1 – 2 times/week	10	3.07 (1.91 – 4.93)		3.09 (1.91 – 5.02)	
≥ 3 times/week	4	3.17 (1.96 – 8.77)		4.43 (2.06 – 9.50)	

[1] Specific gravity adjusted geometric means. ug = micrograms. L = liters.
[2] Specific gravity adjusted BPA only.
[3] Additionally, adjusted for age and gender. CI = confidence interval.

Reported intake of canned foods, beverages from cans or plastic bottles, and meals away from home on the 3-day food records are presented in **Table 8**. A majority of participants reported eating no canned food items (n = 38), while 12 reported eating two or more servings. All participants reported drinking beverages from both metal and plastic containers. All participants reported consuming at least three canned beverages and at least three plastic bottle beverages. Seven participants reported no meals at or from a restaurant, and 29 consumed at least three meals at or from a restaurant.

Table 8 - Mean Urinary BPA Levels (ug/L)[1] and Food Record Data					
		Unadjusted		Age and Gender Adjusted	
Source	N	Mean (95% CI)[1, 3]	P-value[3]	Mean (95% CI)[1, 4]	P-value[4]
Total Canned Food[2]			<0.001		<0.001
None/3 days	38	2.74 (2.21– 3.41)		2.71 (2.18 – 3.37)	
>0 - <3 servings/3 days	17	3.17 (2.29 – 4.40)		2.89 (2.02 – 4.12)	
≥ 3 servings/3 days	12	6.44 (4.36 – 9.49)		6.55 (4.43 – 9.70)	
Total Restaurant Meals[2]			0.30		0.32
None/3days	7	3.72 (2.14 – 6.49)		3.63 (2.05 – 6.41)	
1 meal/3 days	14	2.68 (1.81 – 3.97)		2.55 (1.67 – 3.91)	
2 meal/3 days	17	3.51 (2.45 – 5.01)		3.40 (2.35 – 4.90)	
3 meal/3 days	14	4.51 (3.04 – 6.68)		4.39 (2.94 – 6.55)	
≥4 meal/3 days	15	2.72 (1.86 – 3.98)		2.71 (1.85 – 3.98)	
Total Canned Beverage[2]			0.66		0.67
3 servings/3 days	6	3.31 (1.80 – 6.10)		3.36 (1.79 – 6.30)	
4 servings/3 days	10	3.20 (1.99 – 5.13)		3.23 (1.97 – 5.32)	
5 servings/3 days	15	4.10 (2.79 – 6.04)		3.97 (2.67 – 5.90)	
6 servings/3 days	36	3.07 (2.39 – 3.94)		2.98 (2.30 – 3.86)	
Total Plastic Beverage[2]			0.07		0.05
3 servings/3days	17	2.58 (1.83 – 3.66)		2.41 (1.65 – 3.50)	
4 servings/3days	12	3.19 (2.11 – 4.83)		3.04 (2.00 – 4.64)	
5 servings/3days	13	5.25 (3.53 – 7.81)		5.18 (3.47 – 7.72)	
≥6 servings/3days	25	3.16 (2.37 – 4.21)		3.09 (2.31 – 4.12)	

[1]Specific gravity adjusted geometric means.
[2]Summed intake for all 3 days of food records. Serving = 4-ounce portion.
[3] Linear regression. Specific gravity adjusted BPA only.
[4] Linear regression. Additionally, adjusted for age and gender.

BPA Exposure Assessment Module Questions (BEAM) vs. Food Record Intake

To evaluate the ability of the BEAM to estimate typical intake of canned foods and meals eaten away from home, correlations between canned food intake and meals away from home reported on the BPA Module were compared to reported intake on participants' food records (**Figure 4**). Canned food intake on the three days of food records was statistically significantly correlated ($r = 0.30$, $p = 0.01$) with estimated canned food intake for three days on the BEAM, however a $K_w = 0.20$ (data not shown) suggests a poor ability of the two tools to similarly rank participants' canned food intake. A closer examination of the data showed that participants who reported never eating canned food on the BEAM also reported not eating canned food on any food record days. The same was also true at the opposite end of the spectrum. People who reported eating canned food daily on the BEAM, generally reported eating canned foods

on at least one of the food record collection days. Overall, however, participants tended to report eating more canned food on the BEAM (estimated average intake over 12 months) than they reported on the food records (actual intake on three days).

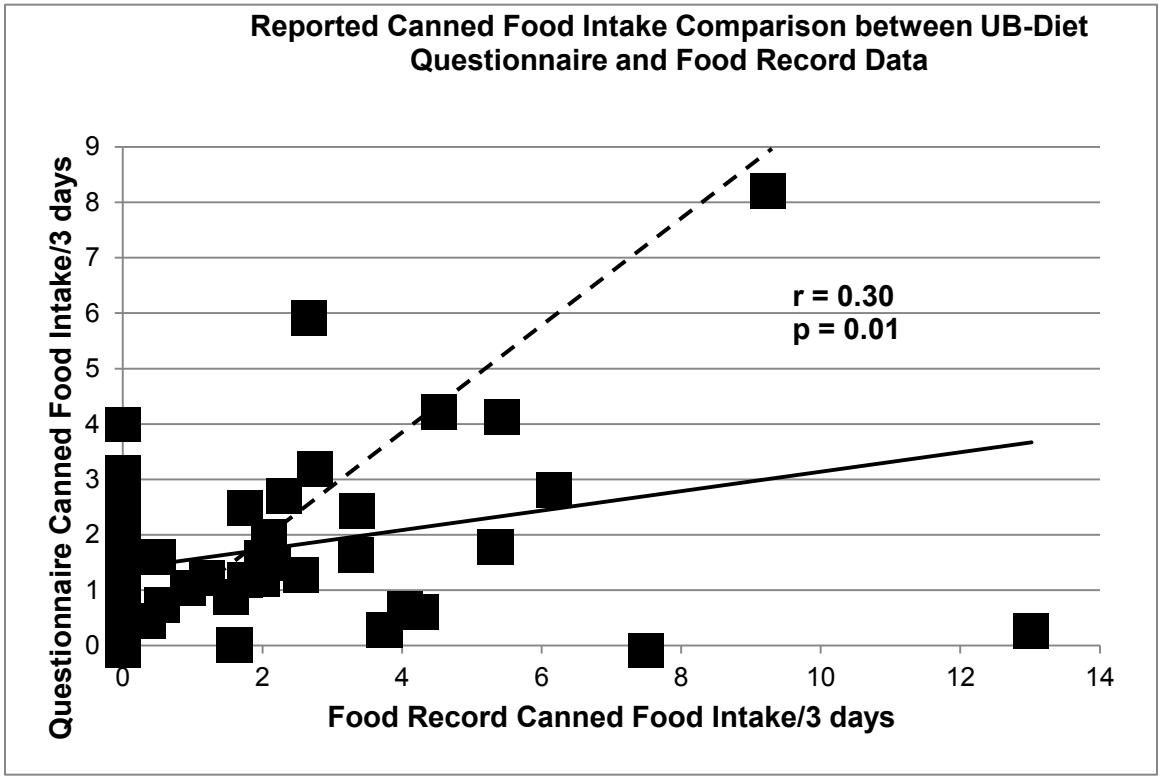

Figure 4 – Reported Canned Food Intake Comparison between UB-Diet Questionnaire and Food Record Data. Pearson correlation r and p-value. Solid black line represents observed regression line. Dashed black line represents expected correlation if near perfect correlation.

Meals away from home were also included in the BEAM because of the potential contribution to BPA exposure levels. Reported meals away from home were positively correlated between the food records and BEAM, although less strongly than the canned food intake (r=0.30, p=0.02). Overall, most participants appeared to under-report the number of meals eaten away from home on the BEAM with 42% of participants reporting eating at least three meals away from home on the food record, whereas only 28% of participants reported eating meals away from home on three or more days per week on the BEAM. There was also little variability in meals away from home reported on the BEAM, with 69% reporting one to two meals per week.

BPA Exposure Assessment Module Data and Urinary BPA Levels

Figure 5 shows correlations between reported canned food intake assessed by the BEAM and urinary BPA levels. Urinary BPA levels and canned food intake assessed by the BEAM were not correlated (r = 0.08, p = 0.51). Similarly, BEAM assessed intake of canned or packaged foods overall (canned foods, microwave meals or foods prepared from packaged mixes), or restaurant meals was not associated with urinary BPA levels in age and gender adjusted regression models (**Tables 6 and 7**).

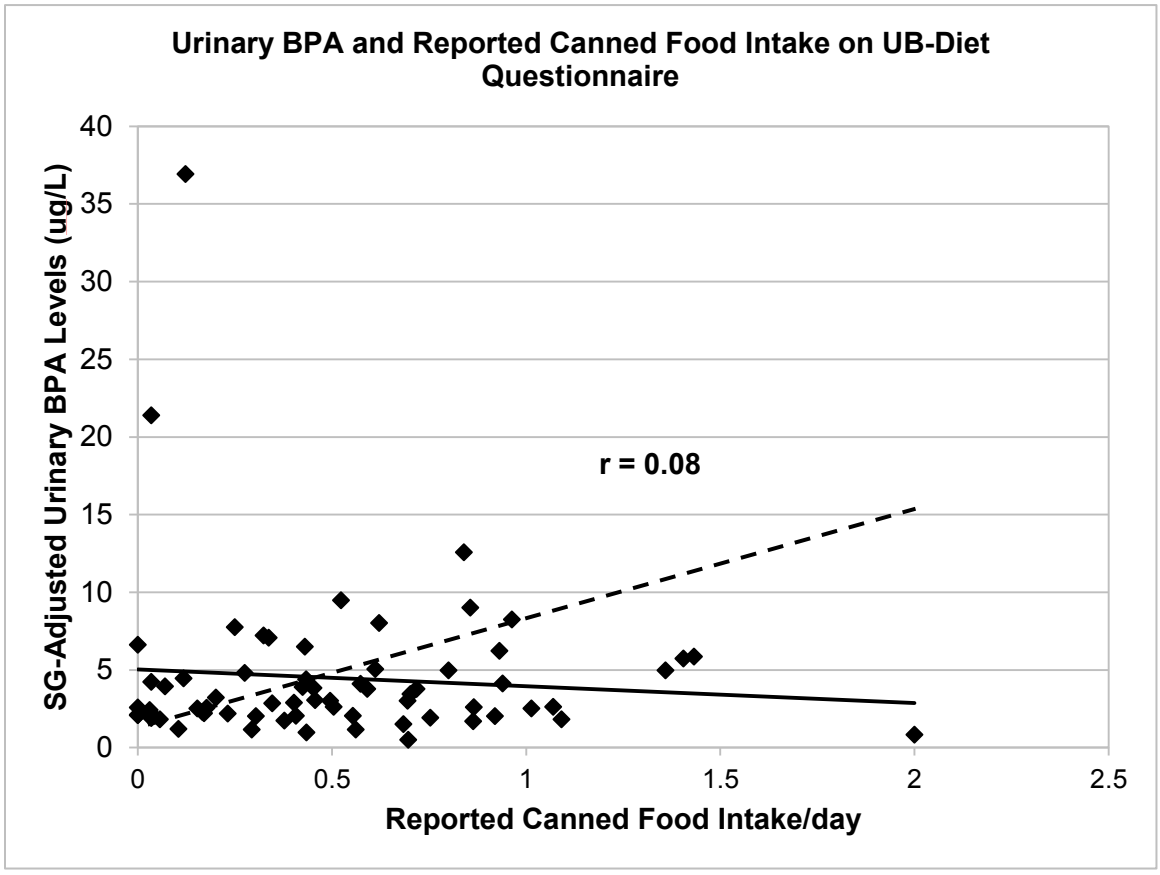

Figure 5 – Urinary BPA and Reported Canned Food Intake on UB-Diet Questionnaire. Spearman correlation r and p-value. Solid black line represents observed regression line. Dashed black line represents expected correlation if the highest urinary BPA levels were observed in frequent canned food consumers (Note: regression line does not account for high urinary BPA outliers).

Adjusted for age and gender, total canned food intake explained only 5% of the variability in urinary BPA levels (p = 0.56). Evaluated in sub-groups, canned vegetable intake explained 7% (p=0.32), canned meal intake explained 4.5% (p=0.39), and canned fruit intake explained 1.7% (p=0.98). Meals eaten away from home, adjusted for age and gender explained 7.3% of the variability in urinary BPA levels (p=0.44). A model including all *a priori* hypothesized dietary predictors explained only 19% of the variability in urinary BPA levels (p=0.32). This was also the model that explained the largest amount of variability in urinary BPA levels. Consistent with regression analyses, weighted Kappa analyses indicate the hypothesized predictor questions were not able to adequately rank participants BPA exposure levels when compared to observed urinary BPA levels (K_w = 0.13) (**Table 9**). Additionally, canned food intake alone was also unable to rank BPA exposure levels (K_w = 0.07).

Table 9 - Weighted Kappa Analysis

	Urinary BPA Tertile [n (%)]			
	1	**2**	**3**	**K_w**
BEAM Score[1],				0.13
Tertile 1	9 (40.9)	7 (31.8)	6 (27.3)	
Tertile 2	7 (31.8)	9 (40.9)	7 (31.8)	
Tertile 3	6 (27.3)	6 (27.3)	9 (40.9)	
Food Record Score[2]				0.21
Tertile 1	10 (45.5)	14 (63.6)	5 (21.7)	
Tertile 2	6 (27.3)	5 (22.7)	4 (17.4)	
Tertile 3	6 (27.3)	3 (13.6)	14 (60.9)	
BEAM Canned Food				0.07
Tertile 1	8 (36.4)	7 (30.4)	7 (30.4)	
Tertile 2	7 (31.8)	9 (39.1)	7 (30.4)	
Tertile 3	7 (31.8)	7 (30.4)	9 (39.1)	
Food Record Canned Food				0.20
Tertile 1	14 (63.6)	18 (78.3)	7 (30.4)	
Tertile 2	6 (27.3)	4 (17.4)	7 (30.4)	
Tertile 3	2 (9.1)	1 (4.4)	9 (39.1)	

[1] (Total canned food*1.0) + (microwave meals*0.25) + (packaged beverages*0.25) + (restaurant meals*0.25)
[2] (Total canned food*1.0) + (packaged beverages*0.25) + (restaurant meals*0.25)
Abbreviatons: BEAM = BPA exposure assessment module, n = number, K_w = weighted kappa.

Food Record Data and Urinary BPA Levels

While the BEAM asks participants about usual intake over the previous twelve months, the food record data captured participants' actual dietary intake for the same time period as the urine sample collection. Mean urinary BPA levels and linear regression results for canned food intake, packaged beverage intake and meals away from home as reported on food records are presented in **Table 8**. Recent total canned food intake was associated with urinary BPA levels in linear regression models ($p < 0.001$). Participants who reported no canned food intake on the food records had the lowest urinary BPA levels (geometric mean: 2.74 µg/L, 95% CI: 2.21 – 3.41 µg/L), while those who reported a total of three or more servings across the three food record days had the highest mean urinary BPA levels (geometric mean: 6.44 µg L, 95% CI: 4.36 – 9.49 µg/L). Number of meals away from home and canned and plastic bottled beverage intake as reported on the food records were not associated with urinary BPA levels.

Figure 6 illustrates the observed regression line, the expected regression line and Spearman correlation for the comparison between reported canned food intake as assessed by the food records and urinary BPA levels. The stronger positive correlation of $r = 0.34$ ($p = 0.004$) is in agreement with the statistically significant linear regression results for food record reported canned food intake. In models including age and gender, total canned food intake over three days explained 21.6% of the variability in urinary BPA levels ($p=0.01$). Restaurant meals explained 9% ($p=0.32$), plastic bottled beverage intake explained 13% ($p=0.05$) and canned beverage intake explained 4% ($p=0.67$). The model including all *a priori* predictors (age, gender, canned food intake, restaurant meals, canned and plastic bottled beverage intake) explained 47% of the variability ($p<0.001$), but only canned food ($p<0.001$) and plastic bottled beverage ($p=0.004$) intake were statistically significant predictors of urinary BPA levels .

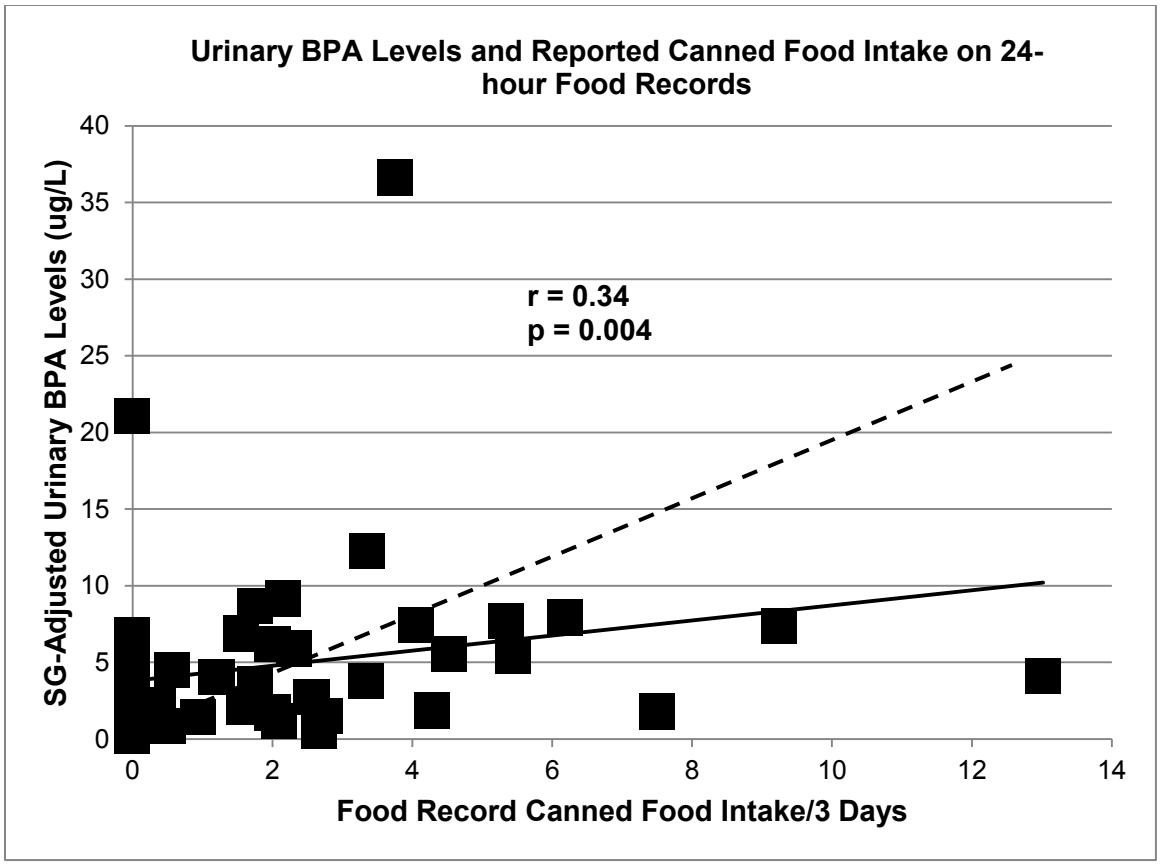

Figure 6 – Urinary BPA levels and Reported Canned Food Intake on 24-hour Food Records. Spearman correlation r and p-value. Solid black line represents observed regression line. Dashed black line represents expected correlation if the highest urinary BPA levels were observed in frequent canned food consumers (Note: regression line does not account for high urinary BPA outliers).

While food record data were better able to explain variability in urinary BPA levels, similar to the BEAM data, food records performed poorly at predicting ranks for BPA exposure levels when compared to observed urinary BPA levels (K_w = 0.20) (**Table 9**). Participants in the middle tertile for measured urinary BPA levels, tended to be misclassified to the lowest tertile for predicted level. The ability to rank participants using only reported canned food intake was also poor with a K_w = 0.21. When comparing reported canned food intake on the food record with measured urinary BPA levels, participants were much more likely to have higher urinary BPA levels (2nd or 3rd tertile), but report little or no canned food intake.

Discussion

We found that a questionnaire module based on published data of food sources of BPA exposure was unable to rank study participants by urinary BPA levels. Recent intake of canned foods as assessed by food records was more predictive of urinary BPA levels, perhaps, reflecting the importance of recent exposure on urinary BPA levels for this rapidly metabolized environmental chemical exposure. Regardless of diet assessment method, very little of the variability in urinary BPA levels was explained by documented dietary sources (canned foods) of BPA in this study, suggesting that canned foods are not the only, and perhaps not the primary, route of BPA exposure. While the participants who reported consuming canned foods tended to have higher urinary BPA levels, several of the participants with the highest urinary BPA levels reported consuming no canned food items. This could indicate that there are other unidentified, important sources of exposure beyond canned food, and these sources likely vary between participants.

Both the questionnaire and food record data indicate a wide range of exposure to canned food in this study population. Canned food intake was positively correlated between the two different measurement tools, indicating that the questionnaire was able to capture canned food intake. However, the moderate correlation suggests that there were differences in long-term reported intake (questionnaire) compared to recent intake (food records). Compared to the 24-hour food record data, the BPA module questions appeared to perform better among the never and frequent consumers of canned food intake, suggesting that consumption of canned foods for infrequent consumers may not be adequately captured by 3 days of food records. The variability in canned food intake throughout the year (these food items are typically heated, and served/eaten in colder months of the year) could explain why canned food intake, as assessed by the BEAM,

were not associated with urinary BPA levels. Additionally, when we compared total canned food intake versus individual canned food sub-groups (meals, vegetables, fruits) as assessed by the questionnaire, the variability in urinary BPA levels explained by total canned food intake was less than expected. This could be attributed to inconsistencies in BPA levels in canned food items. Studies suggest that BPA levels in food items, even from the same company, are highly variable (9, 33, 39, 41, 105, 193, 196). These inconsistencies could make it difficult to estimate dietary BPA exposure and could bias associations towards the null.

The association between recent canned food intake assessed by food records and urinary BPA levels in the current study population agrees with previous research. While some studies indicate that diet accounts for more than 90% of potential BPA exposure in the environment of the general population (16, 77), other studies have found that diet explains a significantly lower proportion of urinary BPA levels (59, 78, 79, 102). Intervention studies have demonstrated the ability to lower, but not eliminate detection of urinary BPA among study participants (29, 30, 62, 77). In the current study, recent canned food intake was associated with urinary BPA levels, but only accounted for 21.6% of variability in urinary BPA levels in a free-living adult population. A previous study of children found that diet accounted for just 17% of the variability in creatinine adjusted urinary BPA levels (77). This suggests that canned food intake is an important source of exposure, but that it cannot account for all of the differences in exposure and eliminating canned foods, or BPA-containing epoxy resins from can linings, will not eliminate BPA exposure.

In this study, additional sources of BPA exposure were considered. Restaurant and packaged meals (microwave or box mixes) represent another dietary source of exposure, as these meals could contain canned food or be exposed to equipment or

food storage containers containing BPA. Restaurant meals and packaged food intake was not associated with urinary BPA levels in the current study. The diversity of restaurant and packaged meal options likely biased the findings towards the null. For example, some restaurants rely predominantly on canned and packaged food items, while other restaurants prepare food from scratch. Thus, even though a participant may report frequently consuming meals in restaurants, overall, the association between restaurant meals and urinary BPA levels would be attenuated. Few previous studies have evaluated BPA levels in relation to restaurant meals and intake of non-canned packaged foods. An analysis of fast food items in Canada did observe measureable amounts of BPA in some fast food items (9).

