Evaluation of Bisphenol A Dermal Exposure and Toxicokinetics among Cashiers: Final Progress Report

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List of Terms and Abbreviations

BPA – bisphenol A
BPS – bisphenol sulfone, bisphenol S
RM – ResearchMatch.org or Research Match
LOD – limit of detection
GM – geometric mean
NHANES – National Health and Nutrition Examination Survey

Abstract

The expanding service industry in the U.S. carries with it unique exposures and risks. A case in point is cashiers' exposure to BPA that coats receipt tape as thermal developer. Such exposures are of particular concern among cashiers because the workforce is dominated by women of childbearing age and there is evidence to suggest that BPA may act as an endocrine disruptor. A critical data gap to evaluating this risk is the level and extent of exposure associated with handling receipt tape. To address this gap, we conducted two related experiments. The first was a 6-person controlled exposure study where subjects handled receipts in a prescribed fashion and exposure was evaluated based on transfer (receipt tape and hands) and pre- and post-exposure (~21 hours) urinary biomarker measurements. The second study was observational where pre- and post-shift urinary BPA and BPS were measured for 25 cashiers.

Our results are preliminary. In the controlled exposure experiment, blood collection was abandoned due to unavoidable contamination from collection supplies. In both experiments, BPA and BPS were successfully measured in environmental and biological media; however, a clear exposure signal was not evident. Among cashiers, on average the post-shift concentration exceeded pre-shift by 30% but that difference was not significant ($p>0.05$). The levels of BPA detected in cashiers was within the 50 – 75% NHANES observed range, despite a protocol aimed at minimizing the dominant source of exposure, diet. Taken together, preliminary results suggest that the exposure signal associated with receipt handling may be indistinguishable from intrapersonal variability given the limitations of this study design. However, we cannot conclude that cashier exposure to receipt tape is unimportant, since uncertainty remains about the long-term effects of low-level chronic exposure to endocrine disrupting compounds like BPA and BPS. Future research should focus primarily on BPS exposure and other alternative thermal developers that arrive on the market, since much less is known about their potential adverse health effects and exposure sources and levels in the general population.

Section 1

Significant (Key) Findings

The main aims of this research project were to: 1) Conduct a controlled human exposure experiment (6 subjects; 4 exposed to BPA-coated receipts and 2 exposed to BPA-free receipts) to provide a detailed mass balance and toxicokinetic evaluation of the dermal absorption of BPA from coated cash register receipts, metabolism, distribution, and elimination in urine, and 2) Quantitatively evaluate dermal exposure to BPA and BPS among cashiers based on the change in urine levels from pre to post shift.

We had hypothesized that we would see an increase in urinary excretion of BPA in the BPA-receipt-handling group of the first experiment, and an increase in urinary excretion of BPS in the BPS-receipt-handling group. We hypothesized that post-shift urinary BPA and BPS concentrations would be higher than pre-shift concentrations for the thermal developer to which a cashier was exposed.

The key significant findings from this project include:

1. Our extensive evaluation of available blood collection devices, supplies and techniques revealed measurable contamination of BPA into blood specimens in the same concentration range that we expected in the receipt-handling experiment (Teeguarden et al., 2015). Therefore, we concluded that no meaningful data were possible using blood measurements.

2. Over the course of this study the proportion of receipts in the marketplace coated with BPA compared to an alternative developer has shifted from 40-80% to 20-30%, with many cashiers now exposed to BPS rather than BPA.

3. The data suggests that dermal uptake and metabolism may be slower for BPA than has been observed for the dietary ingestion route of exposure. BPA transferred to the skin from handling receipt papers appears to be eliminated in urine later than would be expected based on the previously published half-life of 4-6 hours and complete urinary elimination in 24 hours.

4. There may be some important differences between BPA and BPS in terms of dermal transfer, uptake and metabolism. In general in our experimental study, the amount of BPA in the BPA-receipt-handling group was clearly higher than in the BPS-receipt-handling group. However, a similar elevation of BPS in the BPS-receipt-handling group was not evident. This question requires further investigation.

5. Observed exposures to thermal developers (BPA and BPS) in cashiers working typical shifts tended to fall in the range of what is normal for the U.S. population. However, since the study attempted to minimize dietary exposure to BPA, it is possible that the dermal contribution constitutes a significant addition to total exposure among cashiers; especially those who might have a higher background level because of their dietary habits. It is likely that our results underestimate the dermal contribution to total exposure because the timing of our post-shift sample probably occurred before the peak of urinary BPA or BPS. Although BPA and BPS concentrations on average were higher post-shift relative to pre-shift, the difference was not significant.

Translation of Findings

On the whole, these results suggest that cashiers may be subject to increased exposure to the thermal developer chemical (BPA or BPS) that coats the receipts handled in their workplace. However, the exposure levels are still quite low, and orders of magnitude below the reference dose (RfD) of 50 µg/kg-day set by the U.S. Environmental Protection Agency. Should subsequent research call into question the protective value of this RfD, it will be important to reexamine these results in context of a revised safety level. There is still more to learn, especially regarding the roll of lotions or hand sanitizers and hand-washing habits in increasing or decreasing exposure, and the potential for substantially higher exposures for certain individuals who may have higher background/dietary exposures to BPA or BPS or be particularly vulnerable to endocrine disruptive effects.

Outcomes/Impact

The findings from this research hold great significance for worker health and safety. The substantial U.S. retail workforce is made up of a large fraction of women who are of reproductive age and therefore particularly vulnerable to the possible reproductive and endocrine disruptive effects of BPA or BPS. We can now say with some confidence that cashiers are not generally exposed to excessive amounts of BPA or BPS from dermal contact with receipts. However, their exposure is not unimportant, since uncertainty remains about the long-term effects of low-level chronic exposure to endocrine disrupting compounds like BPA and BPS. Future research should focus primarily on BPS exposure and other alternative thermal developers that arrive on the market, since much less is known about their potential adverse health effects and exposure sources and levels in the general population.

Our data also suggest that we need to shift our focus to the potential health impacts of workers' exposure to BPS, since the market has substantially changed with regard to thermal developers in the last 2-3 years. While BPA has been studied extensively, with some questions about exposure and health effects yet to be settled, BPS has seen much less scientific and public scrutiny.

We have found that BPA and BPS may remain in the body longer when exposed through the dermal rather than ingestion route, which is another area for future study, since BPA has long been assumed unlikely to cause widespread adverse effects due to its quick first-pass metabolism and short residence time in the body. This assumption may not hold for those cashiers and other workers who are dermally exposed.

Our evaluation of blood collection devices and conclusion that contamination was impossible to avoid contributes important information to the field of BPA exposure research as a whole, since contamination from laboratory and clinical environments has long been suspected but sources and causes not fully elucidated.

Section 2

Scientific Report

Background

Approximately 6 billion pounds of BPA is produced annually worldwide and used in a variety of consumer products (Vogel, 2009). Although BPA has long been recognized as a component of polycarbonate plastics and epoxy resins that pose an ingestion hazard, a concern has emerged over the dermal exposure hazard among workers and consumers resulting from its use in thermal printing papers including cash register receipts (Biedermann, Tschudin, & Grob, 2010; Geens, Goeyens, & Covaci, 2011; Liao & Kannan, 2011a). Considering that as much as 40-80% of receipts may be coated with BPA (Biedermann et al., 2010; Lunder, Andrews, & Houlihan, 2010; Mendum, Stoler, VanBenschoten, & Warner, 2011; Schreder, 2010) and there are 3.1 million cashiers (U.S Bureaus of Census & Labor Statistics, 2010) in the U.S. who handle this material frequently over work shifts, there is an enormous potential for exposure. At the time our study began, there had only been one published report of the potential for dermal transfer of BPA from receipts to the skin (Biedermann et al., 2010). Additional suggestive evidence is provided by Braun et al. who describe elevated exposures among cashiers based on urinary BPA concentrations among pregnant women (n=17) working as cashiers (Braun et al., 2011). In vitro evidence based on viable human skin explants and cultured pig ear skin models have shown that BPA is readily absorbed through (46-65%) and metabolized by the skin (Zalko, Jacques, Duplan, Bruel, & Perdu, 2011).