Despite current literature suggesting canned foods and diet as a primary source of exposure, there is increasing debate as to whether diet truly is the primary source of BPA exposure given the lack of paired dietary intake data and data on urinary or serum BPA concentrations (30, 61, 102, 105). In addition to dietary sources, low levels of BPA have been observed in drinking water and dust particles, however current data indicate these contribute only minimally to exposure (16, 30, 105, 208). Handling receipt paper and smoking filtered cigarettes (BPA is used in the filter) is also thought to be sources of BPA exposure (11, 15, 30, 38, 78, 105, 209). Smokers were excluded from the UB-Diet Study and handling of receipt paper was not associated with urinary BPA levels in this study (data not presented). A recent study observed associations between personal product usage, such a mouthwash, and higher urinary BPA levels (94, 95), which is consistent with recent evidence suggesting BPA can be absorbed sublingually (106). The data from this analysis supports the presence of additional sources of BPA exposure that were not captured in our data collection.

Strengths and Limitations

This study has several strengths. The first is the simultaneous collection of both FFQ and food record data and urine samples, allowing for evaluations of associations between reported dietary intake and BPA exposure in a free-living health adult population. Another strength of this study was that urine for the BPA measurements was collected on multiple days and at multiple times on each day. This better reflects average levels of exposure than a single spot urine sample, which is more meaningful when trying to evaluate the ability of a questionnaire to capture typical exposure levels for a period of time.

This study also had several limitations. Data collection occurred over the course of a week, which did not allow for an evaluation of whether BPA levels and source of exposure vary across seasons or from year-to-year. It could be that the BEAM would perform better if we had averaged urinary BPA levels from multiple time points throughout the year. Additionally, the inability of the BEAM questions to predict urinary BPA levels could be due to the small study sample size.

However, given the limited data on major sources of BPA exposure in free-living populations, this study still provides useful information. Diet is considered the major source of BPA exposure in the general population based on knowledge about food packaging materials, yet the findings of this study suggest that we do not yet have a clear understanding about sources of BPA exposure. Previous research measuring BPA in our environment has focused on dietary sources of BPA from canned foods or polycarbonate plastic storage containers, perhaps reinforcing that canned food intake is the primary source of exposure while providing little insight into other potential sources. Recent studies have detected BPA, typically at lower levels than canned foods, but not always, in non-canned products (16, 29). While recent canned food intake in our study

was associated with higher urinary BPA levels, it did not explain much of the variability in urinary BPA levels. The currently available data on sources of BPA exposure in the general population is likely not complete.

Conclusion

The ability to accurately and inexpensively assess exposure to environmental chemicals is an important challenge facing epidemiologic studies of the health outcomes related to these exposures. The results from this study indicate that further research is needed to better characterize sources of BPA exposure in free-living adult populations. Future studies should: include more frequent assessment of potential BPA exposures as they likely vary over time, use more detailed dietary intake assessment tools such as food records or 24-hour recalls with trained interviewers, collect data on other potential sources of BPA in participants' environments (water, dust, personal products) and include a larger number of study participants.

Chapter 4
Food and Nutrient Intakes and Urinary BPA Levels

Introduction

Food and water provide us with essential nutrients, however, food and water are also sources of exposure to environmental chemicals, including pesticides (210, 211), food packaging and processing-derived contaminants such as bisphenol A (BPA) and phthalates (5-10, 39, 113, 177), and naturally occurring contaminants such as arsenic (212, 213). Due to the use of BPA-containing epoxy resins and polycarbonate plastics in food packaging, diet has long been considered the primary route of exposure to BPA in the general population (30). Recent studies also suggest that BPA can be absorbed dermally or inhaled, but the contributions of non-oral routes of exposure are considered to be quite low (16, 30, 105, 208).

Extensive data demonstrates the presence of BPA in canned foods (9, 30, 32, 33, 39-53), and biomonitoring data shows that BPA is detectable in the urine of the vast majority of the general population (3, 7, 8, 23, 54, 174). However, there is very little research evaluating how ingested BPA is absorbed, distributed, metabolized and excreted in humans, and whether BPA consumed as a part of mixed meals (especially interactions between nutrients and dietary components, such as dietary fats and fibers) alters absorption and metabolism of ingested BPA. This information is essential for evaluating associations between BPA exposure and human health in free-living populations.

Dietary factors have been found to influence pharmacokinetics or toxicokinetics of drugs and other chemical exposures (214-216). Current knowledge about BPA absorption, distribution, metabolism and excretion (ADME) in humans is largely from acute dosing toxicology studies with small numbers of study participants (168, 169), in

which BPA was administered under fasting conditions rather than with a mixed meal. The relevance of the existing BPA ADME data to the chronic low level BPA exposure that is typical in free-living human populations is unclear (105). The human diet is complex and varied. Components in the diet, especially macronutrients such as dietary fats and fiber, likely impact BPA absorption, metabolism, and excretion. It is possible that the availability of BPA for absorption will differ according to the food matrix in which it is ingested. Alternatively, dietary composition could influence rates of BPA conjugation by UDP-glucuronosyltransferases (UGTs), by either competing with BPA for metabolism or influencing UGT levels through increasing/decreasing production or degradation of enzymes (111, 217, 218). Endocrine disrupting chemicals, similar to endogenous hormone levels, are considered to have activity at very low levels, so small changes in the availability of free BPA could potentially alter observed health outcomes (4, 10, 25, 26).

Several intervention studies have clearly shown that increasing or decreasing exposure to packaged foods, particularly canned foods, can increase or decrease urinary BPA levels (58-60, 74), however, how much BPA is absorbed from the foods, how rapidly it is metabolized and whether diet composition influences ADME has not been investigated (16). Additionally, studies evaluating the relationship between diet (except for canned food intake) and BPA exposure levels have not been conducted. Dietary intake of BPA is likely related to consumption of processed foods (as part of packaging or introduced during processing), overall quantity of food consumed (higher intake may theoretically lead to higher potential for exposure), intake of certain macronutrients, and exposure to other environmental chemicals (such as phthalates, which are also present in food packaging). If these factors are associated with both BPA levels and risk for chronic disease, they could confound or modify observed associations

with chronic health conditions. Most current studies of BPA exposure and various health outcomes did not consider dietary factors (e.g. caloric intake) as potential covariates or effect modifiers in the analyses.

In this preliminary study, data collected in the Urinary Biomarkers of Dietary Intake Study (UB-Diet Study) was used to evaluate associations between dietary factors and urinary BPA levels. The study data allowed us to evaluate associations between urinary BPA levels and reported dietary intake of nutrients and food groups collected during the same time period. We hypothesized that urinary BPA levels would be positively associated with caloric intake due to higher potential BPA exposure with greater food intake. Additionally, we hypothesized that total fat and fiber intakes would be associated with urinary BPA levels, based on their ability to change GI physiology (e.g. pH, motility, bioavailability). We further hypothesized that intake of whole grains, refined grains, vegetables, fruits, high fat dairy, red meats, process meats, fried foods, sweets, and artificially- and sugar-sweetened beverages would be associated with urinary BPA levels due to fat, fiber, caloric and/or phytochemical content and/or exposure to food packaging (**Table 10**).

Methods

This analysis was a secondary analysis of the Urinary Biomarkers of Dietary Intake Study (UB-Diet Study). The UB-Diet Study was a cross-sectional study of 68 generally healthy adults designed to test the feasibility of using a questionnaire to assess relative dietary BPA exposure in observational studies. The study was conducted at the University of Minnesota's Epidemiological Clinical Research Center (ECRC). The study was approved by the Institutional Review Board at the University of Minnesota, and all study participants provided informed consent to participate in the study.

Study Population

Participant recruitment occurred between August 2012 and January 2013. Advertisements in Minneapolis community newspapers and on Craigslist, and flyers were posted on the University of Minnesota campus were used to recruit study participants. Potential participants were instructed to contact the study coordinator by telephone or e-mail. In order to be included in the study, participants had to be: (1) between 20 to 59 years of age; (2) a resident in the seven county Minneapolis-St. Paul metro area in Minnesota (Anoka, Carver, Dakota, Hennepin, Ramsey, Scott and Washington counties); (3) able to give informed consent; (4) available during the study dates; (5) able to speak English; (6) without a history of cancer (excluding non-melanoma skin cancer), heart attack, diabetes or cerebrovascular event; (7) a non-smoker; and (8) without a body weight change of more than 10% in the previous 6 months. Pregnant and lactating women were excluded.

The primary goal of this study was to evaluate dietary intake of BPA, so participants were additionally screened to determine a general level of canned food consumption to ensure a range of potential BPA exposure levels. Potential participants were asked eleven questions about dietary habits, including canned food intake, fruit and vegetable intake and meals eaten away from home (**Appendix 2**). Responses were used to categorize potential participants into four potential exposure levels: the first group included participants who reported eating canned food less than one time per week, the second group who consume ≥ one to < three items per week, the third group who consume ≥ three and < five per week, and the final group were those who reported eating five or more canned items per week. Each exposure level group was capped at 26 participants. A total of 182 people were screened for eligibility, with a final number of

68 participants included in the study. For the current analyses, data from the 67 participants with complete food records were included.

Demographic Data Collection

Demographic and lifestyle (e.g. age, education, income, physical activity) data was collected using a questionnaire designed specifically for use in this study, the Urinary Biomarkers of Dietary Intake Study (UB-Diet Study) Questionnaire. Questions from previously validated questionnaires, including NHANES surveys, were used to develop the UB-Diet Study Questionnaire (167, 196). Physical activity data was collected from questions asking participants to self-report the number of hours of mild (little effort; e.g. slow walking, bowling, golfing, fishing relaxing yoga), moderate (not exhausting, but increases heart rate; e.g. walking quickly, baseball, easy bicycling, dancing, volleyball) and strenuous (heart beats rapidly; e.g. running, swimming laps, tennis soccer, vigorous yoga) physical activity each week (none, <0.5 hours, 0.5 – 2 hours, 2.5 – 4.0 hours, 4.5 – 6.0 hours, 6 or more hours). This data was then used to categorize participants into high, moderate or low usual physical activity levels. Those in the high physical activity group reported at least 5.5 hours of total physical activity per week with at least 2.5 hours of either moderate or strenuous activity. Those in the low physical activity reported mild physical activity only or reported < 2.5 hours of mild and either <2.5 hours of moderate activity and <0.5 hours of strenuous activity or <0.5 hours moderate activity and <2.5 hours of strenuous activity.

Height, weight and waist circumference (WC) were measured at the first of two study visits. Height was measured without shoes using a wall-mounted stadiometer (Holtain Ltd., Crymych, Dyfed, UK). Weight was measured in kilograms with the participant wearing street clothes (without shoes) using an electronic scale (BWB-800,

Tanita Corporation, Arlington Heights, IL). Waist circumference was measured just above the iliac crest using a non-stretch, retractable measuring tape with a tensioning device (Gulick II Tape Measure, Country Technology, Gays Mills, WI). BMI was calculated as weight (kg)/[height (meters)]^2.

Food Record Data

During the data and biospecimen collection week, participants were asked to record all foods and beverages consumed on two weekdays (Tuesday and Thursday) and one weekend day (Saturday) (197). On each of the data collection days, participants completed a 24-hour food record and collected three urine specimens. Food records and urine specimens were collected on the same days to allow for a direct evaluation of the associations between recent food intake and BPA exposure levels. The food record instructions directed participants to include details about the food packaging and brand names. At the second study visit, study staff reviewed the food records with participants for completeness and to clarify any questions about food record data.

Biospecimen Collection and Processing

Participants collected nine urine samples, three spot urine samples on each of the two weekdays and one weekend day that corresponded with the days on which 24-hour food records were collected. To capture a range of exposure, participants collected the first morning void (first void, at or after 5 am), a mid-day sample (between 11 – 2 pm), and an evening sample (between 6 – 9 pm). Urinary BPA levels have high intra-person variability (170-172), and a recent study found the BPA concentrations from multiple, single spot urine collections resulted in estimated BPA levels that were close to the mean concentrations observed after multiple 24-hour urine collections (172).

Participants were given nine-labeled, sterile, commercial 4-ounce polypropylene containers (which do not contain BPA (65)) and instructions for urine collection. Participants recorded the time of sample collection on the specimen cup label, and refrigerated urine specimens until the second study visit. Participants were also given a cooler with ice packs for transporting specimens. Total urinary BPA has been shown to be stable during short-term storage (198).

Specific gravity of the individual samples and the pooled samples was measured using a digital handheld refractometer (ATAGO PAL-10S, ATAGO U.S.A., Inc., Bellevue, WA), with automatic temperature compensation. The nine individual urine samples for each participant were then pooled, mixed thoroughly, and aliquoted into 5mL polypropylene vials. All samples were stored at -70° C until sent for analysis. Samples were shipped as a single batch on dry ice overnight to NMS Labs (Willow Grove, PA) for the BPA analysis. Blinded replicate samples were included to evaluate data quality.

Total (free and conjugated) urinary BPA was measured by gas chromatography – mass spectrometry (GC-MS) (199). The detection limit was 0.50ng/mL, and blinded replicate coefficient of variation was 14%.

Data Preparation

Data from the UB-Diet Study Questionnaire was manually entered into a REDCap database using the double data entry method (202). Nutrient intake data was calculated from the food record data using the Nutrition Data System for Research (NDSR, version 2012) (200, 201). Data on canned food intake and restaurant meals were manually abstracted from the food records and entered into the study database. Since urinary BPA measurements were measured in a pooled sample from all three collection days, nutrient, food group totals, servings of canned food, and the number of

restaurant meals were summed for a three day total. A serving of canned foods was defined a 4-ounce serving of the food item. Any meal eaten at a restaurant was counted as one restaurant meal, with the exception of eating occasions that only included baked goods (muffins, cake, etc.) and beverages (lattes, smoothies, etc.).

Nutrient intake levels and number of servings from food groups were evaluated in relation to urinary BPA levels. Since urinary BPA levels were measured on a pooled sample, nutrient intakes and food group servings were summed for the three days in this analysis to reflect the same time period. NDSR software automatically calculates the number of servings consumed from pre-specified food groups. These foods groups and the serving size definitions are available online on the Nutrition Coordinating Center's website (219). Due to small samples size, smaller subgroups were summed into larger food group categories. The list of food groups, included food items and the median and range of servings for food groups are listed on **Table 10**.

Urinary BPA concentrations were adjusted for dilution by multiplying values (ug/L) by [1.024 -1)/ (specific gravity -1)] (203, 204). Urinary BPA concentrations less than the limit of detection (LOD) (0.50ug/L) were divided by the square root of 2, which is a standard approach imputing data for samples below LOD (205).

Table 10 - Food Grouping Details				
Food Group	**Tertile 1 Median (Range)**	**Tertile 2 Median (Range)**	**Tertile 3 Median (Range)**	**Examples of Included Foods and Rationale for Inclusion**
Urinary BPA (SG-adjusted, ng/L)	1.85 (0.49 – 2.20)	2.99 (2.27 – 4.23)	6.83 (4.38 – 36.9)	Not Applicable 9 samples from 3 days pooled
Whole Grain (servings/3 days)[1]	0.69 (0 – 2.27)	4.00 (2.32-5.51)	8.22 (5.72-19.3)	Food Examples: Whole grain only: Grains, Flour and Dry Mixes Loaf-type bread and plain roles Other Breads (quick breads, muffins, tortillas) Crackers Pasta Ready-to-eat cereals (unsweetened and presweetened) Rationale: Whole grain foods contribute to fiber intake, which may influence speed of transit and GI tract, and thus, influence BPA absorption by increasing the time food is in contact with the GI tract (220).
Refined Grain (servings/3 days)[1]	6.32 (0 – 8.39)	12.9 (8.66 – 15.4)	21.9 (12.6 – 32.0)	Food Examples: Refined grain only: Grains, Flour and Dry Mixes Loaf-type bread and plain roles Other Breads (quick breads, muffins, tortillas) Crackers Pasta Ready-to-eat cereals (unsweetened and presweetened) Rationale: Refined grain intake was included for comparison with whole grain intake.
Vegetables (servings/3 days)[1]	4.62 (1.03 – 7.05)	8.96 (7.13 – 11.7)	17.5 (12.0 – 50.2)	Food Examples: All non-starch (e.g. potatoes) vegetables + tomatoes (fresh, frozen, canned or cooked) Rationale:

				Canned vegetables are a source of exposure to BPA (54). Vegetables are also a source of fiber, which could influence absorption (220) and a source of many phytochemicals that may influence levels of biotransformation enzymes levels, which could potential alter metabolism and excretion of BPA (111, 112, 217, 218, 221).
High Fat Dairy (servings/3 days)[1]	0.48 (0 – 1.14)	2.08 (1.17 – 2.95)	4.25 (3.08 – 9.82)	Food Examples: Whole milk Flavored whole milk (e.g. chocolate milk) Whole milk yogurt Full fat cheese Cream Rationale: High fat foods are considered to affect GI physiology, potentially altering absorption of BPA (222, 223).
Reduced/Low Fat Dairy (servings/3 days)[1]	0.81 (0 – 1.70)	2.67 (1.70 – 3.93)	5.99 (4.50 – 14.6)	Food Examples: Fat Free/Low Fat/ Reduced Fat milk Flavored Fat Free/Low Fat/ Reduced Fat milk (e.g. chocolate milk) Fat Free/Low Fat/ Reduced Fat yogurt Low Fat/Reduced fat cheese Fat Free/Low Fat/ Reduced Fat Cream Rationale: Evaluated to provide comparison to high fat dairy.
Red Meat (servings/3 days)[1]	0	1.92 (0.62 – 3.03)	6.0 (3.5 – 18.0)	Food Examples: Beef, Lamb, Veal, Game Rationale: Contributes to fat intake, which is considered to affect GI physiology, potentially altering absorption of BPA (222, 223).
Processed Meat (servings/3 days)[1]	0.74 (0 – 2.08)	3.18 (2.44 – 4.38)	7.53 (4.50 – 31.6)	Food Examples: Cold cuts, sausages, cured pork Rationale: Contributes to fat intake, which is considered to affect GI

				physiology, potentially altering absorption of BPA.(222, 223)
Sweets/Desserts (servings/3 days)[1]	0 (0 – 0.29)	1.57 (0.50 – 2.50)	4.63 (2.59 – 12.3)	Food Examples: Ice cream, popsicle, pudding, cakes, cookies, pies, pastries, Danish, doughnuts, cobblers miscellaneous desserts (excluded candy) Rationale: May also contribute to fat intake and a higher caloric intake, which are considered to affect GI physiology, potentially altering absorption of BPA (222, 223).
Alcohol (servings/3 days)[1]	0	1.00 (0.004-1.67)	4.67 (2.00-15.2)	Food Examples: Beer, wine, liquor, cordial Rationale: Alcohol consumption is associated with higher caloric intake, and may influences absorption, metabolism and excretion of dietary components (224, 225).
Artificially Sweetened Beverages (servings/3 days)[1]	0	1.50 (0.33-2.25)	5.75 (2.50-20.0)	Food Examples: Any artificially sweetened beverages (e.g. teas, coffee, energy drinks, fruit drinks, soda) Rationale: Most artificially sweetened beverages are in cans or plastic bottles, which may serve as a source of exposure to BPA (28, 29, 40, 71, 74, 75, 226).
Food groups less frequently consumed by study participants (*categorized as consumed, not consumed*)				
Food Group		**Median (range)** [2]		**Examples of included foods**
Fruits (servings/3 days)[1]		1.18 (0.11 – 3.21)		Food Examples: All fruits (fresh, frozen, canned, or cooked) Rationale: Canned fruits may increase exposure to BPA (54). Additionally, fruits serve as a source of fiber, which may influence absorption (220) and a source of many phytochemicals that have been shown to influence biotransformation enzyme levels, which could potential alter

		metabolism and excretion of BPA (111, 112, 217, 218, 221).
Fried Foods (servings/3 days)[1]	2.55 (0.65 – 9.48	Food Examples: Fried chicken, fried fruit (e.g. fried bananas), fried fish, fried shellfish, fried vegetable (e.g. fried green beans), fried potatoes Rationale: High fat foods are considered to affect GI physiology, potentially altering absorption of BPA (222, 223).
Sugar-Sweetened Beverages (servings/3 days)[1]	2.50 (0.75-8.00)	Food Examples: Soda, sweet tea, sweetened coffee, fruit drinks, energy drinks Rationale: Most sugar-sweetened beverages are in cans or plastic bottles, which may serve as a source of exposure to BPA (28, 29, 40, 71, 74, 75, 226).

[1]Number of servings per day summed for a total number of servings for 3 days. Serving size definitions preset by Nutrition Data System for Research (NDSR). See reference (219)

[2] Among study participants who consumed an item in the food group at least once during the three days of food record data collection.

Data Analysis

Urinary BPA levels and nutrient intake values were log-transformed to normalize the distribution. Caloric intake was normally distributed among study participants, and thus, was not log-transformed. Food group servings were categorized into tertiles. Fruits, fried foods and sugar-sweetened beverages, which too many participants reported not consuming to be categorized into tertiles and were re-categorized into dichotomous variables (e.g. consumed/did not consume).

Spearman correlations and Chi-square tests were initially used to evaluate associations between food record data (food group servings and nutrient intakes), population demographics and lifestyle habits, and urinary BPA levels. Spearman correlations were used because of outliers for several nutrients and urinary BPA levels. Age and gender adjusted linear regression models were used to evaluate associations between population characteristics, urinary BPA levels, and nutrient intakes.

Multivariable linear regression was used to evaluate associations between urinary BPA levels and reported macronutrient intakes and servings from food groups. Urinary BPA and intake of specific macronutrients, urinary BPA was categorized into tertiles and mean nutrient intakes were calculated for each tertile of exposure. Since foods groups were categorical, mean urinary BPA levels were calculated for each tertile for servings from food groups. All models were adjusted for age, gender, education, BMI and caloric intake. The covariates were chosen *a priori* based on associations observed in previous studies with BPA and/or macronutrient and food group intakes.

Participants with missing data on the food records and questionnaire were excluded from a particular analysis if the missing data included the exposure or outcome variables of interest. Sensitivity analyses were performed excluding participants with

missing urine samples (n=6). Reported caloric intakes were all within plausible ranges (>1,000 kcals/day and <5,000 kcals/day).

All data analyses were performed using SAS 9.2 (SAS Institute Inc., Cary, NC). P-values of < 0.05 were considered statistically significant.

Results

The UB-Diet Study population was primarily young (20 – 29 years) (54%), college educated (59.7%) and female (65.7%) (**Table 11**). Most participants (64%) had a normal BMI (<25kg/m^2), fifteen were overweight (25.0 ≤ BMI <30), and nine were obese (BMI ≥ 30). Fifteen participants had an elevated waist circumference (≥ 88 cm in women/102 cm in men). A majority of participants reported high levels of physical activity (59.7%). Most participants also reported consuming at least one meal at a restaurant over the three day time period (89.6%), with fifteen consuming four or more meals away from home. Twenty-nine (43%) participants reported consuming canned foods at any time during the three days of food record data collection.