The workplace dermal exposure that cashiers receive occurs on top of background levels that are not unsubstantial. Considering the large-scale production and use of BPA in consumer products, it is not surprising that the U.S. population is generally exposed to background levels of BPA. Evidence of BPA exposure, uptake, and internal dose comes from broad-based studies establishing the presence of BPA in human urine (Calafat, Ye, Wong, Reidy, & Needham, 2008; Chapin et al., 2008), serum (Calafat et al., 2008; Yamada et al., 2002), amniotic fluid (Yamada et al., 2002), breast milk (Ye, Bishop, Needham, & Calafat, 2008; Ye, Kuklenyik, Needham, & Calafat, 2006), colostrum (Kuruto-Niwa, Tateoka, Usuki, & Nozawa, 2007), umbilical cord blood (Tan, 2003), and adipose tissue (Fernández et al., 2007) in populations around the world which span a multitude of ages, races, ethnicities, and life stages (i.e. pregnancy, etc.). In a nationally representative sample of the U.S. population, BPA was detected in the urine of 96.2% of respondents, with a geometric mean of 2.6 µg/L (2.6 µg/g creatinine) (Calafat et al., 2008).

The current study was motivated, in part, by our own analysis of NHANES 2003-2004 data suggesting an occupational exposure concern with receipt tape as a likely source. We examined occupational factors and BPA exposure for women of reproductive age (16-44 years old) and for all workers. Clustering effects and sampling weights were taken into account (Centers for Disease Control and Prevention & National Center for Health Statistics (NCHS), n.d.). In examining the data for women of reproductive age, we observed significantly higher geometric mean (GM) creatinine-adjusted urinary BPA concentrations among women who were currently working in the retail industry and in the communications industry, as well as for those who reported their occupation to be “supervisors and proprietors, sales,” compared to the overall GM for all working women of reproductive age ($p<0.001$ for each). When all workers were considered, “food store retail industry” workers was the only group that stood out with creatinine-adjusted urinary BPA concentrations (GM=4.71 µg/g creatinine; n=19) significantly higher ($p=.001$) than workers in all other industries (GM=2.35 µg/g creatinine; n=896) (Seryak, Lynch, Andridge, & Buckley, 2011).

There is considerable evidence to suggest that non-occupational background exposure to BPA comes mostly through diet (Chapin et al., 2008; Vandenberg, Hauser, Marcus, Olea, & Welshons, 2007; von Goetz, Wormuth, Scheringer, & Hungerbühler, 2010). BPA has been measured in samples of foods stored in epoxy-resin-lined cans (Cao et al., 2008; Goodson, Robin, Summerfield, & Cooper, 2004; Kubwabo et al., 2009; Le, Carlson, Chua, & Belcher, 2008; Munguia-Lopez & Soto-Valdez, 2001) and also comes from leaching of reusable polycarbonate drinking bottles (Carwile et al., 2009). Rudel et al. observed a 66% reduction in urinary BPA levels associated with an intervention consisting of eliminating foods and beverages that may have come in contact with BPA-containing materials (Rudel et al., 2011). Our study relied on some of these strategies to minimize dietary background contributions and to isolate the dermal contribution. While a few studies have attempted to estimate cashier and consumer exposure to BPA from receipt-handling simulations (Ehrlich, Calafat, Humblet, Smith, & Hauser, 2014; Hormann et al., 2014; Porras, Heinälä, & Santonen, 2014), ours is only the second to report observations of cashiers' actual exposures during a normal work day (Thayer et al., 2015).

The health risks associated with BPA exposure are controversial; however, there is ample evidence for concern, especially considering the size of the impacted workforce (i.e. 1.3 million), potential for exposure, and vulnerability (i.e. women of reproductive age). Most of the effects that have been observed and hypothesized are endocrine-mediated.

Specific Aims

We revised Specific Aim 1 to reflect our decision to eliminate all blood samples from the study. After our extensive evaluation of available blood collection devices, supplies and techniques, we found they yielded measurable contamination of BPA into blood specimens in the same concentration range that we would expect to observe in our experiment (Teeguarden et al., 2015). Therefore, we concluded that no meaningful data were possible using blood measurements.

Mid-way through data collection (Nov/Dec 2014) for Specific Aim 2, it became apparent that the proportion of stores using BPA-containing receipts compared to the alternative, bisphenol sulfone (BPS), was much smaller (20-30%) than we anticipated based on the most recent literature from 2010-2012 (Lunder et al. 2010; Liao & Kannan 2011; Geens et al. 2012). In consultation with our scientific program official, we altered our enrollment method to accept all interested and eligible cashiers regardless of the thermal developer content (BPA or BPS) of their store's receipts. Without this change we would have been unable to enroll enough BPA-receipt-handling cashiers during the study period because of the infrequency of its current use. Related revisions to Aim 2 are presented below.

Specific Aim 1 (Experimental study): Conduct a controlled human exposure experiment (6 subjects; 4 exposed to BPA-coated receipts and 2 exposed to BPA-free receipts) to provide a detailed mass balance and toxicokinetic evaluation of the dermal absorption of BPA from coated cash register receipts, metabolism, distribution, and elimination in urine. This analysis will be based on measurements of BPA loss from receipts after prescribed hand contact and repeated measures of BPA in urine for up to 10 hours post exposure.

Specific Aim 2 (Observational study): Quantitatively evaluate dermal exposure to BPA and BPS among cashiers. Cashiers (n=28; exposed to thermal receipts coated with either BPA or BPS) will be recruited through advertisements in local newspapers and existing Ohio State University networks. The presence of BPA or BPS on receipt tape will be confirmed, and cashier exposure will be evaluated based on the change in urine levels from pre to post shift.

Methods

The full protocols for each aim were approved by the Ohio State University's (OSU) Institutional Review Board (IRB) and the OSU Clinical Research Center's (CRC) Scientific Advisory Committee. All participants provided written informed consent prior to their participation.

Aim 1 (Experimental study)

Since the start of our study, concerns about blood collection devices contaminating samples had been raised by several BPA researchers (Birnbaum et al. 2012; Vandenberg et al. 2014). We conducted extensive research on available devices and components and contacted the manufacturers to confirm the materials used in each. Based on those results, our collaborator, Dr. Dan Doerge at the FDA, tested the set-up we expected would be least likely to contaminate blood samples with BPA. Using both water and clean (BPA-free) rat serum, he found that serial blood sample collection using these supplies/devices yielded measurable contamination in the same concentration range as we hypothesized we would find during our experiment. Therefore, we concluded that no meaningful data were possible using blood measurements, and we decided to eliminate all blood samples from this study.

Sample Size

We collected a convenience sample comprised of 4 participants in the BPA-coated receipt group and 2 participants in the BPS-coated receipt group (i.e. comparison group). Groups had equal numbers of males and females. Sample size was based on a balance between cost and number of participants.

Eligibility

Potential participants were screened for eligibility based on the following criteria: age 21-55 years, healthy (no colds, GI, kidney, or liver disease), non-smoking, non-pregnant, HIV and hepatitis free, not on anticoagulant medication, no problems with low blood pressure, no allergy, sensitivity or intolerance to wheat or gluten, and no cuts, eczema, or abrasion on the hands. Individuals were excluded if their occupation involved handling receipts. Participants were recruited from the OSU and central-Ohio community.

Recruitment/enrollment

Participants were recruited by ResearchMatch.org. ResearchMatch is a national, electronic, web-based volunteer recruitment tool that was created through the Clinical & Translational Science Awards Consortium in 2009 and is maintained at Vanderbilt University. Of the 6 participants enrolled in the study, 5 were recruited directly through the RM system and the sixth learned of the study from one of the others and contacted us to participate.