Total urinary BPA, caloric intake, total fat, and available carbohydrate intake (total carbohydrate minus dietary fiber) by population characteristics are presented in **Table 11**. Several population characteristics were associated with intake of macronutrients; however, they generally were not associated with urinary BPA levels. Canned food intake was statistically significantly positively associated with urinary BPA levels ($p<0.001$), but not associated with macronutrient intakes. Participants with a BMI ≥ 30 kg/m^2 had the highest mean urinary BPA levels (Mean = 4.09 ug/mL, 95% CI: 2.37 – 7.06), but the association was not statistically significantly different from the mean BPA in the normal (<25 kg/m^2: Mean = 3.49, 95% CI: 2.64 – 4.60) and overweight BMI (25 - <30 kg/m^2: Mean = 2.59, 95% CI: 1.67 – 4.01) categories and there was no clear trend to the association.

The number of servings from food groups (**Table 10**) varied widely. In general, reported intake of fried foods, fruit and sugar-sweetened beverages were low in this population. Reported number of servings for food groups generally did not differ by population characteristics (data not shown). Age was associated with high fat dairy intake ($p = 0.05$), but there was no trend to the association. Women were more likely to consume reduced fat or low fat dairy products ($p = 0.05$) and participants who reported eating out 2 or more meals tended to have a higher number of servings of refined carbohydrate foods ($p = 0.01$).

Macronutrient intakes were not statistically significantly associated with total urinary BPA levels (**Table 12**). While not statistically significant, mean caloric intake increased with increasing urinary BPA tertiles. Intake of total protein, total fat, saturated fat and monounsaturated fats tended to be higher in those with lower urinary BPA levels, while fiber intake tended to be lowest in those with lower BPA levels.

No statistically significantly associations with urinary BPA levels were observed by number of servings from any of the food groups (**Table 13**). While not statistically significant, participants reporting a higher number of servings of refined grains, vegetables and red meats tended to have higher urinary BPA levels compared to those who reported consuming no or low numbers of servings from these food groups. Conversely, participants who reported never or rarely consuming alcohol or artificially sweetened beverages were found to have higher urinary BPA levels.

Table 11 – Mean Urinary BPA Levels and Macronutrient Intakes by Population Characteristics									
		Total BPA (ug/L)[1, 2]		Calories (kcal/3d)[2]		Total Fat (gm/3d)[1, 2]		Available CHO (gm/3d)[1, 2]	
	N	Mean (95% CI)	p	Mean (95% CI)	p	Mean (95% CI)	p	Mean (95% CI)	p
Age			0.63		0.11		0.17		0.20
20–29 years	36	3.26 (2.49-4.26)		6,344 (5,710-6,979)		217.8 (187.7-252.8)		684.1 (615.7-760.2)	
30–39 years	13	3.73 (2.46-5.66)		7,538 (6,553-8,524)		284.0 (225.4-358.0)		796.4 (676.1-938.1)	
40–55 years	18	2.86 (1.99-4.09)		6,288 (5,440-7,135)		228.7 (187.4-279.0)		657.8 (571.4-757.2)	
Gender			0.47		0.17		0.17		0.34
Male	23	3.03 (2.22-4.13)		6,929 (6,174-7,684)		252.7 (212.2-301.0)		727.4 (642.2-824.0)	
Female	44	3.48 (2.78-4.36)		6,275 (5,729-6,820)		217.3 (191.5-246.5)		675.8 (617.6-739.5)	
Education			0.75		0.07		0.03		0.90
<College Graduate	27	3.31 (2.62-4.42)		6,234 (5,545-6,922)		228.5 (195.3-267.3)		686.9 (610.2-773.3)	
College Graduate	25	2.94 (2.14-4.04)		7,307 (6,549-8,064)		278.9 (234.7-331.4)		708.6 (622.1-807.1)	
Advanced Degree	15	3.61 (2.42-5.38)		6,208 (5,269-7,147)		190.1 (153.5-235.5)		715.1 (608.5-840.4)	
BMI			0.38		0.23		0.38		0.07
<25 kg/m^2	43	3.49 (2.64-4.60)		6,677 (6,041-7,312)		217.6 (199.4-272.6)		730.5 (681.6-782.8)	
25 - <30 kg/m^2	15	2.59 (1.67-4.01)		6,024 (5,027-7,021)		237.4 (206.9-272.6)		659.5 (591.3-735.5)	
≥ 30 kg/m^2	9	4.09 (2.37-7.06)		7,340 (6,107-8,573)		246.0 (206.9-292.1)		615.2 (536.9-704.8)	
WC			0.38		0.36		0.54		0.75
<88/102 cm	52	3.11 (2.50-3.86)		6,490 (5,966-7,015)		230.3 (203.9-260.2)		696.7 (638.6-760.1)	
≥88/102 cm	15	3.89 (2.49-6.08)		7,055 (5,971-8,139)		251.4 (195.4-323.5)		719.6 (593.9-861.6)	
Physical Activity			0.44		0.009		0.006		0.02
High	40	3.08 (2.42-3.92)		7,898 (6728-9,068)		278.8 (213.4-364.2)		911.3 (751.3-1105.5)	
Moderate	17	3.91 (2.69-5.69)		5,798 (4,913-6,684)		177.3 (144.9-217.0)		657.8 (568.4-761.3)	
Low	10	2.85 (1.78-4.90)		6,595 (6,039-7,151)		248.7 (219.1-282.3)		676.2 (617.0-741/1)	
Restaurant Meals			0.32		0.12		0.34		0.03
0	7	3.63 (2.05-6.41)		6,711 (5,360-8,062)		232.6 (168.8-320.6)		688.1 (553.4-855.6)	
1	14	2.55 (1.67-3.91)		5,784 (4,772-6,795)		206.5 (162.5-262.6)		559.1 (475.0-658.1)	
2	17	3.40 (2.35-4.90)		6,329 (5,456-7,201)		217.5 (176.8-267.5)		711.4 (618.0-818.8)	
3	14	4.39 (2.94-6.55)		7,589 (6,640-8,539)		282.3 (225.4-353.7)		786.2 (674.7-916.3)	
≥4	15	2.71 (1.85-3.98)		6,601 (5,691-7,510)		238.1 (191.9-295.5)		743.5 (642.1-860.9)	
Canned Food			<0.001		0.38		0.77		0.87
None	41	2.71 (2.18-3.37)		6,504 (5,929-7,078)		228.2 (199.4-261.0)		694.0 (630.9-763.3)	
>0 - <3 servings	14	2.89 (2.02-4.12)		6,287 (5,260-7,314)		239.0 (187.9-304.0)		662.7 (560.1-787.3)	
≥ 3 servings	12	6.55 (4.43-9.70)		7,237 (6,181-8,293)		251.7 (196.5-322.3)		765.1 (642.2-911.5)	

[1] Linear Regression. Adjusted for age and gender. [2] Geometric means/3 days. Abbreviations: BMI = body mas index, CHO = carbohydrates, CI = confidence intervals, Cm = centimeters, d = day, gm = grams, kcal = kilocalories, ug = micrograms, WC = waist circumference.

Table 12 – Mean Nutrient Intakes by Urinary BPA Tertile				
	Urinary BPA Tertile			
	Tertile 1 Mean (95% CI)[1, 2]	Tertile 2 Mean (95% CI)[1, 2]	Tertile 3 Mean (95% CI)[1, 2]	p
Calories (Kcal/3d)	6,327 (5,535-7,118)	6,507 (5,670-7,343)	7,049 (6,218-7,880)	0.43
Total Fat (g/3d)[3]	245.5 (221.6-272.0)	228.5 (205.0-254.6)	211.5 (189.6-235.8)	0.16
Saturated Fat (g/3d)[3]	82.1 (70.9-95.0)	74.6 (64.4-86.5)	68.7 (59.3-79.6)	0.25
MUFA (g/3d)[3]	83.7 (73.7-95.1)	80.2 (70.5-91.2)	72.2 (63.5-82.2)	0.25
PUFA (g/3d)[3]	49.4 (42.9-56.9)	50.0 (43.4-57.6)	48.0 (41.6-55.3)	0.91
Cholesterol (mg/3d)[3]	832.8 (667.3-1,039)	595.5 (476.8-743.9)	595.7 (476.6-744.8)	0.07
Total Protein (g/3d)[3]	250.5 (229.4-273.6)	240.2 (218.9-263.6)	232.0 (211.3-254.8)	0.50
Available Carbohydrate (g/3d)[3]	659.0 (603.5-719.5)	728.8 (667.3-769.0)	710.7 (650.5-776.5)	0.27
Total Fiber (g/3d)[3]	54.9 (46.6-64.7)	65.5 (55.1-77.9)	68.5 (57.6-81.6)	0.17
Added Sugar (g/3d)[3]	138.7 (109.9-175.1)	151.1 (118.2-193.2)	139.3 (108.7-178.4)	0.85
Sodium (mg/3d)[3]	11,075 (10,305-11,903)	10,967 (10,164-11,835)	10,674 (9,886-11,525)	0.77

[1]Evaluated as 3-day total. Means represent totals for 3 days.
[2]Adjusted for age, gender, BMI, education, caloric intake (except in calories model).
[3]Geometric means/3 days.
Abbreviations: CI = Confidence Intervals, d = days, g = grams, kcal = kilocalories, mg = milligrams, MUFA = monounsaturated fat, PUFA = polyunsaturated fat.

Table 13 – Mean Urinary BPA Levels by Food Group Serving Tertile					
Food Groups (range per tertile)	**N**	**Mean (95% CI)[1, 3]**	**p**	**Mean (95% CI)[2, 3]**	**p**
Whole Grain			0.61		0.65
Tertile 1 (0 – 2.27 servings/3d)	22	3.10 (2.76-4.26)		3.11 (2.20-4.40)	
Tertile 2 (2.32 – 5.51 servings/3d)	23	3.77 (2.76-5.14)		3.70 (2.63-5.21)	
Tertile 3 (5.72 – 19.3 servings/3d)	22	3.12 (2.27-4.29)		2.99 (2.12-4.22)	
Refined Grain			0.30		0.25
Tertile 1 (0 – 8.39 servings/3d)	22	2.78 (2.03-3.80)		2.60 (1.83-3.69)	
Tertile 2 (8.66 – 15.4 servings/3d)	23	3.35 (2.47-4.56)		3.41 (2.47-4.70)	
Tertile 3 (12.6 – 32.0 servings/3d)	22	3.92 (2.87-5.38)		3.83 (2.74-5.36)	
Fruits			0.59		0.54
Did not consume	45	3.44 (2.75-4.29)		3.40 (2.66-4.34)	
Consumed	22	3.09 (2.25-4.25)		3.00 (2.14-4.20)	
Vegetables			0.47		0.45
Tertile 1 (1.03 – 7.07 servings/3d)	22	3.01 (2.19-4.12)		2.89 (2.04-4.09)	
Tertile 2 (7.13 – 11.7 servings/3d)	23	3.14 (2.30-4.27)		3.12 (2.26-4.30)	
Tertile 3 (12.0 – 50.2 servings/3d)	22	3.89 (2.84-5.35)		3.90 (2.74-5.55)	
High Fat Dairy			0.09		0.09
Tertile 1 (0 – 1.14 servings/3d)	22	2.78 (2.04-3.78)		2.77 (1.98-3.89)	
Tertile 2 (1.17 – 2.95 servings/3d)	23	4.34 (3.21-5.87)		4.45 (3.15-6.27)	
Tertile 3 (3.08 – 9.82 servings/3d)	22	3.00 (2.20-4.09)		2.90 (2.01-4.18)	
Reduced/Low Fat Dairy			0.84		0.79
Tertile 1 (0 – 1.70 servings/3d)	22	3.49 (2.54-4.81)		3.56 (2.53-5.03)	
Tertile 2 (1.70 – 3.93 servings/3d)	23	3.40 (2.49-4.65)		3.24 (2.24-4.68)	
Tertile 3 94.50 – 14.6 servings/3d)	22	3.08 (2.23-4.23)		2.98 (2.07-4.29)	
Red Meat			0.05		0.10
Tertile 1 (0 servings/3d)	24	3.03 (2.26-4.06)		2.99 (2.16-4.15)	
Tertile 2 (0.62 – 3.03 servings/3d)	22	2.72 (2.00-3.69)		2.67 (1.93-3.70)	
Tertile 3 (3.5 – 18.0 servings/3d)	21	4.55 (3.33-6.22)		4.39 (3.11-6.20)	
Processed Meat			0.36		0.48
Tertile 1 (0 – 2.08 servings/3d)	22	3.78 (2.76-5.18)		3.64 (2.58-5.15)	
Tertile 2 (2.44 – 4.38 servings/3d)	23	2.79 (2.05-3.79)		2.78 (1.99-3.87)	
Tertile 3 (4.50 – 31.6 servings/3d)	22	3.50 (2.55-4.80)		3.48 (2.44-4.94)	
Fried Foods			0.99		0.97
None	45	3.32 (2.65-4.16)		3.26 (2.55-4.17)	
Consumed	22	3.32 (2.43-4.53)		3.24 (2.30-4.57)	
Sweets/Desserts			0.26		0.36
Tertile 1 (0 – 0.29 servings/3d)	22	3.19 (2.33-4.37)		3.13 (2.22-4.41)	
Tertile 2 (0.50 – 2.50 servings/3d)	23	4.03 (2.96-5.48)		3.90 (2.79-5.46)	
Tertile 3 (2.59 – 12.3 servings/3d)	22	2.82 (2.06-3.86)		2.83 (1.97-4.04)	
Alcohol			0.46		0.58
Tertile 1 (0 servings/3d)	29	3.59 (2.72-4.73)		3.59 (2.50-4.94)	
Tertile 2 (0.004 – 1.67 servings/3d)	15	3.63 (2.47-5.33)		3.42 (2.29-5.11)	
Tertile 3 (2.00 – 15.2 servings/3d)	23	2.84 (2.08-3.87)		2.84 (2.03-3.87)	
Sugar Sweetened Beverages			0.64		0.63
None	55	3.25 (2.66-3.98)		3.20 (2.59-3.97)	
Consumed	12	3.64 (2.37-5.59)		3.63 (2.23-5.89)	
Artificially Sweetened Beverages			0.45		0.32
Tertile 1 (0 servings/3d)	29	2.79 (2.88-4.99)		3.81 (2.86-5.07)	
Tertile 2 (0.33 – 2.25 servings/3d)	16	2.99 (2.07-4.34)		2.78 (1.91-4.31)	
Tertile 3 (2.50 – 20 servinngs/3d)	22	3.01 (2.19-4.13)		2.78 (1.95-3.97)	

[1]Linear Regression-Unadjusted [2]Linear Regression – Adjusted for education, BMI, age, gender, kcal.
[3]Geometric Mean. Abbreviations: CI = confidence intervals, d = days.

Discussion

In this pilot study, urinary BPA levels were generally not associated with reported food or nutrient intakes on 24-hour food records from the same time period. This was a small study, which likely limited our ability to detect associations, however, there were some trends observed in our data that warrant further considerations. Higher caloric and total fiber intake and higher intake of refined grains, vegetables and red meat were observed among participants with higher urinary BPA levels. Conversely, higher total fat intakes were observed among participants with lower BPA levels. This could have implications for research evaluating associations between BPA exposure levels and chronic disease outcomes, which are also often associated with dietary intake. While our study did not observe statistically significant associations, diet remains an important variable to evaluate when addressing risk of BPA exposure because it often serves as the vehicle for BPA exposure.

Given that certain food items, such as canned foods are known to be a source of BPA exposure, and that a higher intake of food overall should theoretically lead to higher potential for dietary BPA exposure, it is unlikely that BPA exposure is completely independent of dietary habits. In our study, higher urinary BPA levels were observed in participants with higher caloric intakes. This suggests that caloric intake and intake of BPA may not be independent. Therefore, associations between total BPA and prevalence of chronic disease observed in previous cross-sectional studies may be confounded by dietary factors, such as total caloric intake.

Diet also has the potential to influence internal BPA levels by influencing absorption, metabolism, and/or excretion (ADME) of BPA. While total urinary BPA is indicative of the amount of total BPA exposure, it does not capture actual internal levels of unconjugated BPA (biologically active), which are considered the most relevant for

evaluating associations between BPA exposure and chronic disease risk (16). Available data regarding human BPA absorption, metabolism, distribution and excretion come from acute dose toxicology studies, in which a small number of participants consumed labeled BPA with water only (without food). Toxicokinetic data from these acute dosing studies in humans, and animal studies, have reported that BPA is completely absorbed in the gastrointestinal (GI) tract and excreted in the urine within approximately 24-hours (168, 169, 227, 228). However, these studies used high levels of labeled BPA consumed without food, which is not representative of typical human exposure. Most humans are not exposed to large oral doses of BPA, and most likely consume BPA as part of a complex mixture of food components that might influence absorption or metabolism. Diet has been shown to influence ADME for many xenobiotics (214-216). For example, higher folate intake appears to increase detoxification and elimination of inorganic arsenic (229).

In this study, participants with higher total fiber and caloric intake tended to have higher urinary BPA levels, while participants with higher total fat intake tended to have lower urinary BPA levels. Total fat, calories and fiber intake all have the potential to influence gastrointestinal physiology, and thus, could influence absorption of BPA. Some ways that dietary composition influences absorption include delaying or increasing gut motility, or physically/chemically interacting with BPA (222, 223). High fat and high caloric meals are particularly likely to influence GI physiology as evidenced by the U.S. Food and Drug Administration requirement that drugs undergo bioavailability testing using high fat and caloric diets (222). High fat (222, 223) and/or fiber (220) content all tend to slow gastric emptying, which could lead to more complete BPA absorption by prolonging GI contact time. Conversely, fiber intake leads to bulking and may bind up components in food leading to lower absorption (220). Total fat intake was inversely

associated with BPA, which is contrary to what would be expected, but the results from this study would suggest that fiber may increase absorption. However, it cannot be ruled out that those who consumed more fiber also simply had higher overall exposure to BPA (via food or environmental exposure), since BPA was not directly measured in food, water and environments.

In the present study, participants with a higher vegetable intake had higher urinary BPA levels. This finding could be related to greater overall consumption of vegetables among people with higher urinary BPA levels or associations with dietary fiber intake, but bioactive components in vegetables (phytochemicals) may also alter the rate of BPA metabolism and excretion by altering enzyme activity or expression.. BPA is mainly metabolized in the liver via conjugation by UDP-glucuronosyltransferases (UGTs), but sulfotransferases (SULTs) can also conjugate BPA (93, 96), with being UGT2B15 the primary enzyme isoform responsible for BPA metabolism (96, 99). Phytochemicals, including flavonoids, are also metabolized by UGTs and could limit BPA conjugation if they are preferentially metabolized (111, 218). Conversely, some phytochemicals have been shown to increase hepatic UGT activity in animals, which could increase conjugation of BPA, and limit the amount of free BPA that enters circulation (217, 218).

Once BPA is glucuronidated, it can be deconjugated by β-glucuronidases, which are present in most tissues, including the liver, kidney, spleen and endocrine organs (110, 112, 221). Plant foods contain *D*-glucaric acid, which is metabolized to D-glucaro-1,4-lactone, an inhibitor of β-glucuronidase activity (112, 221). In human studies, serum β-glucuronidase activity has been shown to be inversely associated with consumption of plant foods, and intake of dietary fiber and plant proteins (112, 221). β-glucuronidase deconjugation of BPA has been suggested as a factor to consider in determining internal exposure to unconjugated BPA (110) and provides an additional route by which fiber and

vegetable intake could influence BPA metabolism and excretion. Studies have suggested that serum BPA levels in the nanomolar to micromolar range could adversely impact health (25). If food components have the ability to influence the absorption, metabolism, or excretion of BPA, even if the change is small, it could have health implications (25).

To date, no studies have analyzed both the BPA content of foods consumed by study participants and circulating BPA levels. It is unclear whether the presence of fat, fiber or phytochemicals might impact the rate or amount of BPA absorption, distribution, metabolism or excretion. Several studies in humans have fed participants packaged food items and measured serum and/or urinary BPA levels, however, none of these studies measured the BPA content of the food samples (58-60, 230). Estimating BPA exposure by food category can be problematic, since measured BPA levels are inconsistent in canned food items, even for the same food items from the same company (42). Additionally, while many canned fruits are in cans with epoxy resin linings, some fruits do not have this lining because of desirable reactions between components in the metal can and the fruits (231). Thus, while these studies indicate that diet is source of BPA exposure, without measurements of BPA levels in the foods these studies cannot provided much evidence for evaluating the ADME of BPA.

The present study had several strengths and limitations. A major strength of this study was the simultaneous collection of multiple urine samples and 24-hour food records. This allowed for a direct comparison of actual dietary intake on the same days as urinary BPA levels were measured in a free-living adult population, which to our knowledge has not been previously evaluated. Additionally, the collection of multiple urine samples provided a broader picture of exposure levels for this highly variable chemical exposure. A major limitation of this study was sample size. It is likely that this

study had limited power to detect smaller, but possibly meaningful associations. Another limitation of this study was the short duration. This study collected data for a single week, which does not account for how diet and exposure to BPA can vary over time. For caloric intake and BPA to influence risk for obesity or other chronic disease outcomes, long-term exposure levels are more relevant.

Future studies should consider the potential for dietary factors to alter associations between BPA and disease risk. Large population-based studies should consider food and nutrient intake, especially total caloric intake, as potential confounders or modifiers of the association between BPA exposure and chronic disease outcomes. Studies are also needed that evaluate the ADME of BPA with considerations for how human populations are actually exposed to BPA, often via diet. Duplicate diet studies testing BPA exposure in mixed meals with different macronutrient composition would be a useful approach for evaluating absorption, metabolism and excretion of low level BPA exposure consumed as part of the diet. BPA measured in a duplicate sample of the food would provide actual BPA intake data and serum and urinary BPA levels could then be monitored to determine actual absorbed levels of BPA, and metabolism rates of BPA after food consumption.

Conclusions

To date, few studies have evaluated how dietary intake, beyond canned food consumption, might influence BPA exposure. This study provides some suggestive evidence that dietary factors, such as caloric intake, may be associated with urinary BPA levels. Further research evaluating the association between dietary factors and BPA absorption, metabolism and excretion are needed. Studies evaluating the association

between BPA exposure and disease outcomes should consider dietary factors as potential confounders or effect modifiers.

Chapter 5
Conclusions and Future Directions

A PubMed search of the chemical "bisphenol A" on December 19, 2013 identified nearly 8,000 publications. Despite this extensive number of research articles, reviews and commentaries, there remains substantial debate as to whether BPA poses a hazard to human health. In the fall of 2013, two sharply contrasting opinion articles were published in multiple prominent journals presenting arguments for (101, 232-236) and against (100) policy actions to limit use of BPA and other endocrine-disrupting chemicals (EDC) in the European Union (100, 101). This major debate has focused on whether classic toxicology principles and research approaches are appropriate for EDCs, including BPA.

Classic toxicokinetics and exposure-outcome assessments typically evaluate large dose exposures to chemicals and often assume monotonic dose-response relationships. Assumptions about the safety of BPA have been made based on these traditional acute dose toxicokentic studies. It has been assumed that absorption, distribution, metabolism and excretion (ADME) data from single acute oral doses of labeled BPA, consumed with only water, directly translate to chronic, low-level BPA exposure that humans typically encounter through the diet. It has additionally been assumed that dermal or inhalation exposures contribute no or very little to human BPA exposure. It has been further assumed that, due to rapid first pass metabolism, humans are internally exposed to very low or no biologically active (unconjugated) BPA. Existing data suggest that these assumptions may not be true and must be tested.

This dissertation presents a review and critical evaluation of existing literature on associations between BPA and body composition. This dissertation also describes the Urinary Biomarkers of Dietary Intake Study (UB-Diet Study), which was designed and

conducted to address some of the current gaps and limitations in BPA research. As discussed in Chapter 2, human studies provide suggestive evidence of an association between BPA exposure and obesity, but have largely been cross-sectional and have important limitations, such as spot sample measurements of BPA exposure.

The considerable cost of serum and urinary BPA assays, which has limited researchers' ability to measure BPA exposures in large prospective studies, led to the hypothesis that a questionnaire that collects data on known sources of BPA exposure may be a lower cost approach to estimate BPA exposure. The BPA exposure assessment module (BEAM) was developed and evaluated in the Urinary Biomarkers of Dietary Intake Study to test this hypothesis (Chapter 3). In addition to collecting data using a questionnaire, the participants completed 24-hour food records, which captured recent dietary intake data for the same days that urine samples were collected. This allowed for an evaluation of the relationship between dietary habits and urinary BPA levels. The results indicate that the assumption that diet, especially canned food intake, is the primary source of exposure may not be valid. The questionnaire was not able to accurately rank participants' urinary BPA levels, and while recent canned food intake was associated with urinary BPA levels, consumption of canned foods only explained approximately one-fifth of the variability in urinary BPA levels. Additionally, several participants who reported consuming no canned foods had high urinary BPA levels.

Chapter 4 presents the argument for more research on the association between dietary factors and BPA absorption, distribution, metabolism and elimination (ADME). The case was presented for why epidemiologic studies should consider dietary factors in their assessments of associations between BPA exposure and chronic diseases. Since diet is associated with many disease outcomes and is also considered the major source of BPA exposure, there is the potential for diet to confound BPA-chronic disease

associations. Additionally, factors such as poor quality diets and other chemical contaminants in the diet may modify associations between BPA exposure and chronic disease risk. Although the UB-Diet Study had a limited number of study participants, the study findings suggest that BPA levels may be associated with higher caloric and fiber intake, lower total fat intake and higher intakes of vegetables, refined grains and red meats. Other studies have indicated that these food groups may also be associated with the risk of becoming obese or of developing other chronic diseases (237-239).

Collectively, results from the systematic review and the UB-Diet Study indicate that more research is needed. Over the last ten years, data indicating that low-level BPA exposure may adversely affect health has begun to accumulate, and suggest that there are many assumptions regarding BPA that still need to be tested.

Future Directions

Gaps in our current understanding of human BPA exposure range from the sources of exposure to the potential health outcomes. Future studies should continue to investigate sources of exposure to BPA and variability in exposure levels. Studies that collect detailed dietary data (e.g. food records), environmental data (e.g. dust samples), and personal product usage (e.g. shampoo, mouthwash, medications), in conjunction with biospecimens, at several time points throughout the year and across multiple years would help clarify sources of exposure and the stability of average exposures over time. Spot urinary BPA measurements are known to be highly variable (170, 171), but it is unclear if average exposure levels in humans are consistent over time. These studies would also be useful for identifying correlated dietary and lifestyle habits or chemical exposures that may confound or modify associations between BPA exposure and health.

Many of the previous studies on the health effects of BPA exposure did not address whether correlated exposures, such as nutrient intakes or other chemical exposures, influence observed exposure-outcome associations. An example of the importance of considering potential interactions between chemicals is a recent *in vitro* study that evaluated the combined effects of several anti-androgenic chemicals, including BPA, in a human breast cancer cell line (240). This study found that combinations of chemicals, acting through similar and dissimilar pathways, were able to produce joint effects with very low concentrations of chemicals. While challenging to evaluate and interpret all of the possible exposure combinations, researchers need to work towards evaluating combined exposures, which are more reflective of actual human exposure.

In addition to the need for improved characterization of sources of exposure and correlated exposures, is the need for research examining the toxicokinetics of BPA exposure with considerations for typical human exposure routes and levels. Currently available ADME data for BPA come from two small acute dose oral BPA exposure studies in humans (169, 176) and several animal studies (227, 228), and may not be relevant to typical human exposures. Duplicate diet studies that measure BPA in food samples in combination with serum and urinary BPA levels before, during and after consumption of food samples would help elucidate absorption, metabolism and excretion after a typical human BPA exposure as part of a mixed diet. The measurement of BPA in all foods consumed, including water, would also allow researchers to evaluate the proportion of exposure that is from non-dietary sources. This research would test several long-held assumptions regarding routes of exposure and toxicokinetics of BPA that have, in turn, led to further assumptions about the ability of BPA to effect health by altering circulating levels of the estrogenic, unconjugated BPA.

Finally, due to concerns about the health implications of BPA exposure in the perinatal period, most animal studies and many human studies have focused on pregnant and neonatal populations. While these represent critical periods of exposure, chronic, low level BPA exposure is ongoing throughout life, and thus, exposure during adulthood could also have health implications. For example, cross-sectional studies have observed associations between sex hormone levels and urinary BPA levels (80, 117, 119, 120, 159, 160). Sex hormone levels may be associated with risk for hormonally mediated cancers, such as breast cancer (241, 242). To date, few studies have evaluated whether BPA exposure is associated with risk for breast cancer in humans. A case-control study found the risk for breast cancer was associated with employment in jobs with higher potential BPA exposure, such as food canning, however, this study did not have the ability to evaluate actual BPA exposure levels and numerous other chemical exposures are likely associated with occupation (243). Another recent study observed a positive association between serum BPA levels and mammographic breast density, a risk factor for breast cancer (244), however this study was cross-sectional and was based on a single BPA measurement (245). Human studies to date have been largely cross-sectional, with single-spot serum or urinary BPA measurements and have lacked adequate evaluations of potential confounding and effect modifying variables. Further research is needed in adult populations to address these knowledge gaps, particularly prospective studies with adequate consideration for confounding and effect modification.

Additionally, there is the challenge of determining whether any BPA exposure level is safe. In population-based epidemiological studies, researchers are reliant on both “unexposed” and “exposed” groups. Current biomonitoring data suggest that there may be no such thing as an “unexposed” group, which poses a challenge for

researchers. However, prospective studies can still be useful to investigate associations with the caveat that, if no association is observed, it may be due to lack of a truly "unexposed" population.

Conclusions

The U.S. Food and Drug Administration (137), World Health Organization (54) and European Food Safety Authority (246) have all indicated that further research on the health effects of BPA is critical. Biomonitoring data demonstrates that most, if not all, of the general population is chronically exposed to BPA (3, 23). Diet is considered to be an important source of BPA exposure since some types of food and beverage packaging contains BPA that can transfer into the food or beverage (4, 7, 10). More research is needed to characterize sources of BPA exposure and to evaluate the toxicokinetics of small amounts of BPA consumed as part of a mixed diet. It is critical to determine if dietary levels of BPA exposure can lead to health effects, particularly because of the potential to reduce dietary exposures through changes in food manufacturing regulations.

Collectively, *in vitro* and animal data indicate low level BPA exposure may adversely impact health, but significant debates regarding toxicokinetics and limitations in human studies limit researchers ability to adequately assess the risk of low dose BPA exposure. Lack of evidence does not mean lack of risk, and it is essential to improve our understanding of such a ubiquitous industrial chemical. Research is needed to improve our ability to assess the health risk posed by BPA.

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Appendix 1: BPA Content in Foods

As a reference, 50ug/kg bodyweight/day is the current safe level for BPA (3500ug/day for a 70 kg adult).(24)

Table 1 – Levels of BPA Detected in Food Items

Food Type	Studies	Location of Study[a]	Observed Levels of BPA (ug/kg)	Comments N = # of products (portion measured)
Vegetables				
Artichoke, can	Vinas *et al* (2010)(52) Brotons *et al* (1995)(32)	Spain Spain	18.8 ± 1.8[h] 47.7 (16.7)[h]	N = 3 (solid portion) N = NS (liquid portion)
Asparagus, can	Yonekubo *et al* (2009)(247) Sajiki *et al* (2007)(56) Brotons *et al* (1995)	Japan Japan Spain	3.30[e] 78.0[h] ND[h]	N = 1 (total contents) N = 1 (multiple replicates)(total contents) N = NS (liquid portion) (LOD NS)
Baby corn, can	Sajiki *et al* (2007)	Japan	44.0[h]	N = 1 (multiple replicates) (total contents)
Bamboo, can	Geens *et al* (2010)(40) Lim *et al* (2009)(57)	Belgium S. Korea	28.0[e] <2.0[e]	N = 1 (solid portion) N = 1 (solid portion)
Bean shoots, can	Vinas *et al* (2010)	Spain	<LOD [h]	N = 3 (total content)
Beets, can	Cao *et al* (2011) Thomson *et al* (2005)(44)	Canada New Zealand	3.45[e] 13.0 – 24.0[g]	N = 1 (contents prepared) (1:1 ratio raw:can) N = 4 (total contents)
Black olives, can	Geens *et al* (2010)	Belgium	21.4[e]	N = 1 (solid portion)
Cauliflower, raw	Cao *et al* (2011)	Canada	0.41[e]	N = 1
Carrots, can	Geens *et al* (2010) Goodson *et al* (2002)(33)	Belgium United Kingdom	25.9[e] 10.0 – 42.0[f]	N = 1 (solid portion) N = 12 (total contents)
Carrots, glass	Geens *et al* (2010)	Belgium	0.52[e]	N = 1 (solid portion)
Chestnut, can	Lim *et al* (2009)	S. Korea	<2.0[e]	N = 1 (solid portion)
Corn, can[b]	Noonan *et al* (2011)(41)	United States	4.2 – 76.0[f]	N = 3 (3 replicates per sample) (solid

Table 1 – Levels of BPA Detected in Food Items

Food Type	Studies	Location of Study[a]	Observed Levels of BPA (ug/kg)	Comments N = # of products (portion measured)
	Schecter *et al* (2010)(42)	United States	0.25 – 0.78[g]	portion)
	EWG (2007)(46)	United States	<2.0[g]	N = 3 (total contents)
	Braunrath *et al* (2005)(248)	Austria	28.0 (3.1)[h]	N = 2 (portion NS)
	Cao *et al* (2011)	Canada	83.7[e]	N = 1 (solid portion)
	Geens *et al* (2010)	Belgium	67.4[e]	N = 1 (contents prepared)(1:2- frozen:can)
	Rastkari *et al* (2010)(45)	Iran	<0.30 – 5.16[h]	N = 1 (solid portion)
	Thomson *et al* (2005)	New Zealand	<10.0 – 20.0[g]	N = 12 (portion NS)
	Sajiki *et al* (2007)	Japan	3.0 – 20.0[f]	N = 12 (portion NS)
	Sun *et al* (2006)(51)	Singapore	0.07[h]	N = 1 (multiple replicates) (total contents)
	Lim *et al* (2009)	S. Korea	<2.0 – 21.5[g]	N = 2 (portion NS)
	Vinas *et al* (2010)	Spain	< [h]	N = 3 (solid portion)
	Garcia-Prieta *et al* (2008)(48)	Spain	55.0 ± 1.0[h]	N = NS (Liquid portion)
	Brotons *et al* (1995)	Spain	15.0 (8.6)[h]	N = 6 (portion NS)
	Goodson *et al* (2002)	United Kingdom	16.0[h]	N = 3 (portion NS)
				N = 3 (total contents)
Corn, glass	Geens *et al* (2010)	Belgium	0.94[e]	N = 1 (solid portion)
Green beans, can[b]	Noonan *et al* (2011)	United States	16.0 – 730.0[f]	N = 7 (solid portion)
	Schecter *et al* (2010)	United States	26.6 – 65.0[g]	N = 3 (total contents)
	EWG (2007)	United States	<2.0 – 203.5[g]	N = 3 (portion NS)
	Cao *et al* (2011)	Canada	5.59[e]	N = 1 (contents prepared)(1:1 ratio raw:
	Sajiki *et al* (2007)	Japan	17.0[h]	can)
	Garcia-Prieta *et al* (2008)	Spain	103.0 ±3.0	N = 1 (multiple replicates) (total contents)
	Brotons *et al* (1995)	Spain	29.8 (13.3)[h]	N = 3 (solid portion)
	Goodson *et al* 2002)	United Kingdom	36.0 – 37.0[f]	N = NS, (liquid portions)
				N = 6 (total contents)
Green olives, plastic	Geens *et al* (2010)	Belgium	0.24[e]	N = 1 (solid portion)

Table 1 – Levels of BPA Detected in Food Items				
Food Type	**Studies**	**Location of Study[a]**	**Observed Levels of BPA (ug/kg)**	**Comments N = # of products (portion measured)**
Heart of Palm, can	Sajiki *et al* (2007) Brotons *et al* (1995)	Japan Spain	15.0[h] ND[h]	N = 1 (multiple replicates) (total contents) N = NS (liquid portion) (LOD NS
Mixed vegetables, can	Noonan *et al* (2011) Schecter *et al* (2010) EWG (2007) Cao *et al* (2010a)(39) Geens *et al* (2010) Vinas *et al* (2010) Brotons *et al* (1995)	United States United States United States Canada Belgium Spain Spain	11.0[h] 2.29 – 4.16[g] <2.0 – 330.0[g] 4.3 – 92.0[g] 53.0[e] 254.0 ± 14.0 22.4 (9.6)[h]	N = 1 (3 replicate samples) N = 3 (total contents) N = 6 (portion NS) N = 15 (total contents) N = 1 (solid portions) N = 3 (portion NS) N = NS (liquid portion)
Mixed vegetables, glass	Geens *et al* (2010)	Belgium	1.02[e]	N = 1 (solid portion)
Mushroom, can	Noonan *et al* (2011) Cao *et al* (2011) Geens *et al* (2010) Yonekubo *et al* (2009) Sajiki *et al* (2007) Sun *et al* (2006) Lim *et al* (2009) Vinas *et al* (2010) Brotons *et al* (1995)	United States Canada Belgium Japan Japan Singapore S. Korea Spain Spain	13.0[h] 1.17[e] 116.3[e] 1.90[e] 4.0 – 36.0[f] 0.04[h] <2.0[e] < LOD[h] 12.0 (11.7)[h]	N = 1 (3 samples per product) (solid portion) N = 1 (contents prepared) N = 1 (solid portion) N = 1 (total contents) N = 1 (multiple replicates (total contents) N = 2 (portion NS) N = 1 (solid portion) N = 3 (portion NS) N = NS (liquid portion)
Olives, type NS, can	Thomson *et al* (2005) Sajiki *et al* (2007)	New Zealand Japan	<10.0 -23.0[g] 8.0[e]	N = 2 (total contents) N = 1 (multiple replicates) (total contents)
Peas, can[b]	Noonan *et al* (2011) Schecter *et al* (2010) EWG (2007) Braunrath *et al* (2005) Cao *et al* (2011)	United States United States Unites States Austria Canada	3.0 - 310.0[f] 2.65 – 3.97[g] <2.0 – 203.5[g] 8.50 (2.0)[h] 16.8[e]	N = 5 (3 replicates per product)(solid portion) N = 3 (total contents) N = 3 (portion NS) N = 1 (solid portion)

Table 1 – Levels of BPA Detected in Food Items				
Food Type	**Studies**	**Location of Study[a]**	**Observed Levels of BPA (ug/kg)**	**Comments N = # of products (portion measured)**
	Thomson *et al* (2005) Sun *et al* (2006) Vinas *et al* (2010) Garcia-Pieta *et al* (2008)(48) Brotons *et al* (1995) Goodson *et al* (2002)	New Zealand Singapore Spain Spain Spain United Kingdom	<10.0 – 17.0[g] 0.05[h] 317.0 ± 26.0[h] 69.0 ± 1.0[h] 76.3 (29.3)[h] 16.0[h]	N = 1 (contents prepared)(1:1 frozen:can) N = 4 (total contents) N = 2 (portion NS) N = 3 (portion NS) N = 3 (solid portion) N = NS (liquid portion) N = 6 (total contents)
Red cabbage, glass	Geens *et al* (2010)	Belgium	0.10[e]	N = 1 (solid portion)
Red pepper, can	Garcia-Prieta *et al* (2008)	Spain	72.0 ± 3.0[h]	N = 3 (solid portion)
Spinach, can	Noonan *et al* (2011)	United States	23.0[h]	N = 1 (3 replicates)
Tomatoes (includes sauce and paste), can[b]	Noonan *et al* (2011) Schecter *et al* (2010) EWG (2007) Braunrath *et al* (2005) Cao *et al* (2011) Cao *et al* (2010a) Geens *et al* (2010) Rastkari *et al* (2010) Grumetto *et al* (2008)(249) Yonekubo *et al* (2009) Sajiki *et al* (2007) Lim *et al* (2009) Thomson *et al* (2005)	United States United States United States Austria Canada Canada Belgium Iran Italy Japan Japan S. Korea New Zealand	<2 .0 – 43.0[f] <0.20[g] <2.0 – 8.94 20.0 (2.9)[e] 2.59[e] <0.6 – 2.1[g] 19.3[e] <0.30 - 5.12[h] <3.70 - 115.3[g] 6.30 – 14.2[g] 5.0 – 26.0[f] 11.0[e] <10.0 – 21.0[g]	N = 6 (3 samples per product)(solid portion) N = 3 (total contents)(tomato paste) N = 3 (portion NS) N = 1 (total can) N = 1 (contents prepared) N = 6 (tomato paste) N = 1 (tomato paste) N = 12 (tomato paste) N = 12 (tomato paste) N = 42 N = 1 (multiple replicates) (total contents) N = 1 (sauce) N = 5 (total contents)

Table 1 – Levels of BPA Detected in Food Items				
Food Type	**Studies**	**Location of Study[a]**	**Observed Levels of BPA (ug/kg)**	**Comments N = # of products (portion measured)**
	Brotons *et al* (1995) Goodson *et al* (2002)	Spain United Kingdom	<LOD[h] 26.0 – 27.0[f]	N = NS (liquid portion) (LOD NS) N = 6 (total contents)
Tomatoes, plastic	Geens *et al* (2010)	Belgium	0.11[e]	N = 1 (Tetra Pak) (solid portion)
Vegetables, type NS, can	Mariscal-Arcas *et al* (2009)(43)	Spain	7.88 (12.48) ug/L[h]	N = 20 (portion unclear)
Wax beans, can	Noonan *et al* (2011)	United States	140.0[e]	N = 1 (3 samples per product) (solid portion)
Fruits				
Applesauce, can	Cao *et al* (2011) Geens *et al* (2010)	Canada Belgium	<0.38[e] 0.20[e]	N = 1 N = 1 (solid portion)
Apricots, can	Cao *et al* (2011) Thomson *et al* (2005)	Canada New Zealand	0.57[e] <10.0[g]	N = 1 (portion NS) N = 4 (total contents)
Cherries, can	Cao *et al* (2011)	Canada	3.24[e]	N = 1 (portion NS)
Cranberry sauce, can	EWG (2007)	United States	<2.0[g]	N = 3 (portion NS)
Grapes, can	Sajiki *et al* (2007) Lim *et al* (2009)	Japan S. Korea	 8.48[e]	N = 1 (multiple replicates) (total contents) N = 1 (total contents)
Lychee, can	Braunrath *et al* (2005)	Austria	6.8 (2.6)[h]	N = 1 (total contents)
Mango, can	Braunrath *et al* (2005) Sun *et al* (2006) Garcia-Prieta *et al* (2008)	Austria Singapore Spain	24.0 (4.0)[h] 0.16[h] 24.4 ± 0.7[h]	N = 1 (total contents) N = 2 (portion NS) N = 3 (solid portion)
Mixed fruit, can[b]	Noonan *et al* (2011) EWG (2007) Geens *et al* (2010)	United States United States Belgium	<2.0 – 19.0[f] <2.0 – 10.6[g] 17.0[e]	N = 5 (3 samples per product) (solid portion) N = 6 (portion NS) N = 1 (solid portion)

Table 1 – Levels of BPA Detected in Food Items

Food Type	Studies	Location of Study[a]	Observed Levels of BPA (ug/kg)	Comments N = # of products (portion measured)
	Garcia-Prieta *et al* (2008)	Spain	7.8 ± 0.2[h]	N = 3 (solid portion)
	Thomson *et al* (2005)	New Zealand	<10.0[g]	N = 3 (total contents)
	Lim *et al* (2009)	S. Korea	<2.0[g]	N = 9 (total contents)
	Goodson *et al* (2002)	United Kingdom	19.0 – 38.0[f]	N = 8 (total contents)
Peaches, can[b]	Noonan *et al* (2011)	United States	<2.0 – 9.3[f]	N = 5 (solid portion)
	EWG (2007)	United States	<2.0 – 7.43[g]	N = 2 (portion NS)
	Braunrath *et al* (2005)	Austria	6.4 (0.70)[h]	N = 1 (total contents)
	Cao *et al* (2011)	Canada	<0.38[e]	N = 1 (portion NS)(1:1 ratio of raw:canned)
	Geens *et al* (2010)	Belgium	20.0[e]	N = 1 (solid portion)
	Thomson *et al* (2005)	New Zealand	<10.0[g]	N = 4 (total contents)
	Sajiki *et al* (2007)	Japan	< 0.20 ug/L[h]	N = 1 (multiple replicates) (total contents)
	Lim *et al* (2009)	S. Korea	4.14 – 54.6[g]	N = 1 (total contents)
	Garcia-Prieta *et al* (2008)	Spain	10.3 ± 0.2[h]	N = 3 (solid portion)
Pears, can	EWG (2007)	United States	<2.0 – 26.9[g]	N = 3
	Geens *et al* (2010)	Belgium	10.1[e]	N = 1 (solid portion)
Pineapple, can[b]	Noonan *et al* (2011)	United States	<2 .0 – 13.0[f]	N = 5 (3 samples per product) (solid portion)
	Schecter *et al* (2010)	United States	<0.20[g]	N = 3
	EWG (2007)	United States	<2.0 – 26.9[g]	N = 1 (portion NS)
	Braunrath *et al* (2005)	Austria	5.0 (1.2)[h]	N = 1 (total contents)
	Cao *et al* (2011)	Canada	1.20[e]	N = 1 (portion NS)
	Thomson *et al* (2005)	New Zealand	<10.0[g]	N = 4 (total contents)
	Sajiki *et al* (2007	Japan	<0.20 ug/L[h]	N = 1 (multiple replicates) (total contents)
	Sun *et al* (2006)	Singapore	0.03[h]	N = 2 (portion NS)
	Lim *et al* (2009)	S. Korea	<2.0[e]	N = 1 (total contents)
Pineapple, glass	Geens *et al* (2010)	Belgium	1.23[e]	N = 1 (solid portion)
Pineapple, plastic	Geens *et al* (2010)	Belgium	0.11[e]	N = 1 (solid portion)