Study procedures

Pre-exposure period. To minimize BPA levels in urine for the pre-exposure period, participants were asked to fast from 12:00 am (midnight) or whenever they went to bed (whichever was earlier) and to avoid handling receipts or cash. They were also instructed to refrain from the use of lotions and hand sanitizers from the beginning of the fast through the end of their study participation. Consumption of unfiltered tap water from the stainless steel bottle we provided was allowed and encouraged for hydration throughout the entire day preceding the study. Upon arrival to the CRC facilities around 9:00 a.m., informed consent was obtained, height, weight and vitals were measured, and a urine sample was collected. Then a fresh breakfast designed to minimize BPA dietary exposure was provided. The breakfast included eggs, coffee, water, toast with butter and/or jam and fresh fruit. A short interview

assessed compliance with overnight fasting and collected basic demographic information about participants. Participants' hands were each traced on graph paper in order to estimate surface area.

Exposure period. All procedures were supervised by study personnel and conducted in the clinical facilities of the CRC with assistance from research nurses. Standard (7.9 cm wide) thermal receipt roll known to contain BPA was used to expose the 4 BPA-group participants (Kanzaki Specialty Papers, Ware, MA). A similar size thermal receipt roll known to be BPA-free and alternately coated with BPS was used for the 2 comparison-group participants (Appleton Papers, now doing business as Apvion, Appleton, WI). Each volunteer was coached to perform a receipt-handling procedure consisting of passing a 10-inch long receipt through the fingertips of both hands repeatedly for 2 minutes. This action was immediately followed by folding the receipt in half and holding it pressed between the fingers and palms of both hands with the thermal BPA-side in contact with the skin for one minute for a total of 3 minutes of receipt-handling time. The participant then placed the handled receipt back into its amber glass storage jar. There was then a one minute break and afterwards the receipt-handling procedure was repeated three more times using a fresh 10-inch long receipt each time, with a 1-minute break between each repetition for a total of 4 receipt-handling cycles. Each of the handled tapes was stored in its amber glass jar until extraction. For each handled tape, a control, untouched, 10-inch tape strip was cut immediately following each handled tape and stored in a separate amber glass jar until extraction.

In total, each participant provided 10-15 urine samples (depending on urine void frequency and bedtime) over the course of the study day (about 21-22 hours). Samples were frozen and shipped to Dr. Daniel Doerge at the U.S. Food and Drug Administration for laboratory analysis of total and free BPA and BPS concentrations by high-performance liquid chromatography tandem mass spectrometry (HPLC-MS/MS). At Ohio State we also used Nymox TobacAlert to test one urine sample per participant (the last one) for cotinine concentration, providing an estimate of exposure to tobacco smoke (primary and secondary). Urine samples were analyzed for creatinine using the Dimension Xpand Clinical Chemistry System (Siemens Medical Diagnostics, Decatur, Ga.) The method is an adaptation of the Jaffe reaction reported by Larsen (1972). Samples were run in singular. The analytical sensitivity was 0.05 mg/dL.

Aim 2 (Observational study)

Sample size

Sample size calculations were based on conservative effect sizes estimated from NHANES 2003-2004 BPA data (Centers for Disease Control and Prevention (CDC) and National Center for Health Statistics (NCHS) 2003) and previously published data (Ye et al. 2011). We considered this estimate to be conservative because the timing of our sampling is optimized to detect a difference whereas the NHANES sampling was not. We assume 2-tailed tests and a 0.05 level of significance. In NHANES 2003-2004, mean creatinine-adjusted natural log-transformed urinary BPA was 1.55 (SD=0.89) for workers in the "retail-food store" industry compared to 0.85 (SD=0.81) for workers in any other industry. In the proposed study, each subject will be measured pre-shift and post-shift, so using a correlation factor of r=0.23 derived from the between-person portion of the variance from Ye (2011), we calculated the standard deviation of the difference to be 1.1 (Ye et al. 2011). Using these values, we estimated that we would need 23 cashiers to have 85% power to detect a non-zero change in natural log-transformed creatinine-adjusted urinary BPA concentration pre-shift to post-shift using a standard t-test. We planned to recruit 24 BPA-exposed cashiers to account for the possibility of a drop-out. We also planned to enroll 4 cashiers unexposed to BPA-coated receipts (ones who work in stores with BPA-free receipts) to serve as a comparison group.