Table 1 – Levels of BPA Detected in Food Items				
Food Type	**Studies**	**Location of Study[a]**	**Observed Levels of BPA (ug/kg)**	**Comments N = # of products (portion measured)**
Plums and prunes, can	Cao *et al* (2011)	Canada	0.62[e]	N = 1 (portion NS)(1:1 ratio of raw:canned)
Raisins	Cao *et al* (2011)	Canada	0.51[e]	N = 1
Strawberries, fresh	Cao *et al* (2011) Sajiki *et al* (2007)	Canada Japan	<0.38[e] 2.0[h]	N = 1 N = 1 (multiple replicates)
Dairy				
Butter	Cao *et al* (2011)	Canada	0.53[e]	N = 1
Cheese	Cao *et al* (2011)	Canada	2.24[e]	N = 1
Cheese, processed	Cao *et al* (2011)	Canada	0.68[e]	N = 1
Cream, paper	Sajiki *et al* (2007)	Japan	0.20 – 1.0[f]	N = 1 (multiple replicates) (total contents)
Evaporated milk, can	Schecter *et al* (2010) EWG (2007) Cao *et al* (2011) Maragou *et al* (2006)(250) Goodson *et al* (2002)	United States United States Canada Greece United Kingdom	<0.20[g] <2.0 – 9.0[g] 15.3[e] <1.7 – 15.2ug/L[g] 11.0 – 14.0[f]	N = 3 N = 3 N = 1 N = 8 N = 6 (total contents)
Yogurt, paper	Cao *et al* (2011) Sajiki *et al* (2007)	Canada Japan	<0.20[e] 0.30[h]	N = 1 N = 1 (multiple replicates) (total contents)
Meat and Fish				
Anchovies, can	Geens *et al* (2010)	Belgium	0.90[e]	N = 1 (solid portion)
Anchovies, glass	Geens *et al* (2010)	Belgium	0.67[e]	N = 1 (solid portion)
Beef, can	Schecter *et al* (2010) Sajiki *et al* (2007)	United States Japan	0.80 – 1.71[g] 9.0 – 10.0[f]	N = 3 (total contents) N = 1 (multiple replicates) (total contents)
Beef, fresh, all types	Cao *et al* (2011) Sajiki *et al* (2007)	Canada Japan	<0.38[g] 0.20[h]	N = 3 N = 1 (multiple replicates) (total contents)

Table 1 – Levels of BPA Detected in Food Items

Food Type	Studies	Location of Study[a]	Observed Levels of BPA (ug/kg)	Comments N = # of products (portion measured)
Chicken, can	Schecter *et al* (2010)(42) Sajiki *et al* (2007)	United States Japan	0.82 – 0.88[g] 4.0[h]	N = 3 (total contents) N = 1 (multiple replicates) (total contents)
Cod liver, can	Poustka *et al* (2007)	Czech Republic	<3.0 – 94.0	N = 7 (total contents)
Corned beef, can	Goodson *et al* (2002)	United Kingdom	59.0 – 70.0[f]	N = 9 (total contents)
Crab, can	Lim *et al* (2009)	S. Korea	<2.0 – 23.4[g]	N = 2 (solid portion)
Ham, can	Goodson *et al* (2002)	United Kingdom	35.4 – 42.2[f]	N = 9 (total contents)
Fish, type NS, can[b]	Cao *et al* (2011) Mariscal-Arcas *et al* (2009)	Canada Spain	106.0[e] 12.6 (6.6) ug/L[h]	N = 1 (portion NS) N = 10 (portion unclear)
Fish, marine	Cao *et al* (2011)	Canada	0.48[e]	N = 1 (portion NS)
Luncheon meat, can	Cao *et al* (2011) Poustka *et al* (2007)(50) Sun *et al* (2006)	Canada Czech Republic Singapore	10.5[e] <3.0 – 51.1[g] 0.14[h]	N = 1 (portion NS) N = 11 (total contents) N = 2 (portion NS)
Mackerel, can	Noonan *et al* (2011) Podlipna *et al* (2007)(49) Poustka *et al* (2007) Sajiki *et al* (2007) Lim *et al* (2009) Bendito *et al* (2009)(251) Goodson *et al* (2002)	United States Austria Czech Republic Japan S. Korea Spain United Kingdom	22.0[h] 0.2 – 0.4[g] <3.0 – 102.3[g] 3.0[h] 32.5 - 123.1[g] 20.0 ± 5.0[h] <7.0[h]	N = 1 (3 samples per product) (solid portion) N = 2 (oil and brine)(solids) N = 10 (total contents) N = 1 (multiple replicates) (total contents) N = 3 (solid portion)(in tomato sauce) N = 3 (solid portion)(oil) N = 1 (total contents)
Meatballs, can	Bendito *et al* (2009)	Spain	< 9.0	N = 3
Meat, type NS, canned	Mariscal-Arcas *et al* (2009) Thomson *et al* (2005) Lim *et al* (2009) Goodson *et al* (2002)	Spain New Zealand S. Korea United Kingdom	10.9 (10.8) ug/L[h] <20.0 – 98.0[g] <2.0 – 51.0[g] 52.0 – 53.0[f]	N = 5 (portion unclear) N = 6 (total contents) N = 13 (solid portion) N = 6 (total contents)(chicken and ham in

Table 1 – Levels of BPA Detected in Food Items				
Food Type	**Studies**	**Location of Study[a]**	**Observed Levels of BPA (ug/kg)**	**Comments N = # of products (portion measured)**
				sauce
Mussels, can	Lim *et al* (2009) Bendito *et al* (2009)	S. Korea Spain	11.0[e] 121.0 ± 2.0[h]	N = 1 (solid portion) N = 3 (solid portion)
Oyster, smoked, can	Lim *et al* (2009)	S. Korea	44.7[e]	N = 1 (solid portion)
Pate, can	Poustka *et al* (2007)	Czech Republic	<3.0 – 70.7	N = 16 (total contents)
Pork, can	Sajiki *et al* (2007)(56) Sun *et al* (2006) Bendito *et al* (2009) Goodson *et al* (2002)	Japan Singapore Spain United Kingdom	10.0 – 20.0[f] 0.04[h] 37.0 ± 5.0[h] 16.0 – 17.0[f]	N = 2 (multiple replicates) (total contents) N = 2 N = 3 N = 6 (total contents)
Salmon, can[b]	Geens *et al* (2010) Thomson *et al* (2005) Sajiki *et al* (2007) Lim *et al* (2009) Goodson *et al* (2002)	Belgium New Zealand Japan S. Korea United Kingdom	3.40[e] <20.0 – 24.0[g] 1.0 – 13.0[f] <2.0 – 27.4[g] 10.0 – 18.0[f]	N = 1 (solid portion) N = 4 (solid portion) N = 2 (multiple replicates) (total contents) N = 2 (solid portion) N = 24 (total contents)
Sardines, can	Podlipna *et al* (2007) Braunrath *et al* (2005) Poustka *et al* (2007) Bendito *et al* (2009) Goodson *et al* (2002)	Austria Austria Czech Republic Spain United Kingdom	0.2 – 1.4[g] 2.1 (0.3)[h] <3.0 – 203.0[g] 119.0 ± 5.0[h] 13.0 – 32.0[f]	N = 5 (oil) (solid portion) N = 1 (solid portion) (oil) N = 21 (multiple years) (total contents) N = 3 (oil) (solid portion) N = 15 (total contents) (in tomato sauce)
Saury, can	Lim *et al* (2009)	S. Korea	21.4 – 125.3[f]	N = 3 (solid contents)
Shellfish, can	Cao *et al* (2011)	Canada	0.89[e]	N =1 (portion NS)
Tuna, oil and water pack, can[d]	Noonan *et al* (2011) Schecter *et al* (2010) EWG (2007) Podlipna *et al* (2007)	United States United States United States Austria	5.80 – 17.0[f] <0.20 – 3.77[g] <2. 0 – 108.0[g] 0.9 – 7.7[f]	N = 5 (3 samples)(water and oil) (solid portion) N = 6 (total contents) (water) N = 6 (portion NS) (water/oil NS)

Table 1 – Levels of BPA Detected in Food Items				
Food Type	**Studies**	**Location of Study[a]**	**Observed Levels of BPA (ug/kg)**	**Comments N = # of products (portion measured)**
	Braunrath *et al* (2005) Cao *et al* (2010a) Poustka *et al* (2007) Geens *et al* (2010) Thomson *et al* (2005) Sajiki *et al* (2007) Lim *et al* (2009) Bendito *et al* (2009) Goodson *et al* (2002)	Austria Canada Czech Republic Belgium New Zealand Japan S. Korea Spain United Kingdom	43.0 (6.4)[h] 9.0 – 534.0[g] <3.0 – 138.4[g] 126.4 –169.3[g] <20.0 – 109.0[g] 2.0 – 23.0[f] <3.0 – 116.9[g] 129.0 ± 6.0[h] 26.0 – 31.0[f]	N = 10 (oil and brine) (solid portion) N = 1 (portion NS) N = 15 (total contents)(water/oil NS) N = 13 (total contents) N = 1 (solid portion) (water and oil) N = 4 (solid portion)(water/oil NS) N = 4 (multiple replicates) (total contents) N = 8 (solid contents) N = 3 (solid portion) (oil) N = 9 (total contents)(brine)
Tuna, mixed dish, can	Sun *et al* (2006) Goodson *et al* (2002)	Singapore United Kingdom	0.11[h] 41.0 – 44.0[f]	N = 2 (portion NS) N = 6 (total contents)
Wieners and sausages, can	Cao *et al* (2011) Geens *et al* (2010) Goodson *et al* (2002)	Canada Belgium United Kingdom	0.48[e] 26.7[e] 21.0 – 33.0[f]	N = 1 (portion NS) N = 1 (solid portion) N = 6 (total contents)
Wieners and sausages, glass	Geens *et al* (2010)	Belgium	0.86[e]	N = 1 (solid portion)
Grains				
Cereals (rice and bran)	Cao *et al* (2011)	Canada	0.65[e]	N = 1
Rye bread	Cao *et al* (2011)	Canada	1.73[e]	N = 1
White bread	Cao *et al* (2011)	Canada	0.40[e]	N = 1

Table 1 – Levels of BPA Detected in Food Items

Food Type	Studies	Location of Study[a]	Observed Levels of BPA (ug/kg)	Comments N = # of products (portion measured)
While flour (wheat)	Cao *et al* (2011)	Canada	0.44[e]	N = 1
Beverages				
Apple juice, can	Schecter *et al* (2010) Cao *et al* (2011)	United States Canada	0.46 – 0.48[g] 0.35[e]	N = 3 N =1
Beer, can	Braunrath *et al* (2005) Cao *et al* (2011) Cao *et al* (2010b)(252) Geens *et al* (2010) Goodson *et al* (2002)	Austria Canada Canada Belgium United Kingdom	1.50 ug/L[h] 0.20[e] 0.08 – 0.54 ug/L[g] 0.16-0.56 ug/L[g] <7.0[h]	N = 1 N = 1 (1:1 ratio of bottle:can(9)) N = 8 N = 7 N = 18
Coffee, can	Cao *et al* (2011) Kang *et al* (2002)(253) Lim *et al* (2009)	Canada Japan S. Korea	0.22[e] 33.0 – 134.0[g] 11.7 – 136.1[g]	N = 1 (Unclear if prepared or beans) N = 30 (Instant coffee) N = 5 (Unclear if prepared or beans)
Coffee, plastic	Sajiki *et al* (2007)	Japan	0.30 – 1.0[f]	N = 2 (multiple replicates) (total contents)
Dry/Hard Cider, can	Goodson *et al* (2002)	United Kingdom	<7.0[h]	N = 3
Energy drinks, can	Braunrath *et al* (2005) Cao *et al* (2009) Geens *et al* (2010)	Austria Canada Belgium	<0.90 – 3.4ug/L[f] <0.045 – 4.5 ug/L[g] 0.16-4.79 ug/L[g]	N = 2 N =12 N = 4
Fruit juice, type NS, can	Mariscal-Arcas *et al* (2009)	Spain	3.85 (12.48) ug/L[h]	N = 20
Mixed fruit juice, can	Geens *et al* (2010)	Belgium	0.80-0.05 ug/L[g]	N = 2
Orange	Geens *et al* (2010)	Belgium	3.96 ug/L[e]	N = 1

Table 1 – Levels of BPA Detected in Food Items				
Food Type	**Studies**	**Location of Study[a]**	**Observed Levels of BPA (ug/kg)**	**Comments N = # of products (portion measured)**
juice, can				
Soft drinks, can	EWG (2007) Braunrath *et al* (2005) Cao *et al* (2011) Cao *et al* (2010b) Cao *et al* (2009) Geens *et al* (2010) Thomson *et al* (2005) Goodson *et al* (2002)	United States Austria Canada Canada Canada Belgium New Zealand United Kingdom	<2.0 – 8.21[g] 0.10 – 0.70ug/L[f] 0.32[e] 0.02 – 0.20 ug/L[g] 0.032 – 2.23ug/L[g] <0.02 –8.1 ug/L[g] <10.0[g] <7.0[h]	N = 12 N = 4 N = 1 N = 10 N = 54 N = 20 (Most were below 1ug/L) N = 4 N = 27 (5 types)
Sport drinks, can	Geens *et al* (2010)	Belgium	1.12-2.00 ug/L[g]	N = 3
Tonic water, can	Cao *et al* (2009) Geens et al (2010)	Canada Belgium	<0.045 ug/L[g] 0.06 ug/L[e]	N = 2 N = 1
Tea, any type, can	Cao *et al* (2011) Cao *et al* (2009) Geens *et al* (2010) Lim *et al* (2009)	Canada Canada Belgium S. Korea	<0.20[e] 0.075 – 0.63 ug/L[g] 0.66 – 0.88 ug/L[g] <2.0 – 14.3[g]	N = 1 (Unclear if canned) N = 4 N = 4 N = 3
Vegetable juice, can	Schecter *et al* (2010) Cao *et al* (2011) Yonekubo *et al* (2009)	United States Canada Japan	0.71 – 0.80[g] 0.53[e] <0.30 ug/L[g]	N = 3 N = 1 N = 2
Wine, carton	Brenn-Struckhofova (2006)(53)	Austria	<0.20 – 1.0 ug/L[g]	N = 11 (Tetra-Brik)(white)
Wine, glass	Brenn-Struckhofova (2006) Cao *et al* (2011)	Austria Canada	<0.20 – 1.6 ug/L[g] 0.74[e]	N = 17 (red + white, detected in vat) N = 1
Other				

Table 1 – Levels of BPA Detected in Food Items				
Food Type	**Studies**	**Location of Study[a]**	**Observed Levels of BPA (ug/kg)**	**Comments N = # of products (portion measured)**
Baked potato (w/skin)	Cao *et al* (2011)	Canada	0.82[e]	N = 1
Baking powder	Cao *et al* (2011)	Canada	0.64[e]	N = 1
Beans, baked, can[b]	Noonan *et al* (2011) Geens *et al* (2010) Thomson *et al* (2005) Sun *et al* (2006) Lim *et al* (2009) Goodson *et al* (2002)	United States Belgium New Zealand Singapore S. Korea United Kingdom	12.0 – 46.0[f] 1.30[e] <10.0[g] 0.04[h] <2.0 – 4.69[h] 9.0 – 14.0[f]	N = 2 (3 samples per product) (solid portion) N = 1 (solid portion)(Haricot beans and sauce) N = 4 (solid portion) N = 2 (potion NS) N = 4 (solid portion) N = 9 (total contents)
Beans, refried, can[b]	Noonan *et al* (2011)	United States	10 – 790.0[f]	N = 4 (3 samples per product) (solid portion)
Beans, sweet red, can	Lim *et al* (2009)	S. Korea	<2.0[e]	N = 1
Beans, type NS or plain, can	Braunrath *et al* (2005) Mariscal-Arcas *et al* (2009)	Austria Spain	26.0 – 35.0[f] 24.57 (17.1) ug/L[h]	N = 2 (solid portion) N = 10 (portion unclear)
Beef chow mein (carry-out)	Cao *et al* (2011)	Canada	1.93[e]	N = 1
Broth, canned	Noonan *et al* (2011) Sajiki *et al* (2007)	United States Japan	13.0[h] 6.0 – 9.0[f]	N = 1 (3 replicates per product) (total contents) N = 2 (multiple replicates) (total contents)
Chicken	Cao *et al* (2011)	Canada	1.45[e]	N = 1

Table 1 – Levels of BPA Detected in Food Items				
Food Type	**Studies**	**Location of Study[a]**	**Observed Levels of BPA (ug/kg)**	**Comments N = # of products (portion measured)**
burgers (whole sandwich-restaurant)				
Chili, can[b]	Noonan *et al* (2011) Schecter *et al* (2010)	United States United States	30.0 – 150.0[f] 3.47 – 5.59[g]	N = 10 (3 replicate per product)(total contents) N = 3 (total contents)
Coconut cream or milk, can	Braunrath *et al* (2005) Thomson *et al* (2005) Yonekubo *et al* (2009) Sajiki *et al* (2007) Lim *et al* (2009)	Austria New Zealand Japan Japan S. Korea	29.7 (1.5)[h] <20.0 – 192.0[g] 27.0[e] 56.0 – 247.0[f] 6.94[e]	N = 1 N = 3 N = 1 N = 2 (multiple replicates) (total contents) N = 1
Cookies, plastic	Sajiki *et al* (2007)	Japan	1.0 – 14.0[f]	N = 4 (multiple replicates) (total contents)
Custard, can	Goodson *et al* (2002)	United Kingdom	<7.0[h]	N = 3 (total contents)
Fast food sandwiches (type NS)	Cao *et al* (2011) Sajiki *et al* (2007)	Canada Japan	1.61[e] 3.0[h]	N = 1 N = 1 (multiple replicates) (total contents)
French fries	Cao *et al* (2011)	Canada	1.10[e]	N = 1
Frozen/ microwave meals	Cao *et al* (2011) Mariscal-Arcas *et al* (2009)	Canada Spain	2.02[e] 1.33 (0.82) ug/L[h]	N = 1 N = 20 (portion NS)
Hamburgers (whole sandwich-	Cao *et al* (2011)	Canada	10.9[e]	N = 1

Table 1 – Levels of BPA Detected in Food Items				
Food Type	**Studies**	**Location of Study[a]**	**Observed Levels of BPA (ug/kg)**	**Comments N = # of products (portion measured)**
restaurant)				
Hot dogs (includes bun-restaurant)	Cao *et al* (2011)	Canada	2.32[e]	N = 1
Honey, plastic	Cao *et al* (2011)	Canada	0.50[e]	N = 1
Meat sauce, can	Yonekubo *et al* (2009) Sajiki *et al* (2007) Sun *et al* (2006)	Japan Japan Singapore	4.40[e] <0.20 ug/L – 13.0[f] 0.05[h]	N = 1 (total contents) N = 3 (multiple replicates) (total contents) N = 2 (portion NS)
Pasta, in sauce, can (includes ravioli)[b]	Noonan *et al* (2011) Schecter *et al* (2010) EWG (2007) Cao *et al* (2010a) Geens *et al* (2010) Thomson *et al* (2005) Goodson *et al* (2002)	United States United States United States Canada Belgium New Zealand United Kingdom	10.0 – 62.0[f] <0.20[g] 16.2 – 247.0g 32.0[e] 73.1[e] <10.0[g] < 7.0 – 41.0[f]	N = 11 (3 replicates per sample)(total contents) N = 3 (total contents) N = 6 (portion NS) N = 1 (total contents) N = 1 (solid portion) N = 4 (solid portion) N = 21 (solid portion)
Pasta in sauce, glass	Geens *et al* (2010)	Belgium	0.27[e]	N = 1 (solid portion)
Pasta, in sauce, plastic	Schecter *et al* (2010) Sajiki *et al* (2007)	United States Japan	4.31 – 5.04[g] <0.20 ug/L[h]	N = 3 (total contents) N = 1 (multiple replicates) (total contents)
Pickles, glass	Geens *et al* (2010)	Belgium	0.27[e]	N = 1 (solid portion)
Potatoes,	Goodson *et al* (2002)	United Kingdom	48.0[h]	N = 3 (solid portion)

Table 1 – Levels of BPA Detected in Food Items				
Food Type	**Studies**	**Location of Study[a]**	**Observed Levels of BPA (ug/kg)**	**Comments N = # of products (portion measured)**
can				
Rice pudding, can	Goodson *et al* (2002)	United Kingdom	10.0 – 13.0[f]	N = 9 (solid portion)
Sandwich, tuna, pre-made	Sajiki *et al* (2007)	Japan	<0.20 ug/L – 8.0[f]	N = 6 (multiple replicates) (total contents)
Sauces, type NS, can	Thomson *et al* (2005) Yokenubo *et al* (2009) Sajiki *et al* (2007)	New Zealand Japan Japan	<10.0 – 21.0[g] 0.90 – 55.5[g] 428.0 – 842.0[f]	N = 4 (total contents) N = 6 N = 2 (multiple replicates) (total contents)
Soup, cream, can	Noonan *et al* (2011) Braunrath *et al* (2005) Geens *et al* (2010) Sajiki *et al* (2007) Goodson *et al* (2002)	United States Austria Belgium Japan United Kingdom	32.0[h] 9.60 – 20.7[f] 25.4[e] 1.0 – 156.0[f] <7.0 – 10.0[f]	N = 1 (3 replicates)(total contents) N = 2 (total contents) N = 1 (solid portion) N = 4 (multiple replicates) (total contents) N = 24 (total contents)
Soup, meat, can	Noonan *et al* (2011) Schecter *et al* (2010) EWG (2007) Braunrath *et al* (2005) Sajiki *et al* (2007) Goodson *et al* (2002)	United States United States United States Austria Japan United Kingdom	54.0 – 110.0[f] <0.20 – 7.05[g] <2.0 – 385.0[g] 9.60 – 22.0[f] 2.0 – 77.0[f] <7.0 – 21.0[f]	N = 3 (3 replicates per sample) (total contents) N = 12 (total contents) N = 11 N = 2 (total contents) N = 3 (multiple replicates) (total contents) N = 2 (total contents)
Soup, type NS or other, can	EWG (2007) Braunrath *et al* (2005) Cao *et al* (2010) Thomson *et al* (2005)	United States Austria Canada New Zealand	<15.0 – 191.0[g] 17.0 – 37.6[f] 4.1 – 189.0[g] <10.0 – 16.0[g]	N = 3 (portion NS) N = 2 (total contents) N = 1 (total contents) N = 6 (total contents)
Soup, vegetable,	Noonan *et al* (2011) Schecter *et al* (2010)	United States United States	63.0[h] 7.28 – 22.7[g]	N = 1 (3 samples) (total contents) N = 9 (total contents)

Table 1 – Levels of BPA Detected in Food Items

Food Type	Studies	Location of Study[a]	Observed Levels of BPA (ug/kg)	Comments N = # of products (portion measured)
can	EWG (2007) Geens *et al* (2010) Sajiki *et al* (2007) Goodson *et al* (2002)	United States Belgium Japan United Kingdom	78.2 – 176.0[g] 11.9 – 29.3[g] 48.0[h] <7.0 – 21.0[f]	N = 4 (portion NS) N = 1 (solid portion) N = 1 (multiple replicates) (total contents) N = 18 cans (total contents)
Soup, vegetable, paper	Geens *et al* (2010)	Belgium	0.37[e]	N = 1 (solid portion)
Soup, vegetable, plastic	Geens *et al* (2010) Sajiki *et al* (2007)	Belgium Japan	0.12 – 0.21[g] 3.0[h]	N = 1 (solid portion) N = 1 (multiple replicates) (total contents)
Soy sauce	Cao *et al* (2011)	Canada	0.70[e]	N =1
Sponge pudding, can	Goodson *et al* (2002)	United Kingdom	<7.0[h]	N = 6 (total contents)
Weight loss drink, can	EWG (2007) Cao *et al* (2011) Sajiki *et al* (2007)	United States Canada Japan	<2.0 – 65.5[g] <0.20[e] <0.20[h]	N = 5 (portion NS) N = 1 N = 1 (multiple replicates)
White chocolate, plastic	Sajiki *et al* (2007)	Japan	1.0[h]	N = 1 (multiple replicates) (total contents)
Yeast	Cao *et al* (2011)	Canada	8.52[e]	N =1

[a] Products were bought within these countries, but these countries are not necessarily the country of origin for the food items.

[b] Nielson data from 2007 – 2009 most commonly consumed canned goods in US. Food item(% of canned diet): green beans (6.9%), corn (5.5%), tomatoes (0.6%), peas (1.2%), mixed fruit (4.1%), pineapple (3.6%), peaches (5.8%), ravioli (7.4%), pork and beans/baked beans (7.1%), chili (8.3%), refried beans (4.5%), pasta (4.2%), fish (0.4%), soups (0.9%).(41)

[c] Levels did not differ by different product types such as low/no salt or organic.

[d] Studies that individually assessed oil and water packed did not observe highly different levels between the packing medium (41).

[e] Single measurement.

[f] Range of means from multiple different product samples.

[g] Range of values single measurements from multiple product samples.

Table 1 – Levels of BPA Detected in Food Items				
Food Type	**Studies**	**Location of Study[a]**	**Observed Levels of BPA (ug/kg)**	**Comments N = # of products (portion measured)**

[h] Mean (Standard Deviation).
[i] Levels did not differ substantially between condensed and ready-to-eat.
Abbreviations: kg = kilograms, L = liters, ug = micrograms, ND = not detected.

Table 2-List of Food Items with BPA Levels were below the LOD or LOQ
Vegetables
Asparagus, fresh/frozen(9)
Broccoli, fresh/frozen(9)
Brussels sprouts, fresh/frozen Cabbage, fresh/frozen(9)
Carrots, fresh/frozen(9)
Celery, fresh(9)
Cucumbers, fresh(9)
Green beans, frozen(9)
Lettuce, fresh(9)
Onions, fresh(9)
Peppers, can(32)
Peppers, fresh(9)
Rutabagas, fresh(9)
Spinach, fresh/frozen(9)
Tomatoes , fresh(9)
Fruits
Apples, fresh(9)
Applesauce, plastic(9)
Bananas, fresh(9)
Blueberries, fresh/frozen(9)
Citrus fruit, fresh(9)
Grapes, fresh(9)
Kiwi fruit, fresh(9)
Melons, fresh(9)
Pears, fresh(9)
Raspberries, fresh/frozen(9)
Dairy
Buttermilk, container NS(9)
Chocolate milk , 1%, container NS(9)
Cottage cheese, container NS(9)
Cream, container NS(9)
Ice cream, container NS(9)
Milk, 1%, container NS(9)
Milk, 2%, container NS(9)
Milk, whole, container NS(9)
Milk, type NS, paper(56)
Meat, Eggs and Fish
Chicken(9)
Cold cuts(9)
Eggs(9)
Fish, fresh water(9)
Luncheon meats (non-canned)(9)
Organ meat(9)
Pork, fresh(9)
Pork, cured(9)
Tuna, fresh(56)
Turkey(9)

Veal, cutlets(9)
Grains
Bread, whole wheat(9)
Breads, other(9)
Buns and rolls(9)
Cake(9)
Cereal, cooked wheat(9)
Cereal, corn(9)
Cookies(9)
Crackers(9)
Croissants(9)
Danish(9)
Donuts(9)
Oatmeal(9)
Pasta, dry(9)
Pie, apple(9)
Pie, other(9)
Rice(9)
Beverages
Beer, glass
Citrus juice, frozen/canned/plastic
Orange juice, paper(56)
Sake, paper(56)
Soy milk, container NS(9)
Vegetable juice, paper(56)
Water, mineral, plastic(9)
Water, natural spring, plastic(9)
Water, tap(9)
Other
Chewing gum(9)
Chicken nuggets(9)
Condiments(9)
Fried rice(9)
Gelatin desserts(9)
Herbs and spices(9)
Jams(9)
Microwave popcorn(9)
Nuts(9)
Pasta (mixed dish, non-canned)(9)
Peanut butter(9)
Pizza(9)
Potato, peeled, boiled(9)
Potato chips(9)
Puddings(9)
Pumpkin seeds, plastic(56)
Sauce, plastic(56)
Salt(9)
Soup, cream, plastic(56)
Syrup(9)

Vanilla extract(9) White sugar(9)

Appendix 2: Eligibility Screening Interview

Staff initials:
Interview Date (month/day/year):
Screening Number:

"Hi, is this <<PARTICIPANT NAME>> ? "

If no: "Is <<PARTICIPANT NAME>> available to talk?

If yes: continue with script.

If no: Ask if the person on the phone knows a better time to reach the participant, thank them and indicate you will call back at a later time.

If yes: "Hi, my name is <<YOUR NAME>> and I am calling in response to your message regarding the Urinary Biomarkers of Dietary Intake Study at the University of Minnesota. Are you still interested in participating in this study and is now a good time to talk?"

If not interested: Thank you for your time and have a great day.

If not a good time: When would be a better time to call? (Make note of time on contact log) Great, we will trying calling back at that time.

If yes: Continue with script.

Briefly describe the study:

"The purpose of the Urinary Biomarkers of Dietary Intake Study is to improve researchers' ability to study diet and health outcomes by evaluating chemicals in the urine as markers of dietary intake. For this study you will be asked to fill out questionnaires, attend two study visits, collect urine samples, record your food and beverage intake, and provide a DNA sample. From start to finish your time in this study should not take more than 6 hours over a two week time period and you will be compensated for your time while participating in this study."

"Would you be interested in participating in this study if you meet the inclusion criteria?"

If no: "Would you be willing to share your reason for declining to participate?"

Record reason if willing to share:

"Thank you for your time."

If yes: "Great. I am going to ask you some questions to evaluate whether you are eligible for this study."

1. Where did you hear about the study?	☐ 1. newspaper ad ☐ 2. flyer ☐ 3. friend ☐ 4. family ☐5. other: _____
2. What is your date of birth?	Date of Birth: ☐☐/☐☐/☐☐ Month Day Year If < 20 years or >59 years (not eligible)*
3. Sex (For female) a. Are you pregnant or plan to be pregnant in the next 12 months? b. Are you currently breastfeeding your baby?	☐ Male ☐ Female ☐ Yes* ☐ No ☐ Yes* ☐ No
4. Do you currently smoke or are you a former smoker who has quit in the past 6 months?	☐ Yes* ☐ No
5. What county do you live in?	_____ If does not live in one of the following seven-metro area counties: Anoka, Carver, Dakota, Hennepin, Ramsey, Scott, and Washington then exclude.*
6. Do you currently live in a dormitory?	☐ Yes* ☐ No
7. Are you able to provide informed consent?	☐ Yes ☐ No*
8. Are you able to read and speak English?	☐ Yes ☐ No*
9. Have you ever had cancer, excluding non-melanoma skin cancer?	☐ Yes* ☐ No
10. Have you ever been diagnosed with heart disease or had a heart attack?	☐ Yes* ☐ No
11. Have you ever had a stroke?	☐ Yes ☐ No
12. What is your approximate height?	☐ Feet ☐☐ Inches
13. What is your approximate weight?	☐☐☐ lbs.
14. Have you had any weight loss of more than 10lbs. in the past six months? If so, how much weight have you lost?	☐ Yes ☐ No If yes, ☐☐ lbs.

If any answer corresponds to an asterix the participant is not eligible:

If not eligible: "Unfortunately, you do not meet the inclusion criteria for this study. Thank you very much for your time and participation.

If meet these criteria: continue with next module.

"I am now going to ask you a series of questions related to your diet. Please answer as best you can."

	Never or less than once per week	1 – 2 days/week	3 – 4 days/week	5 or more days/week
15. How many days per week do you eat fresh or frozen fruits?	☐	☐	☐	☐
16. How many days per week do you typically eat fruits from a metal can?	☐ 0 Points	☐ 3 Points	☐ 6 Points	☐ 12 Points
17. How many days per week do you typically eat fresh or frozen vegetables?	☐	☐	☐	☐
18. How many days per week do you typically eat vegetables from a metal can?	☐ 0 Points	☐ 3 Points	☐ 6 Points	☐ 12 Points
19. How often do you typically consume soup that you make from scratch?	☐	☐	☐	☐
20. How often do you typically consume soup from a can?	☐ 0 Points	☐ 3 Points	☐ 6 Points	☐ 12 Points
21. How many days per week do you typically eat lunch at a restaurant (any type) or cafeteria?	☐ 0 Points	☐ 1 Point	☐ 2 Points	☐ 5 Points
22. How many days per week do you or someone in your home prepare dinner?	☐	☐	☐	☐
23. How many days per week do you typically eat dinner out, such as at a restaurant?	☐ 0 Points	☐ 1 Point	☐ 2 Points	☐ 5 Points
24. How often do you eat prepackaged frozen meals?	☐	☐	☐	☐

25. How often do you eat prepackaged meals from a can, such as chili or pasta in sauce?	☐ 0 Points	☐ 3 Points	☐ 6 Points	☐ 12 Points

0 – 3 Points → Group 1
4 – 9 Points → Group 2
9 – 11 Points → Group 3
12+ Points → Group 4

Check study ledger to verify if there is a spot in the corresponding Study Group.

If spot is available continue on to final set of questions.

If not spot available: Unfortunately, we have filled all the spots for participates with your criteria. Would you like us to add you to the wait list for this group in case another participant drops-out?

If wait list is full: Unfortunately, we have filled all the sports for participants with your criteria. Thank you for your time and interest in this study. Have a great day.

IF ELIGIBLE:	
Are you able and willing to commit to 2 study visits and 3 days of data collection between July and September?	☐ Yes ☐ No
Are you willing to collect 3 urine samples on each of three days, including two week days (Tuesday and Thursday) and one on Saturday?	☐ Yes ☐ No
49. Are you willing to collect three full days of food records?	☐ Yes ☐ No
50. Are you willing to complete two questionnaires?	☐ Yes ☐ No
51. Are you interested in participating in this study?	☐ Yes ☐ No

If yes to all questions: Great. Thank you very much for your willingness to participate in this study. I am going to need to collect some information from you and schedule times for your two study visits.

If no to any question: Thank you for your time and have a great day.
If eligible, but not willing to participate:

"Would you be willing to share you reason for declining to participate?"
Record reason if willing to share: _____

"Thank you for your time and have a great day."

Eligible participant information:

Participant Name: _____
Street _____
City, State, ZIP Code _____
Email: _____
Day Phone: (___ ___ ___) ___ ___ ___ - ___ ___ ___ ___
Can we leave a message at this # ☐ Yes ☐No
Evening Phone: (___ ___ ___) ___ ___ ___ - ___ ___ ___ ___
Can we leave a message at this # ☐ Yes ☐No
Cell Phone: (___ ___ ___) ___ ___ ___ - ___ ___ ___ ___
Can we leave a message at this # ☐ Yes ☐No
What is you preferred method of contact for study reminders?
☐ Email
(Preferred Email Address (if different from one provided above):
☐ Phone
(Preferred Phone Number: _____)

Study Visit Dates:

Study Visit One ☐☐/☐☐/☐☐
month day year

Time: _____ am / pm

Study Visit Two ☐☐/☐☐/☐☐
month day year

Time: _____ am / pm

Once this information is collected:

"Great, I think I have all the information I need from you. We will send you a consent form and questionnaires for you to complete in the mail shortly. Please review the consent form and sign it if you agree to consent to participating in this study. Bring the consent form and the completed questionnaires to your first study visit. It is really important that you complete the questionnaires prior to your study visit. If they are not completed the first study visit will take 45 minutes to an hour longer and may need to be rescheduled. Do you have any questions before we conclude? <<ANSWER ANY QUESTIONS>> Do you still have the contact information for the study? If no, provide them with the phone number and email again. Please contact us if you have any questions or if you have any conflicts that arise with your scheduled study visit so we can reschedule. If you elect not to continue to agree to participate in this study at any point, please try to let us know by calling or emailing us. Thank you for your time and your participation in this study. We very much appreciate it. Have a great day."

Final Decision:

□ Agreed to Participate, Study Visits Scheduled

□ Declined to Participate, Reason: _____

□ Not Eligible, Reason: _____

Appendix 3: UB-Diet Study Questionnaire

Background and Diet Habits Questionnaire

Instructions:

- Print legibly using a blue or black ink pen.
- Do not use pencil or felt tip markers.
- When entering letters or numbers, enter one per box and stay within the box.
- Fill in the bubbles completely with a dark mark.
- Only provide one answer for each question unless otherwise instructed. If more than one response applies, please choose the response that is most often true.
- If you wish to change an answer, place an "X" through the first mark, and mark the oval for your preferred answer.
- Do not use "White Out".

IMPORTANT:

We request that the questionnaire be completed by the individual on the label.

Participant ID:

_____

Today's Date (Month/Day/Year):

_____

Your Date of Birth (Month/Day/Year):

_____

GENERAL INFORMATION

1. What is your gender?
   - ⊂⊃ Female
   - ⊂⊃ Male
   - ⊂⊃ Other or prefer not to answer

2. What race/ethnicity do you consider yourself?
   - ⊂⊃ White (non-Hispanic)
   - ⊂⊃ Black or African American (non-Hispanic)
   - ⊂⊃ Hispanic or Latino
   - ⊂⊃ Asian American or Asian
   - ⊂⊃ Hawaiian or Pacific Islander
   - ⊂⊃ American Indian or Native American
   - ⊂⊃ Other (Please Specify: _____)

3. What is the highest level of education that you have completed?
   - ⊂⊃ Less than high school
   - ⊂⊃ Some high school
   - ⊂⊃ High school graduate or GED
   - ⊂⊃ Some college
   - ⊂⊃ Technical or associate's degree
   - ⊂⊃ College graduate
   - ⊂⊃ Advanced college degree (Master's, PhD, MD, JD, etc.)

4. Over the <u>past 12 months</u> what was your primary work status?
   - ⊂⊃ Full-time student, unemployed
   - ⊂⊃ Full-time student, part-time job
   - ⊂⊃ Part-time student, part-time job
   - ⊂⊃ Part-time student, full-time job
   - ⊂⊃ Part-time job(s)
   - ⊂⊃ Full-time job
   - ⊂⊃ Disabled
   - ⊂⊃ Retired
   - ⊂⊃ Unemployed

5. Over the <u>past 12 months</u>, how many times per day did you typically handle cash register receipts, including giving them out or receiving them?
   - ⊂⊃ 0 – 5 times per day
   - ⊂⊃ 6 – 10 times per day
   - ⊂⊃ More than 10 per day

6. Over the <u>past 12 months</u> what was your household's total annual income? (count before tax income from all sources for all household members)
   - ⊂⊃ $0 - $19,000
   - ⊂⊃ $20,000 - $ 44, 999
   - ⊂⊃ $45,000 - $74, 999
   - ⊂⊃ $75,000 and higher
   - ⊂⊃ Don't know or prefer not to answer

7. Over the <u>past 12 months</u>, did you have enough money to buy what you would consider sufficient food for yourself and/or your household?
   - ⊂⊃ Yes
   - ⊂⊃ No
   - ⊂⊃ Don't know or prefer not to answer

8. Over the <u>past 12 months</u>, did you ever cut the size of your meals or skip meals because there was not enough money for food?
   - ⊂⊃ No (skip to Question 9)
   - ⊂⊃ Don't know or prefer not to answer (skip to Question 9)
   - ⊂⊃ Yes

8b. If yes, how often did this happen?

- ⊂⊃ Almost every month
- ⊂⊃ Some months, but not every month
- ⊂⊃ Only 1 or 2 months
- ⊂⊃ Don't know or prefer not to answer

9. In the <u>past 12 months</u>, did you eat any meals from community programs, such as "Meals on Wheels" or a soup kitchen?

- ⊂⊃ Yes
- ⊂⊃ No
- ⊂⊃ Don't know or prefer not to answer

10. In the <u>past 12 months</u>, did you rely on a community food assistance program, such as food shelves or food banks to supplement the food you purchased?

- ⊂⊃ Yes
- ⊂⊃ No
- ⊂⊃ Don't know or prefer not to answer

11. In the <u>past 12 months</u>, did you or any member of your household receive benefits from SNAP, the Supplemental Nutrition Assistance Program (formerly known as the Food Stamp Program)?

- ⊂⊃ Yes
- ⊂⊃ No
- ⊂⊃ Don't know or prefer not to answer

12. What is your current weight?

_____ lbs.

13. How long have you been at your current weight?

- ⊂⊃ Less than 1 year
- ⊂⊃ 1 – 3 years
- ⊂⊃ 3 – 5 years
- ⊂⊃ More than 5 years

14. What is the most you have ever weighed (excluding pregnancy)?

15. In general, would you say your current health is:

- ⊂⊃ Excellent
- ⊂⊃ Very Good
- ⊂⊃ Good
- ⊂⊃ Fair
- ⊂⊃ Poor

16. Do you have any chronic health issues, such as arthritis, food allergies, ulcerative colitis, or migraines?

- ⊂⊃ No
- ⊂⊃ Yes

If yes, please indicate any health issues here:

_____

17. Over the <u>past 12 months</u>, did you take any medications on a weekly or daily basis?

- ⊂⊃ No
- ⊂⊃ Yes

If yes, please list what medications you take and how often you take them here:

_____

_____

_____

18. Over the past 12 months, in a usual week, how many hours did you spend doing **mild exercise** (little effort)? (Examples: walking slowing, bowling, golfing, fishing, relaxing yoga)

- ⊂⊃ None
- ⊂⊃ Less than ½ hour a week
- ⊂⊃ ½ - 2 hours a week
- ⊂⊃ 2½ - 4 hours a week
- ⊂⊃ 4½ - 6 hours a week
- ⊂⊃ 6 or more hours a week

19. Over the past 12 months, in a usual week, how many hours did you spend doing **moderate exercise** (not exhausting)? (Examples: walking quickly, baseball, easy bicycling, volleyball, dancing, skateboarding)

- ⊂⊃ None
- ⊂⊃ Less than ½ hour a week
- ⊂⊃ ½ - 2 hours a week
- ⊂⊃ 2½ - 4 hours a week
- ⊂⊃ 4½ - 6 hours a week
- ⊂⊃ 6 or more hours a week

20. Over the past 12 months, in a usual week, how many hours did you spend doing **strenuous activity** (heart beats rapidly)? (Examples: running, swimming laps, tennis, soccer, basketball, skiing, biking fast, aerobic dancing, vigorous yoga)

- ⊂⊃ None
- ⊂⊃ Less than ½ hour a week
- ⊂⊃ ½ - 2 hours a week
- ⊂⊃ 2½ - 4 hours a week
- ⊂⊃ 4½ - 6 hours a week
- ⊂⊃ 6 or more hours a week

21. Have you ever been a daily smoker?

- ⊂⊃ No (skip to Question 22)
- ⊂⊃ Yes

21b. If you have you ever been a daily smoker, how many years were you a daily smoker?

- ⊂⊃ Less than 5 years
- ⊂⊃ 5 – 10 years
- ⊂⊃ 11 – 15 years
- ⊂⊃ More than 15 years

21c. If you have ever been a daily smoker, how many years has it been since you quit smoking?

- ⊂⊃ Still a current smoker
- ⊂⊃ Less than 1 years
- ⊂⊃ 1 – 5 years
- ⊂⊃ 6 – 10 years
- ⊂⊃ More than 10 years
- ⊂⊃ Never smoked

22. Over the past 12 months, were you routinely exposed to second hand smoke, such as living in a home where other people smoked (exclude short term occasional exposure)?

- ⊂⊃ Yes
- ⊂⊃ No

23. Over the past 12 months, did you take any dietary supplements on a daily basis (For example, multivitamins, calcium, vitamin D, vitamin C)?

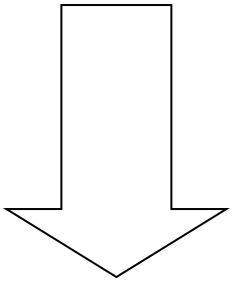
⊂⊃ No

⊂⊃ Yes

If yes, please list which types here:

_____
_____
_____
_____
_____
_____
_____
_____

The survey continues on the next page.



Details about Meal Habits and Locations

24. Over the past 12 months how many days per week did you typically eat **BREAKFAST**?
    - ⊂⊃ Never
    - ⊂⊃ 1 – 2 days per week
    - ⊂⊃ 3 – 4 days per week
    - ⊂⊃ 5 – 6 days per week
    - ⊂⊃ Everyday

25. Where was your **BREAKFAST** most often from?
    - ⊂⊃ Prepared at home or brought from home
    - ⊂⊃ Prepared at another person's home
    - ⊂⊃ Purchased from a work or school cafeteria
    - ⊂⊃ Purchased at a fast food or take-out restaurant (such as McDonald's®, Panera®, Chipotle®)
    - ⊂⊃ Purchased at a sit-down restaurant
    - ⊂⊃ Other (Please specify: _____)

26. Over the past 12 months how many days per week did you typically eat **LUNCH**?
    - ⊂⊃ Never
    - ⊂⊃ 1 – 2 days per week
    - ⊂⊃ 3 – 4 days per week
    - ⊂⊃ 5 – 6 days per week
    - ⊂⊃ Everyday

27. Where was your **LUNCH** most often from?
    - ⊂⊃ Prepared at home or brought from home
    - ⊂⊃ Prepared at another person's home
    - ⊂⊃ Purchased from a work or school cafeteria
    - ⊂⊃ Purchased at a fast food or take-out restaurant (such as McDonald's®, Panera®, Chipotle®)
    - ⊂⊃ Purchased at a sit-down restaurant
    - ⊂⊃ Other (Please specify: _____)

28. Over the past 12 months how many days per week did you typically eat **DINNER**?
    - ⊂⊃ Never
    - ⊂⊃ 1 – 2 days per week
    - ⊂⊃ 3 – 4 days per week
    - ⊂⊃ 5 – 6 days per week
    - ⊂⊃ Everyday

29. Where was your **DINNER** most often from?
    - ⊂⊃ Prepared at home
    - ⊂⊃ Prepared at another person's home
    - ⊂⊃ Purchased at a work or school cafeteria
    - ⊂⊃ Purchased at a fast food or take-out restaurant (such as McDonald's®, Panera®, Chipotle®)
    - ⊂⊃ Purchased at a sit-down restaurant
    - ⊂⊃ Other (Please specify: _____)

30. Over the past 12 months how many days per week did you typically eat AT LEAST ONE meal **AWAY from home** that was NOT prepared by you or at your home?
    - ⊂⊃ None
    - ⊂⊃ 1 – 2 days
    - ⊂⊃ 3 – 4 days
    - ⊂⊃ 5 -6 days
    - ⊂⊃ Everyday

31. Over the past 12 months how many times per week (including all meals and snacks) did you typically eat at **fast food or take-out restaurants** (such as McDonald's®, Panera®, Wendy's®, a deli or Chinese take-out?
    - ⊂⊃ Never
    - ⊂⊃ 1 – 2 times per week
    - ⊂⊃ 3 – 4 times per week
    - ⊂⊃ 5 – 6 times per week
    - ⊂⊃ 7 – 8 times per week
    - ⊂⊃ More than 8 times per week (Please specify the number of times:)

32. Over the past 12 months how many times per week did you typically eat at **sit-down restaurants**?
    - ⊂⊃ Never
    - ⊂⊃ 1 – 2 times per week
    - ⊂⊃ 3 – 4 times per week
    - ⊂⊃ 5 – 6 times per week
    - ⊂⊃ 7 – 8 times per week
    - ⊂⊃ More than 8 times per week (Please specify the number of times:)

33. Over the past 12 months how many times did you usually eat in a **cafeteria at work or school**?
    - ⊂⊃ Never
    - ⊂⊃ 1 – 2 times per week
    - ⊂⊃ 3 – 4 times per week
    - ⊂⊃ 5 – 6 times per week
    - ⊂⊃ 7 – 8 times per week
    - ⊂⊃ More than 8 times per week (Please specify the number of times:)

34. On AVERAGE, over the past 12 months how often did you eat foods that are:

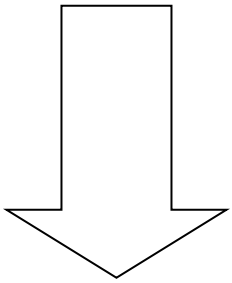
	Never or rarely	Monthly	Weekly	Daily	Daily - Most Meals
a. Organic	⊂⊃	⊂⊃	⊂⊃	⊂⊃	⊂⊃
b. From a package (including cans, microwave meals, cake mix, muffin mix, and boxed meals-such as macaroni and cheese)	⊂⊃	⊂⊃	⊂⊃	⊂⊃	⊂⊃
c. Locally grown	⊂⊃	⊂⊃	⊂⊃	⊂⊃	⊂⊃

Food Intake Details

Additional Instruction for this Section:

- Please try to answer all questions the best you can.
- We ask you to estimate amounts over the past 12 months. We realize that some foods may be eaten only at certain times of the year, however, do the best that you can to estimate how often you eat the food on AVERAGE over 12 months.
- In this survey we will ask you whether you eat certain foods that are canned or from frozen. Canned foods are foods that come in METAL containers, and DO NOT include foods in glass containers or canned at home in glass containers. We will assume that foods that are not prepared from a can or frozen are consumed fresh.
- **NOTE:** Some of the questions in this portion of the survey will be very similar to the questions on the food frequency questionnaire you will also be asked to complete. This questionnaire is being evaluated for use in future studies. Answering all questionnaires on both questionnaires is important for assessing this new survey.