Eligibility

Potential participants were screened for eligibility based on the following criteria: age 21-55 years, healthy (no colds, GI, kidney, or liver disease), non-smoking, non-pregnant, HIV and hepatitis free, no allergy, sensitivity or intolerance to wheat/gluten, and no cuts, eczema, or abrasion on the hands. Additionally, participants worked at least an 8-hour shift with at least 75% of the shift as a cashier, or worked at least 6 hours of any length shift handling receipts. For most of the study we excluded participants (in excess of the 4 initial "controls") who worked with thermal receipts that did not contain BPA. Later in the study, when it became apparent that the proportion of stores using BPA-containing receipts compared to the alternative, bisphenol sulfone (BPS), was much smaller (20-30%) than we anticipated, we adjusted our enrollment method to accept all interested and eligible cashiers regardless of the thermal developer content (BPA or BPS) of their store's receipts.

Recruitment/enrollment

We began recruitment around September 1, 2013 employing a wide array of recruitment strategies, including: ResearchMatch.org, paper flyers posted on public bulletin boards, in-person distribution of paper flyers to store managers, newspaper ads, Craigslist online ads, and social media connections. We also attempted to build a partnership with the United Food and Commercial Workers union (UFCW – Local 1059) that represents many of the workers in this sector; however, the union leadership was unreceptive. As we were finding it more difficult than anticipated to reach and enroll eligible volunteers for the study, we broadened our definition of "cashier" to include all workers who handle thermal receipts frequently throughout the work shift. For instance, this would include servers, bartenders and bank tellers. Accordingly, we revised our recruitment materials to include broader language, for instance, changing the flyer heading to read "Do you work with receipts?" instead of "Are you a cashier?" We also directly targeted for recruitment employees of stores we already knew used BPA-positive receipts, based on our own lab results.

Paper flyers posted on public/community bulletin boards in places like libraries, coffee shops, university buildings and community centers yielded most of our participants. Unfortunately, posting paper flyers requires a lot of staff time and mileage and is not very cost-effective. ResearchMatch.org (RM) proved to be a powerful and cost-effective means of recruitment for this study. We sent email invitations to every potentially eligible registered volunteer living within 50 miles of Ohio State University (n=4,114). Of those, most presumably do not work as cashiers, but this system allowed us a much broader reach than any other method. About 200 RM volunteers agreed to be contacted for additional information; 81% of those who refused to be contacted cited ineligibility as their reason.

Over the subsequent 20 months, we enrolled and completed specimen/data collection from 25 participants. Of the 25 participants, 6 were exposed to BPA-coated receipts, 17 were exposed to BPS-coated receipts, 1 was exposed to a mixture of both BPA- and BPS-coated receipts, and 1 participant was exposed to non-thermal receipts (no BPA or BPS). A total of 336 people contacted us with interest in the study during the enrollment period, of which 25 were enrolled, 121 were ineligible, 6 declined to participate, and 184 became unresponsive prior to eligibility screening or enrollment. 138 of the 184 unresponsives (75%) were ResearchMatch contacts, who clicked "yes" expressing their interest from the initial invitation but never replied to our personal follow-up contact, which may be an indication that they self-determined ineligibility based on the additional information we provided in the follow-up contact.

Results & Discussion

Since the beginning of this study, the distribution of BPA and other developers within the thermal paper market appears to have shifted. Appvion (formerly Appleton Papers, the primary US producer of thermal paper) now only uses their "Alpha Free" point-of-sale thermal paper, which uses Vitamin C as the developer. Until November 2014 Appvion had been using exclusively BPS as a thermal developer since 2006 ("Appvion Launches First Thermal Receipt Paper Made Using Vitamin C in Time for the 2014 Holiday Shopping Season," 2014). Kanzaki, another leading supplier, became entirely BPA-free in 2014 ("Kanzaki Specialty Papers: Safety and Environmental Policies," n.d.). These changes coincide with the change in proportion of stores using BPA or BPS receipts that we observed over the study period of 2013-2015.