The survey continues on the next page.



35. On AVERAGE, over the past 12 months how often did you eat of **canned lunchmeats**, such as SPAM®?
- ⊂⊃ NEVER or less than once per month
- ⊂⊃ 1 time per month
- ⊂⊃ 2 – 3 times per month
- ⊂⊃ 1 time per week
- ⊂⊃ 2 times per week
- ⊂⊃ 3 - 4 times per week
- ⊂⊃ 5 - 6 times per week
- ⊂⊃ 1 time per day
- ⊂⊃ 2 or more times per day

36. Over the past 12 months how often did you eat canned (NOT in pouches) **tuna,** including canned tuna in mixed dishes such as tuna casserole or tuna salad?
- ⊂⊃ NEVER or less than once per month (skip to Question 37)
- ⊂⊃ 1 time per month
- ⊂⊃ 2 – 3 times per month
- ⊂⊃ 1 time per week
- ⊂⊃ 2 times per week
- ⊂⊃ 3 - 4 times per week
- ⊂⊃ 5 - 6 times per week
- ⊂⊃ 1 time per day
- ⊂⊃ 2 or more times per day

36b. When you consume canned (NOT in pouches) tuna how often is it ***water packed***?
- ⊂⊃ Always or Almost Always
- ⊂⊃ About ¾ of the time
- ⊂⊃ About ½ of the time
- ⊂⊃ About ¼ of the time
- ⊂⊃ Never or Almost Never
- ⊂⊃ Don't Know

(Please provide a brief explanation. [e.g. I mainly ate it at a restaurant]).

_____.

37. Over the past 12 months how often did you eat **canned chicken,** including canned chicken in mixed dishes such as chicken salad or chicken casserole?
- ⊂⊃ NEVER or less than once per month
- ⊂⊃ 1 time per month
- ⊂⊃ 2 – 3 times per month
- ⊂⊃ 1 time per week
- ⊂⊃ 2 times per week
- ⊂⊃ 3 - 4 times per week
- ⊂⊃ 5 - 6 times per week
- ⊂⊃ 1 time per day
- ⊂⊃ 2 or more times per day

38. Please list any other MEAT, POULTRY or FISH not listed above that you eat **FROM A CAN** at least once per week and the number of servings you eat per week or day.

_____

39. Over the past 12 months how often did you eat **corn** (fresh, canned or frozen)?

- ⊂⊃ NEVER or less than once per month (skip to Question 40)
- ⊂⊃ 1 time per month
- ⊂⊃ 2 – 3 times per month
- ⊂⊃ 1 time per week
- ⊂⊃ 2 times per week
- ⊂⊃ 3 - 4 times per week
- ⊂⊃ 5 - 6 times per week
- ⊂⊃ 1 time per day
- ⊂⊃ 2 or more times per day

39b. How often was the **corn** from a CAN?

- ⊂⊃ Always or Almost Always
- ⊂⊃ About ¾ of the time
- ⊂⊃ About ½ of the time
- ⊂⊃ About ¼ of the time
- ⊂⊃ Never or Almost Never
- ⊂⊃ Don't Know

(Please provide a brief explanation [e.g. I mainly ate it at restaurants]).

_____.

39c. How often was the **corn** prepared from FROZEN?

- ⊂⊃ Always or Almost Always
- ⊂⊃ About ¾ of the time
- ⊂⊃ About ½ of the time
- ⊂⊃ About ¼ of the time
- ⊂⊃ Never or Almost Never
- ⊂⊃ Don't Know

(Please provide a brief explanation [e.g. I mainly ate it at restaurants]).

_____.

40. Over the past 12 months how often did you eat **green beans** (fresh, frozen, or canned)?

- ⊂⊃ NEVER or less than once per month (skip to Question 41)
- ⊂⊃ 1 time per month
- ⊂⊃ 2 – 3 times per month
- ⊂⊃ 1 time per week
- ⊂⊃ 2 times per week
- ⊂⊃ 3 - 4 times per week
- ⊂⊃ 5 - 6 times per week
- ⊂⊃ 1 time per day
- ⊂⊃ 2 or more times per day

40b. How often were the **green beans** prepared from a CAN?

- ⊂⊃ Always or Almost Always
- ⊂⊃ About ¾ of the time
- ⊂⊃ About ½ of the time
- ⊂⊃ About ¼ of the time
- ⊂⊃ Never or Almost Never
- ⊂⊃ Don't Know

(Please provide a brief explanation [e.g. I mainly ate it at restaurants]).

_____.

40c. How often were the **green beans** prepared from FROZEN?

- ⊂⊃ Always or Almost Always
- ⊂⊃ About ¾ of the time
- ⊂⊃ About ½ of the time
- ⊂⊃ About ¼ of the time
- ⊂⊃ Never or Almost Never
- ⊂⊃ Don't Know

(Please provide a brief explanation [e.g. I mainly ate it at restaurants]).

_____.

41. Over the past 12 months how often did you eat **refried beans, baked beans, plain beans (such as garbanzo beans, black beans and navy beans), or lima beans** (dried, frozen or canned), including ones used as part of a mixed dish, such as chili?

- ⊂⊃ NEVER or less than once per month (skip to Question 42)
- ⊂⊃ 1 time per month
- ⊂⊃ 2 – 3 times per month
- ⊂⊃ 1 time per week
- ⊂⊃ 2 times per week
- ⊂⊃ 3 - 4 times per week
- ⊂⊃ 5 - 6 times per week
- ⊂⊃ 1 time per day
- ⊂⊃ 2 or more times per day

41b. How often were the **refried beans, baked beans, plain beans and lima beans** prepared from a CAN?

- ⊂⊃ Always or Almost Always
- ⊂⊃ About ¾ of the time
- ⊂⊃ About ½ of the time
- ⊂⊃ About ¼ of the time
- ⊂⊃ Never or Almost Never
- ⊂⊃ Don't Know (Please provide a brief explanation [e.g. I mainly ate it at restaurants]).

_____.

41c. How often were the **refried beans, baked beans, plain beans and lima beans** prepared from FROZEN?

- ⊂⊃ Always or Almost Always
- ⊂⊃ About ¾ of the time
- ⊂⊃ About ½ of the time
- ⊂⊃ About ¼ of the time
- ⊂⊃ Never or Almost Never
- ⊂⊃ Don't Know

(Please provide a brief explanation [e.g. I mainly ate it at restaurants]).

_____.

42. Over the past 12 months how often did you eat **greens**, such as spinach, mustard greens and collards (fresh, frozen or canned)?

- ⊂⊃ NEVER or less than once per month (skip to Question 43)
- ⊂⊃ 1 time per month
- ⊂⊃ 2 – 3 times per month
- ⊂⊃ 1 time per week
- ⊂⊃ 2 times per week
- ⊂⊃ 3 - 4 times per week
- ⊂⊃ 5 - 6 times per week
- ⊂⊃ 1 time per day
- ⊂⊃ 2 or more times per day

42b. How often were the **greens** prepared from a CAN?

- ⊂⊃ Always or Almost Always
- ⊂⊃ About ¾ of the time
- ⊂⊃ About ½ of the time
- ⊂⊃ About ¼ of the time
- ⊂⊃ Never or Almost Never
- ⊂⊃ Don't Know

(Please provide a brief explanation [e.g. I mainly ate it at restaurants]).

_____.

42c. How often were the **greens** prepared from FROZEN?

- ⊂⊃ Always or Almost Always
- ⊂⊃ About ¾ of the time
- ⊂⊃ About ½ of the time
- ⊂⊃ About ¼ of the time
- ⊂⊃ Never or Almost Never
- ⊂⊃ Don't Know

(Please provide a brief explanation [e.g. I mainly ate it at restaurants]).

_____.

43. Over the past 12 months how often did you eat **peas** (fresh, frozen or canned)?

- ⊂⊃ NEVER or less than once per month (skip to Question 44)
- ⊂⊃ 1 time per month
- ⊂⊃ 2 – 3 times per month
- ⊂⊃ 1 time per week
- ⊂⊃ 2 times per week
- ⊂⊃ 3 - 4 times per week
- ⊂⊃ 5 - 6 times per week
- ⊂⊃ 1 time per day
- ⊂⊃ 2 or more times per day

43b. How often were the **peas** prepared from a CAN?

- ⊂⊃ Always or Almost Always
- ⊂⊃ About ¾ of the time
- ⊂⊃ About ½ of the time
- ⊂⊃ About ¼ of the time
- ⊂⊃ Never or Almost Never
- ⊂⊃ Don't Know

(Please provide a brief explanation [e.g. I mainly ate it at restaurants]).

_____.

43c. How often were the **peas** prepared from FROZEN?

- ⊂⊃ Always or Almost Always
- ⊂⊃ About ¾ of the time
- ⊂⊃ About ½ of the time
- ⊂⊃ About ¼ of the time
- ⊂⊃ Never or Almost Never
- ⊂⊃ Don't Know

(Please provide a brief explanation [e.g. I mainly ate it at restaurants]).

_____.

44. Over the past 12 months how often did you eat **mixed vegetables or vegetable medleys** (fresh, frozen or canned)?

- ⊂⊃ NEVER or less than once per month (skip to Question 45)
- ⊂⊃ 1 time per month
- ⊂⊃ 2 – 3 times per month
- ⊂⊃ 1 time per week
- ⊂⊃ 2 times per week
- ⊂⊃ 3 - 4 times per week
- ⊂⊃ 5 - 6 times per week
- ⊂⊃ 1 time per day
- ⊂⊃ 2 or more times per day

44b. How often were the **mixed vegetables or vegetable medleys** prepared from a CAN?

- ⊂⊃ Always or Almost Always
- ⊂⊃ About ¾ of the time
- ⊂⊃ About ½ of the time
- ⊂⊃ About ¼ of the time
- ⊂⊃ Never or Almost Never
- ⊂⊃ Don't Know

(Please provide a brief explanation [e.g. I mainly ate it at restaurants]).

_____.

44c. How often were the **mixed vegetables or vegetable medleys** prepared from FROZEN?

- ⊂⊃ Always or Almost Always
- ⊂⊃ About ¾ of the time
- ⊂⊃ About ½ of the time
- ⊂⊃ About ¼ of the time
- ⊂⊃ Never or Almost Never
- ⊂⊃ Don't Know

(Please provide a brief explanation [e.g. I mainly ate it at restaurants]).

_____.

45. Over the past 12 months how often did you eat **mushrooms**?

- ⊂⊃ NEVER or less than once per month (skip to Question 46)
- ⊂⊃ 1 time per month
- ⊂⊃ 2 – 3 times per month
- ⊂⊃ 1 time per week
- ⊂⊃ 2 times per week
- ⊂⊃ 3 - 4 times per week
- ⊂⊃ 5 - 6 times per week
- ⊂⊃ 1 time per day
- ⊂⊃ 2 or more times per day

45b. How often were the **mushrooms** prepared from a CAN?

- ⊂⊃ Always or Almost Always
- ⊂⊃ About ¾ of the time
- ⊂⊃ About ½ of the time
- ⊂⊃ About ¼ of the time
- ⊂⊃ Never or Almost Never
- ⊂⊃ Don't Know

(Please provide a brief explanation [e.g. I mainly ate it at restaurants]).

_____.

45c. How often were the **mushrooms** prepared from FROZEN?

- ⊂⊃ Always or Almost Always
- ⊂⊃ About ¾ of the time
- ⊂⊃ About ½ of the time
- ⊂⊃ About ¼ of the time
- ⊂⊃ Never or Almost Never
- ⊂⊃ Don't Know

(Please provide a brief explanation [e.g. I mainly ate it at restaurants]).

_____.

46. Over the past 12 months how often did you eat **tomatoes (whole, peeled or chopped), tomato sauce, and tomato paste** (fresh or canned), including as part of a mixed dish (e.g. spaghetti)?

- ⊂⊃ NEVER or less than once per month (skip to Question 47)
- ⊂⊃ 1 time per month
- ⊂⊃ 2 – 3 times per month
- ⊂⊃ 1 time per week
- ⊂⊃ 2 times per week
- ⊂⊃ 3 - 4 times per week
- ⊂⊃ 5 - 6 times per week
- ⊂⊃ 1 time per day
- ⊂⊃ 2 or more times per day

46b. How often were the **tomatoes, tomato sauce and tomato paste**, including those used in mixed dishes, prepared from a CAN?

- ⊂⊃ Always or Almost Always
- ⊂⊃ About ¾ of the time
- ⊂⊃ About ½ of the time
- ⊂⊃ About ¼ of the time
- ⊂⊃ Never or Almost Never
- ⊂⊃ Don't Know

(Please provide a brief explanation [e.g. I mainly ate it at restaurants]).

_____.

47. Over the past 12 months how often did you eat **yams or sweet potatoes** (fresh, frozen or canned)?

- ⊂⊃ NEVER or less than once per month (skip to Question 48)
- ⊂⊃ 1 time per month
- ⊂⊃ 2 – 3 times per month
- ⊂⊃ 1 time per week
- ⊂⊃ 2 times per week
- ⊂⊃ 3 - 4 times per week
- ⊂⊃ 5 - 6 times per week
- ⊂⊃ 1 time per day
- ⊂⊃ 2 or more times per day

47b. How often were the **yams or sweet potatoes** prepared from a CAN?

- ⊂⊃ Always or Almost Always
- ⊂⊃ About ¾ of the time
- ⊂⊃ About ½ of the time
- ⊂⊃ About ¼ of the time
- ⊂⊃ Never or Almost Never
- ⊂⊃ Don't Know

(Please provide a brief explanation [e.g. I mainly ate it at restaurants]).

_____.

47c. How often were the **yams or sweet potatoes** prepared from FROZEN?

- ⊂⊃ Always or Almost Always
- ⊂⊃ About ¾ of the time
- ⊂⊃ About ½ of the time
- ⊂⊃ About ¼ of the time
- ⊂⊃ Never or Almost Never
- ⊂⊃ Don't Know

(Please provide a brief explanation [e.g. I mainly ate it at restaurants]).

_____.

48. Please list any other VEGETABLES not listed above that you eat **from a can or frozen** at least once per week, the number of servings you eat per week or day and indicate if the item is canned or frozen.

Vegetable	Servings per week or day	Canned or Frozen?

49. Over the past 12 months how often did you eat **pears** (fresh, frozen or canned)?

- ⊂⊃ NEVER or less than once per month (skip to Question 50)
- ⊂⊃ 1 time per month
- ⊂⊃ 2 – 3 times per month
- ⊂⊃ 1 time per week
- ⊂⊃ 2 times per week
- ⊂⊃ 3 - 4 times per week
- ⊂⊃ 5 - 6 times per week
- ⊂⊃ 1 time per day
- ⊂⊃ 2 or more times per day

49b. How often were the **pears** prepared from a CAN?

- ⊂⊃ Always or Almost Always
- ⊂⊃ About ¾ of the time
- ⊂⊃ About ½ of the time
- ⊂⊃ About ¼ of the time
- ⊂⊃ Never or Almost Never
- ⊂⊃ Don't Know

(Please provide a brief explanation [e.g. I mainly ate it at restaurants]).

_____.

50. Over the past 12 months how often did you eat **oranges and tangerines**, including mandarin oranges and clementines (fresh, frozen or canned)?

- ⊂⊃ NEVER or less than once per month (skip to Question 51)
- ⊂⊃ 1 time per month
- ⊂⊃ 2 – 3 times per month
- ⊂⊃ 1 time per week
- ⊂⊃ 2 times per week
- ⊂⊃ 3 - 4 times per week
- ⊂⊃ 5 - 6 times per week
- ⊂⊃ 1 time per day
- ⊂⊃ 2 or more times per day

50b. How often were the **oranges and tangerines**, including mandarin oranges and clementines prepared from a CAN?

- ⊂⊃ Always or Almost Always
- ⊂⊃ About ¾ of the time
- ⊂⊃ About ½ of the time
- ⊂⊃ About ¼ of the time
- ⊂⊃ Never or Almost Never
- ⊂⊃ Don't Know

(Please provide a brief explanation [e.g. I mainly ate it at restaurants]).

_____.

51. Over the past 12 months how often did you eat **strawberries** (fresh, frozen or canned), including pie fillings?

- ⊂⊃ NEVER or less than once per month (skip to Question 52)
- ⊂⊃ 1 time per month
- ⊂⊃ 2 – 3 times per month
- ⊂⊃ 1 time per week
- ⊂⊃ 2 times per week
- ⊂⊃ 3 - 4 times per week
- ⊂⊃ 5 - 6 times per week
- ⊂⊃ 1 time per day
- ⊂⊃ 2 or more times per day

51b. How often were the **strawberries** prepared from a CAN?

- ⊂⊃ Always or Almost Always
- ⊂⊃ About ¾ of the time
- ⊂⊃ About ½ of the time
- ⊂⊃ About ¼ of the time
- ⊂⊃ Never or Almost Never
- ⊂⊃ Don't Know

(Please provide a brief explanation [e.g. I mainly ate it at restaurants]).

_____.

51c. How often were the **strawberries** prepared from FROZEN?

- ⊂⊃ Always or Almost Always
- ⊂⊃ About ¾ of the time
- ⊂⊃ About ½ of the time
- ⊂⊃ About ¼ of the time
- ⊂⊃ Never or Almost Never
- ⊂⊃ Don't Know (Please provide a brief explanation [e.g. I mainly ate it at restaurants]).

_____.

52. Over the past 12 months how often did you eat **raspberries** (fresh, frozen or canned), including pie fillings?

- ⊂⊃ NEVER or less than once per month (skip to Question 53)
- ⊂⊃ 1 time per month
- ⊂⊃ 2 – 3 times per month
- ⊂⊃ 1 time per week
- ⊂⊃ 2 times per week
- ⊂⊃ 3 - 4 times per week
- ⊂⊃ 5 - 6 times per week
- ⊂⊃ 1 time per day
- ⊂⊃ 2 or more times per day

52b. How often were the **raspberries** prepared from a CAN?

- ⊂⊃ Always or Almost Always
- ⊂⊃ About ¾ of the time
- ⊂⊃ About ½ of the time
- ⊂⊃ About ¼ of the time
- ⊂⊃ Never or Almost Never
- ⊂⊃ Don't Know

(Please provide a brief explanation [e.g. I mainly ate it at restaurants]).

_____.

52c. How often were the **raspberries** prepared from FROZEN?

- ⊂⊃ Always or Almost Always
- ⊂⊃ About ¾ of the time
- ⊂⊃ About ½ of the time
- ⊂⊃ About ¼ of the time
- ⊂⊃ Never or Almost Never
- ⊂⊃ Don't Know

(Please provide a brief explanation [e.g. I mainly ate it at restaurants]).

_____.

53. Over the past 12 months how often did you eat **blueberries** (fresh, frozen or canned), including pie fillings?

- ⊂⊃ NEVER or less than once per month (skip to Question 54)
- ⊂⊃ 1 time per month
- ⊂⊃ 2 – 3 times per month
- ⊂⊃ 1 time per week
- ⊂⊃ 2 times per week
- ⊂⊃ 3 - 4 times per week
- ⊂⊃ 5 - 6 times per week
- ⊂⊃ 1 time per day
- ⊂⊃ 2 or more times per day

53b. How often were the **blueberries** prepared from a CAN?

- ⊂⊃ Always or Almost Always
- ⊂⊃ About ¾ of the time
- ⊂⊃ About ½ of the time
- ⊂⊃ About ¼ of the time
- ⊂⊃ Never or Almost Never
- ⊂⊃ Don't Know

(Please provide a brief explanation [e.g. I mainly ate it at restaurants]).

_____.

53c. How often were the **blueberries** prepared from FROZEN?

- ⊂⊃ Always or Almost Always
- ⊂⊃ About ¾ of the time
- ⊂⊃ About ½ of the time
- ⊂⊃ About ¼ of the time
- ⊂⊃ Never or Almost Never
- ⊂⊃ Don't Know

(Please provide a brief explanation [e.g. I mainly ate it at restaurants]).

_____.

54. Over the past 12 months how often did you eat **any other types of berries**, such as blackberries or cranberries (fresh, frozen or canned), including pie fillings?

- ⊂⊃ NEVER or less than once per month (skip to Question 55)
- ⊂⊃ 1 time per month
- ⊂⊃ 2 – 3 times per month
- ⊂⊃ 1 time per week
- ⊂⊃ 2 times per week
- ⊂⊃ 3 - 4 times per week
- ⊂⊃ 5 - 6 times per week
- ⊂⊃ 1 time per day
- ⊂⊃ 2 or more times per day

54b. How often were the **berries** prepared from a CAN?

- ⊂⊃ Always or Almost Always
- ⊂⊃ About ¾ of the time
- ⊂⊃ About ½ of the time
- ⊂⊃ About ¼ of the time
- ⊂⊃ Never or Almost Never
- ⊂⊃ Don't Know

(Please provide a brief explanation [e.g. I mainly ate it at restaurants]).

_____.

54c. How often were the **berries** prepared from FROZEN?

- ⊂⊃ Always or Almost Always
- ⊂⊃ About ¾ of the time
- ⊂⊃ About ½ of the time
- ⊂⊃ About ¼ of the time
- ⊂⊃ Never or Almost Never
- ⊂⊃ Don't Know

(Please provide a brief explanation [e.g. I mainly ate it at restaurants]).

_____.

55. Over the past 12 months how often did you eat **peaches** (fresh, frozen or canned)?

- ⊂⊃ NEVER or less than once per month (skip to Question 56)
- ⊂⊃ 1 time per month
- ⊂⊃ 2 – 3 times per month
- ⊂⊃ 1 time per week
- ⊂⊃ 2 times per week
- ⊂⊃ 3 - 4 times per week
- ⊂⊃ 5 - 6 times per week
- ⊂⊃ 1 time per day
- ⊂⊃ 2 or more times per day

55b. How often were the **peaches** prepared from a CAN?

- ⊂⊃ Always or Almost Always
- ⊂⊃ About ¾ of the time
- ⊂⊃ About ½ of the time
- ⊂⊃ About ¼ of the time
- ⊂⊃ Never or Almost Never
- ⊂⊃ Don't Know

(Please provide a brief explanation [e.g. I mainly ate it at restaurants]).

_____.

55c. How often were the **peaches** prepared from FROZEN?

- ⊂⊃ Always or Almost Always
- ⊂⊃ About ¾ of the time
- ⊂⊃ About ½ of the time
- ⊂⊃ About ¼ of the time
- ⊂⊃ Never or Almost Never
- ⊂⊃ Don't Know

(Please provide a brief explanation [e.g. I mainly ate it at restaurants]).

_____.

56. Over the past 12 months how often did you eat **pineapple** (fresh, frozen or canned)?

- ⊂⊃ NEVER or less than once per month (skip to Question 57)
- ⊂⊃ 1 time per month
- ⊂⊃ 2 – 3 times per month
- ⊂⊃ 1 time per week
- ⊂⊃ 2 times per week
- ⊂⊃ 3 - 4 times per week
- ⊂⊃ 5 - 6 times per week
- ⊂⊃ 1 time per day
- ⊂⊃ 2 or more times per day

56b. How often was the **pineapple** prepared from a CAN?

- ⊂⊃ Always or Almost Always
- ⊂⊃ About ¾ of the time
- ⊂⊃ About ½ of the time
- ⊂⊃ About ¼ of the time
- ⊂⊃ Never or Almost Never
- ⊂⊃ Don't Know

(Please provide a brief explanation [e.g. I mainly ate it at restaurants]).

_____.

56c. How often was the **pineapple** prepared from FROZEN?

- ⊂⊃ Always or Almost Always
- ⊂⊃ About ¾ of the time
- ⊂⊃ About ½ of the time
- ⊂⊃ About ¼ of the time
- ⊂⊃ Never or Almost Never
- ⊂⊃ Don't Know

(Please provide a brief explanation [e.g. I mainly ate it at restaurants]).

_____.

57. Over the past 12 months how often did you eat **mixed fruit or fruit cocktail** (fresh, frozen or canned)?

- ⊂⊃ NEVER or less than once per month (skip to Question 58)
- ⊂⊃ 1 time per month
- ⊂⊃ 2 – 3 times per month
- ⊂⊃ 1 time per week
- ⊂⊃ 2 times per week
- ⊂⊃ 3 - 4 times per week
- ⊂⊃ 5 - 6 times per week
- ⊂⊃ 1 time per day
- ⊂⊃ 2 or more times per day

57b. How often was the **mixed fruit and fruit cocktail** prepared from a CAN?

- ⊂⊃ Always or Almost Always
- ⊂⊃ About ¾ of the time
- ⊂⊃ About ½ of the time
- ⊂⊃ About ¼ of the time
- ⊂⊃ Never or Almost Never
- ⊂⊃ Don't Know

(Please provide a brief explanation [e.g. I mainly ate it at restaurants]).

_____.

57c. How often was the **mixed fruit or fruit cocktail** prepared from FROZEN?

- ⊂⊃ Always or Almost Always
- ⊂⊃ About ¾ of the time
- ⊂⊃ About ½ of the time
- ⊂⊃ About ¼ of the time
- ⊂⊃ Never or Almost Never
- ⊂⊃ Don't Know

(Please provide a brief explanation [e.g. I mainly ate it at restaurants]).

_____.

58. Please list any other FRUITS not listed above that that you eat **from a can or frozen** at least once per week, the number of servings you eat per week or day and indicate if the item is canned or frozen.

Fruit	Servings per week or day	Frozen or Canned?

59. In the past 12 months how often did you consume **stews and curries**?

- ⊂⊃ NEVER or less than once per month (skip to Question 60)
- ⊂⊃ 1 time per month
- ⊂⊃ 2 – 3 times per month
- ⊂⊃ 1 time per week
- ⊂⊃ 2 times per week
- ⊂⊃ 3 - 4 times per week
- ⊂⊃ 5 - 6 times per week
- ⊂⊃ 1 time per day
- ⊂⊃ 2 or more times per day

59b. How often were the **stews or curries** prepared from a CAN?

- ⊂⊃ Always or Almost Always
- ⊂⊃ About ¾ of the time
- ⊂⊃ About ½ of the time
- ⊂⊃ About ¼ of the time
- ⊂⊃ Never or Almost Never
- ⊂⊃ Don't Know

(Please provide a brief explanation [e.g. I mainly ate it at restaurants]).

_____.

59c. How often were the **stews or curries** prepared from FROZEN or PREPACKAGED MIX (not canned)?

- ⊂⊃ Always or Almost Always
- ⊂⊃ About ¾ of the time
- ⊂⊃ About ½ of the time
- ⊂⊃ About ¼ of the time
- ⊂⊃ Never or Almost Never
- ⊂⊃ Don't Know

(Please provide a brief explanation [e.g. I mainly ate it at restaurants]).

_____.

60. In the past 12 months how often did you eat **chili** (with meat or beans)?

- ⊂⊃ NEVER or less than once per month (skip to Question 61)
- ⊂⊃ 1 time per month
- ⊂⊃ 2 – 3 times per month
- ⊂⊃ 1 time per week
- ⊂⊃ 2 times per week
- ⊂⊃ 3 - 4 times per week
- ⊂⊃ 5 - 6 times per week
- ⊂⊃ 1 time per day
- ⊂⊃ 2 or more times per day

60b. How often was the **chili** ready-to-eat from a CAN (such as Campbell's® Chunky Grilled Steak Chili with Beans)?

- ⊂⊃ Always or Almost Always
- ⊂⊃ About ¾ of the time
- ⊂⊃ About ½ of the time
- ⊂⊃ About ¼ of the time
- ⊂⊃ Never or Almost Never
- ⊂⊃ Don't Know

(Please provide a brief explanation [e.g. I mainly ate it at restaurants]).

_____.

60c. How often was the **chili** a FROZEN ENTREE or prepared from a PREPACKAGED MIX (not canned)?

- ⊂⊃ Always or Almost Always
- ⊂⊃ About ¾ of the time
- ⊂⊃ About ½ of the time
- ⊂⊃ About ¼ of the time
- ⊂⊃ Never or Almost Never
- ⊂⊃ Don't Know (Please provide a brief explanation [e.g. I mainly ate it at restaurants]).

_____.

61. In the past 12 months how often did you eat **spaghetti or another pasta with tomato sauce**?

- ⊂⊃ NEVER or less than once per month (skip to Question 62)
- ⊂⊃ 1 time per month
- ⊂⊃ 2 – 3 times per month
- ⊂⊃ 1 time per week
- ⊂⊃ 2 times per week
- ⊂⊃ 3 - 4 times per week
- ⊂⊃ 5 - 6 times per week
- ⊂⊃ 1 time per day
- ⊂⊃ 2 or more times per day

61b. How often was the **spaghetti or other pasta in tomato sauce** ready-to-eat from a CAN (such as Campbell's SpaghettiOs®)

- ⊂⊃ Always or Almost Always
- ⊂⊃ About ¾ of the time
- ⊂⊃ About ½ of the time
- ⊂⊃ About ¼ of the time
- ⊂⊃ Never or Almost Never
- ⊂⊃ Don't Know

(Please provide a brief explanation [e.g. I mainly ate it at restaurants]).

_____.

61c. How often was the **spaghetti or other pasta in tomato sauce** a FROZEN ENTRÉE or prepared from a PREPACKAGED MIX (not canned)?

- ⊂⊃ Always or Almost Always
- ⊂⊃ About ¾ of the time
- ⊂⊃ About ½ of the time
- ⊂⊃ About ¼ of the time
- ⊂⊃ Never or Almost Never
- ⊂⊃ Don't Know

(Please provide a brief explanation [e.g. I mainly ate it at restaurants]).

_____.

62. In the past 12 months how often did you eat **pasta with oil, cheese or cream sauce** (including macaroni and cheese)?

- ⊂⊃ NEVER or less than once per month (skip to Question 63)
- ⊂⊃ 1 time per month
- ⊂⊃ 2 – 3 times per month
- ⊂⊃ 1 time per week
- ⊂⊃ 2 times per week
- ⊂⊃ 3 - 4 times per week
- ⊂⊃ 5 - 6 times per week
- ⊂⊃ 1 time per day
- ⊂⊃ 2 or more times per day

62b. How often was the **pasta in oil, cheese or cream sauce** a FROZEN ENTRÉE or prepared from a PREPACKAGED MIX (not canned)?

- ⊂⊃ Always or Almost Always
- ⊂⊃ About ¾ of the time
- ⊂⊃ About ½ of the time
- ⊂⊃ About ¼ of the time
- ⊂⊃ Never or Almost Never
- ⊂⊃ Don't Know

(Please provide a brief explanation [e.g. I mainly ate it at restaurants]).

_____.

63. In the past 12 months how often did you eat **Asian-style (stir-fried) noodles and rice** such as chow mein, fried rice and Pad Thai?

- ⊂⊃ NEVER or less than once per month (skip to Question 64)
- ⊂⊃ 1 time per month
- ⊂⊃ 2 – 3 times per month
- ⊂⊃ 1 time per week
- ⊂⊃ 2 times per week
- ⊂⊃ 3 - 4 times per week
- ⊂⊃ 5 - 6 times per week
- ⊂⊃ 1 time per day
- ⊂⊃ 2 or more times per day

63b. How often were the **Asian-style noodles and rice** ready-to-eat from a CAN?

- ⊂⊃ Always or Almost Always
- ⊂⊃ About ¾ of the time
- ⊂⊃ About ½ of the time
- ⊂⊃ About ¼ of the time
- ⊂⊃ Never or Almost Never
- ⊂⊃ Don't Know

(Please provide a brief explanation [e.g. I mainly ate it at restaurants]).

_____.

63c. How often were the **Asian-style noodles and rice** a FROZEN ENTRÉE or prepared from a PREPACKAGED MIX (not canned)?

- ⊂⊃ Always or Almost Always
- ⊂⊃ About ¾ of the time
- ⊂⊃ About ½ of the time
- ⊂⊃ About ¼ of the time
- ⊂⊃ Never or Almost Never
- ⊂⊃ Don't Know

(Please provide a brief explanation [e.g. I mainly ate it at restaurants]).

_____.

64. In the past 12 months how often did you eat **soup** (any type)?

- ⊂⊃ NEVER or less than once per month (skip to Question 65)
- ⊂⊃ 1 time per month
- ⊂⊃ 2 – 3 times per month
- ⊂⊃ 1 time per week
- ⊂⊃ 2 times per week
- ⊂⊃ 3 - 4 times per week
- ⊂⊃ 5 - 6 times per week
- ⊂⊃ 1 time per day
- ⊂⊃ 2 or more times per day

64b. How often was the **soup** ready-to-eat from a CAN?

- ⊂⊃ Always or Almost Always
- ⊂⊃ About ¾ of the time
- ⊂⊃ About ½ of the time
- ⊂⊃ About ¼ of the time
- ⊂⊃ Never or Almost Never
- ⊂⊃ Don't Know

(Please provide a brief explanation [e.g. I mainly ate it at restaurants]).

_____.

64c. How often was the **soup** a FROZEN ENTRÉE or prepared from a PREPACKAGED MIX (not canned)?

- ⊂⊃ Always or Almost Always
- ⊂⊃ About ¾ of the time
- ⊂⊃ About ½ of the time
- ⊂⊃ About ¼ of the time
- ⊂⊃ Never or Almost Never
- ⊂⊃ Don't Know

(Please provide a brief explanation [e.g. I mainly ate it at restaurants]).

_____.

65. In the past 12 months how often did you eat **microwave meals or frozen entrees**?

- ⊂⊃ NEVER or less than once per month
- ⊂⊃ 1 time per month
- ⊂⊃ 2 – 3 times per month
- ⊂⊃ 1 time per week
- ⊂⊃ 2 times per week
- ⊂⊃ 3 - 4 times per week
- ⊂⊃ 5 - 6 times per week
- ⊂⊃ 1 time per day
- ⊂⊃ 2 or more times per day

66. Please list any other MIXED DISHES not listed above that you eat from at least once per week, the number of servings you eat per week or day, and whether it is typically prepared fresh, from a can, frozen or from a package (non-canned).

Mixed Dish	Servings per week or day	Canned, fresh, frozen, packaged, don't know

Beverage Intake Details

67. In the past 12 months how often did you typically drink **water** (including tap, bottled, and carbonated)?

- ⊂⊃ 1 time per month
- ⊂⊃ 2 – 3 times per month
- ⊂⊃ 1 time per week
- ⊂⊃ 2 times per week
- ⊂⊃ 3 - 4 times per week
- ⊂⊃ 5 - 6 times per week
- ⊂⊃ 1 time per day
- ⊂⊃ 2 or more times per day

67b. How often was the **water** you drank TAP WATER, including filtered water?

- ⊂⊃ Always or Almost Always
- ⊂⊃ About ¾ of the time
- ⊂⊃ About ½ of the time
- ⊂⊃ About ¼ of the time
- ⊂⊃ Never or Almost Never
- ⊂⊃ Don't Know

(Please provide a brief explanation [e.g. I mainly ate it at restaurants]).

_____.

67c. When you drank TAP WATER what did you typically drink the water from?

- ⊂⊃ In a cup, glass or mug made of glass
- ⊂⊃ In a cup, glass or mug made of plastic
- ⊂⊃ In a reusable METAL bottle
- ⊂⊃ In a reusable PLASTIC bottle
- ⊂⊃ Other (Please Specify:_____)

67d. How often was the **water** you drank BOTTLED WATER (purchased in a bottle)?

- ⊂⊃ Always or almost always
- ⊂⊃ About ¾ of the time
- ⊂⊃ About ½ of the time
- ⊂⊃ About ¼ of the time
- ⊂⊃ Never or rarely drink

68. In the past 12 months how often did you typically drink **tomato or vegetable juice**?

- ⊂⊃ NEVER or less than once per month (skip to Question 69)
- ⊂⊃ 1 time per month
- ⊂⊃ 2 – 3 times per month
- ⊂⊃ 1 time per week
- ⊂⊃ 2 times per week
- ⊂⊃ 3 - 4 times per week
- ⊂⊃ 5 - 6 times per week
- ⊂⊃ 1 time per day
- ⊂⊃ 2 or more times per day

68b. When you drank **tomato or vegetable juice** was it MOST OFTEN**:**

- ⊂⊃ Canned
- ⊂⊃ Bottled, plastic
- ⊂⊃ Bottled, glass
- ⊂⊃ Other (Please specify:_____)

69. In the past 12 months how often did you typically drink **soft drinks** (including energy drinks)?

- ⊂⊃ NEVER or less than once per month (skip to Question 70)
- ⊂⊃ 1 time per month
- ⊂⊃ 2 – 3 times per month
- ⊂⊃ 1 time per week
- ⊂⊃ 2 times per week
- ⊂⊃ 3 - 4 times per week
- ⊂⊃ 5 - 6 times per week
- ⊂⊃ 1 time per day
- ⊂⊃ 2 or more times per day

69b. When you consumed **soft drinks** were they MOST OFTEN:

- ⊂⊃ Canned
- ⊂⊃ Bottled, plastic
- ⊂⊃ Bottled, glass
- ⊂⊃ Soda Fountain (such as in some restaurants)
- ⊂⊃ Other (Please specify:_____)

70. In the past 12 months how often did you typically drink **beer**?

- ⊂⊃ NEVER or less than once per month (skip to Question 71)
- ⊂⊃ 1 time per month
- ⊂⊃ 2 – 3 times per month
- ⊂⊃ 1 time per week
- ⊂⊃ 2 times per week
- ⊂⊃ 3 - 4 times per week
- ⊂⊃ 5 - 6 times per week
- ⊂⊃ 1 time per day
- ⊂⊃ 2 or more times per day

70b. If you consumed **beer** was it MOST OFTEN:

- ⊂⊃ Canned
- ⊂⊃ Bottled, plastic
- ⊂⊃ Bottled, glass
- ⊂⊃ From a tap
- ⊂⊃ Other (Please specify:_____)

71. In the past 12 months how often did you drink **protein shakes or meal replacement drinks**?

- ⊂⊃ NEVER or less than once per month (skip to Question 72)
- ⊂⊃ 1 time per month
- ⊂⊃ 2 – 3 times per month
- ⊂⊃ 1 time per week
- ⊂⊃ 2 times per week
- ⊂⊃ 3 - 4 times per week
- ⊂⊃ 5 - 6 times per week
- ⊂⊃ 1 time per day
- ⊂⊃ 2 or more times per day

71b. When you drank **protein shakes or meal replacement drinks** were they MOST OFTEN:

- ⊂⊃ Canned
- ⊂⊃ Bottled, plastic
- ⊂⊃ Prepared at a restaurant
- ⊂⊃ Other (Please specify:_____)

72. In the past 12 months how often did you drink **fruit drinks**, (such as Hi-C®, Kool-Aid®, and Hawaiian Punch®)?

- ⊂⊃ NEVER or less than once per month (skip to Question 73)
- ⊂⊃ 1 time per month
- ⊂⊃ 2 – 3 times per month
- ⊂⊃ 1 time per week
- ⊂⊃ 2 times per week
- ⊂⊃ 3 - 4 times per week
- ⊂⊃ 5 - 6 times per week
- ⊂⊃ 1 time per day
- ⊂⊃ 2 or more times per day

72b. When you drank **fruit drinks** were they MOST OFTEN:

- ⊂⊃ Prepared from concentrate
- ⊂⊃ Canned
- ⊂⊃ Bottled, plastic
- ⊂⊃ Bottled, glass
- ⊂⊃ Cardboard carton
- ⊂⊃ Other (Please specify:_____)

73. In the past 12 months how often did you **fruit juices**, (such as orange, apple, grape, and cranberry)?

- ⊂⊃ NEVER or less than once per month (skip to Question 74)
- ⊂⊃ 1 time per month
- ⊂⊃ 2 – 3 times per month
- ⊂⊃ 1 time per week
- ⊂⊃ 2 times per week
- ⊂⊃ 3 - 4 times per week
- ⊂⊃ 5 - 6 times per week
- ⊂⊃ 1 time per day
- ⊂⊃ 2 or more times per day

73b. When you drank **fruit juices** were they MOST OFTEN:

- ⊂⊃ Prepared from concentrate
- ⊂⊃ Canned
- ⊂⊃ Bottled, plastic
- ⊂⊃ Bottled, glass
- ⊂⊃ Cardboard carton
- ⊂⊃ Other (Please specify:_____)

74. In the past 12 months how often did you drink **coffee**?

- ⊂⊃ NEVER or less than once per month (skip to Question 75)
- ⊂⊃ 1 time per month
- ⊂⊃ 2 – 3 times per month
- ⊂⊃ 1 time per week
- ⊂⊃ 2 times per week
- ⊂⊃ 3 - 4 times per week
- ⊂⊃ 5 - 6 times per week
- ⊂⊃ 1 time per day
- ⊂⊃ 2 or more times per day

74b. When you drank **coffee** was it MOST OFTEN:

- ⊂⊃ Prepared from beans/grounds, any package type
- ⊂⊃ Single-serve coffee capsules, plastic (such as Keurig®)
- ⊂⊃ Single-serve coffee capsules, metal (such as Nespresso®)
- ⊂⊃ Ready-to-drink, canned (such as Starbuck's® DoubleShot)
- ⊂⊃ Ready-to-drink, plastic
- ⊂⊃ Pre-made, glass bottle
- ⊂⊃ Other (Please specify:_____)

75. In the <u>past 12 months</u> how often did you drink **tea** (both hot and iced tea)?

- ⊂⊃ NEVER or less than once per month
- ⊂⊃ 1 time per month
- ⊂⊃ 2 – 3 times per month
- ⊂⊃ 1 time per week
- ⊂⊃ 2 times per week
- ⊂⊃ 3 - 4 times per week
- ⊂⊃ 5 - 6 times per week
- ⊂⊃ 1 time per day
- ⊂⊃ 2 or more times per day

75b. When you drank **tea** was it <u>MOST OFTEN</u>:

- ⊂⊃ Prepared from loose tea leaves or tea bags
- ⊂⊃ Ready to drink, in a can
- ⊂⊃ Ready to drink, in a plastic bottle
- ⊂⊃ Ready to drink, in a glass bottle
- ⊂⊃ Other (Please specify:_____)

You have reached the end of this questionnaire. Thank you for your time and participation in this study!

Appendix 4: Calculation of Canned Food Intakes and Foods Included in Canned Food Categories

Over the past 12 months how often did you eat…….		**How often was it CANNED/FROZEN?**	
	Score Weight 1		Score Weight 2
Never	0	Never/Don't Know ¼ of Time ½ of Time ¾ of Time Always/Almost Always	0 0.25 0.5 0.75 1.0
1 time per month	0.035		
2 – 3 times per month	0.0875		
1 time per week	0.14		
2 times per week	0.29		
3 – 4 times per week	0.5		
5 – 6 times per week	0.79		
1 time per day	1.0		
2 or more times per day	2.0		

Score Calculation Equation:
Score weight 1 * Score weight 2 = canned/frozen intake

Example:
Canned Corn
Person 1 – Never eats canned corn
Score = 0

Person 2 – 1 time per week, canned ½ of the time
Score = 0.14*0.5 = 0.07

Person 3 – 1 time per day, canned ¼ of the time
Score = 1.0*0.25 = 0.25

Food Items Included in Canned Food Groups			
Canned Vegetables	**Canned Fruits**	**Canned Meals**	**Total Can**
• Corn • Green beans • Greens (spinach, mustard, collard) • Peas • Mixed vegetable/vegetable medley • Mushrooms • Tomatoes/tomato sauce/tomato paste • Yams/sweet potato	• Pears • Peaches • Oranges/tangerines • Strawberries • Raspberries • Blueberries • Other berries (cranberries, cherries) • Pineapple • Mixed fruit/fruit cocktail	• Stews + Curries • Chili • Spaghetti or other pasta in tomato sauce • Asian-style noodle/rice • Soup	• Canned Vegetables • Canned Fruits • Canned Meals • Lunch meats • Tuna • Chicken • Other (sardines) • Refried/baked/plain (navy, black, garbanzo beans)/lima beans