Aim 1 (Experimental study)

Total BPA urinary concentrations ranged from <LOD to 5.43 ng/mL. The maximum (5.43 ng/mL) was an unexpectedly high morning, pre-exposure sample, observed despite the subjects reported compliance with fasting instructions and no other likely sources of exposure found through interview. It was more than twice the concentration of the next highest sample (2.41 ng/mL) and was the only sample with a concentration greater than the 75th percentile in NHANES 2011-2012 (LaKind & Naiman, 2015). Most (81%) of the samples fell below the 25th percentile in NAHNES. Since the study covered nearly 24 hours of urine sampling, we compared the total BPA excreted in urine (per kg body weight) for each participant to estimates for daily intake of BPA in the general population based on NHANES 2011-2012 (LaKind & Naiman, 2015). In the BPA receipt-handling group, total BPA excretion over the study day was around the median daily intake in NHANES of about 50 ng/kg day. For the two participants who handled BPS-coated receipts, total BPA excretion was 5.6 and 5.7 ng/kg day, respectively – falling well below the 25th percentile of daily intake (~12 ng/kg day) (LaKind & Naiman, 2015).

Total urinary BPS concentrations ranged from <LOD to 0.82 ng/mL in our study. The median concentration observed in the US for total urinary BPS has been reported as 0.262 ng/mL (Liao et al., 2012). BPS levels in urine have not been reported in a population-based study such as NHANES. Total BPS excretion ranged from 1.8 to 14.6 ng/kg-day, with the maximum observation belonging to the BPS-receipt-handling group, but the second highest total excretion (10.3 ng/kg-day) belonging to a participant in the BPA-receipt-handling group. The remainder of the participants were clustered around 2-4 ng/kg-day total excretion of BPS, including 3 BPA-receipt-handling and 1 BPS-receipt-handling participants.

All field and laboratory blanks (hand wipes, solvents, synthetic urine, etc.) were below the limit of detection for both BPA and BPS.

The amount of BPA or BPS extracted from the post-exposure hand wipes (before hand washing) is shown in Table 1. Hand wipes from those handling BPA receipt tape contained BPA mass amounts that ranged from <LOD to 4245 ng. Hand wipes from the two-person BPS-handling group contained 3642 to 4717 ng BPS. For two wipes, a small amount of unexpected BPS was measured in the BPA receipt handling group.

Table 1. Total BPA and BPS extracted from post-exposure hand wipes for each participant.

Samp ID	Participant ID	Receipt group	Total BPA extracted ng	Total BPS extracted ng
#50	101	BPA	4245	331
#52	103	BPA	1160	79
#53	104	BPA	<LOD	<LOD
#54	105	BPA	1859	<LOD
#51	102	BPS	<LOD	3462
#55	106	BPS	<LOD	4717

The mass of BPA and BPS extracted from handled and unhandled receipts is given in Table 2. These data will be analyzed to evaluate the mass of BPA and BPS transferred from the receipt tape to the hands, and the analysis in support of the mass balance will be conducted in the context of the manuscript.

The concentration of BPA and BPS in all urine specimens and ancillary information are presented in Table 3. These data are in the process of being evaluated for significance, trends and meaning with respect to exposure and pharmacokinetics.

Table 2. Mass of BPA and BPS (g) per kg of paper for each handled (H) and unhandled (U) paper sample, by group.

BPA-receipt-handling group

Sample ID	g BPA/ kg paper	g BPS/ kg paper
103-U1	319	<LOD
103-H1	320	<LOD
103-U2	332	<LOD
103-H2	325	<LOD
103-U3	330	<LOD
103-H3	322	<LOD
103-U4	309	<LOD
103-H4	270	<LOD
101-U1	340	<LOD
101-H1	300	<LOD
101-U2	307	<LOD
101-H2	324	<LOD
101-U3	302	<LOD
101-H3	316	<LOD
101-U4	322	<LOD
101-H4	317	<LOD
105-U1	326	<LOD
105-H1	317	<LOD
105-U2	300	<LOD
105-H2	311	<LOD
105-U3	300	<LOD
105-H3	318	<LOD
105-U4	315	<LOD
105-H4	305	<LOD
104-U1	274	<LOD
104-H1	329	<LOD
104-U2	302	<LOD
104-H2	287	<LOD
104-U3	320	<LOD
104-H3	320	<LOD
104-U4	314	<LOD
104-H4	332	<LOD

BPS-receipt-handling group

Sample ID	g BPA/ kg paper	g BPS/ kg paper
106-U1	<LOD	255
106-H1	<LOD	262
106-U2	<LOD	199
106-H2	<LOD	179
106-U3	<LOD	194
106-H3	<LOD	180
106-U4	<LOD	189
106-H4	<LOD	177
102-U1	<LOD	244
102-H1	<LOD	197
102-U2	<LOD	201
102-H2	<LOD	243
102-U3	<LOD	213
102-H3	<LOD	238
102-U4	<LOD	221
102-H4	<LOD	214

Table 3. Total BPA and BPS concentrations and masses in every urine sample for every subject. Subjects #101, 103, 104, 105 were in the BPA-receipt-handling group, and subjects #102 & 106 were in the BPS-receipt-handling group.

Subject ID	Specimen #	Time	Creatinine conc. urine mg / dL urine	Urine volume mL	Total BPA in urine ng / mL	Mass BPA in urine ng	Total BPS in urine ng / mL	Mass BPS in urine ng
103	Day 1 #1	852	24.7	395	0.17	68.34	0.17	66.36
103	Day 1 #2	1035	35.2	285	0.30	86.07	0.22	63.27
103	Day 1 #3	1142	41.5	160	0.38	60.16	0.18	28.16
103	Day 1 #4	1242	19.1	265	0.50	131.97	0.08	20.41
103	Day 1 #5	1342	13.7	422	0.32	133.77	0.05	21.94
103	Day 1 #6	1643	74	250	1.32	331.00	0.38	94.50
103	Day 1 #7	1804	28.6	300	0.38	113.70	0.14	41.40
103	Day 1 #8	2002	49.8	220	0.68	148.50	0.29	64.02
103	Day 1 #9	2121	39.6	180	0.77	138.78	0.33	58.86
103	Day 2 #1	0036	32.2	600	0.38	229.20	0.28	167.40
103	Day 2 #2	543	87.7	320	0.71	226.24	0.45	142.40
101	Day 1 #1	820	255	275	5.34	1469.60	0.51	141.08
101	Day 1 #2	958	123.6	150	1.73	258.90	0.27	40.05
101	Day 1 #3	1105	62.9	100	0.60	59.50	0.11	11.40
101	Day 1 #4	1202	40	310	0.27	83.70	0.07	22.32
101	Day 1 #5	1302	40.4	200	0.22	43.60	0.11	22.20
101	Day 1 #6	1500	108.4	124	1.12	138.38	0.24	29.14
101	Day 1 #7	1700	125.8	126	1.22	154.22	0.25	31.25
101	Day 1 #8	1900	111.4	160	1.01	162.08	0.19	29.76
101	Day 1 #9	2130	36.5	550	0.28	151.80	0.06	30.80
101	Day 2 #1	530	86.3	570	0.61	348.84	0.11	61.56
104	Day 1 #1	927	67.8	100	0.76	76.20	0.13	12.90
104	Day 1 #2	1058	22.9	500	0.19	96.50	0.04	19.00

Subject ID	Specimen #	Time	Creatinine conc. urine mg / dL urine	Urine volume mL	Total BPA in urine ng / mL	Mass BPA in urine ng	Total BPS in urine ng / mL	Mass BPS in urine ng
104	Day 1 #3	1158	26.5	485	0.11	52.87	0.03	15.04
104	Day 1 #4	1258	20	320	0.14	44.80	0.03	8.00
104	Day 1 #5	1358	15.9	500	0.17	86.00	0.03	12.50
104	Day 1 #6	1515	24.8	370	0.34	125.06	0.05	17.02
104	Day 1 #7	1602	11.6	420	0.39	165.06	0.02	6.72
104	Day 1 #8	1815	70	235	1.29	301.98	0.07	17.39
104	Day 1 #9	2158	91.9	310	1.63	504.68	0.08	24.18
104	Day 2 #1	740	103.8	625	2.41	1507.50	0.15	91.25
105	Day 1 #1	943	58.8	300	1.56	468.30	0.04	10.50
105	Day 1 #2	1122	25.9	330	0.15	48.51	<LOD	
105	Day 1 #3	1230	24.5	230	0.14	31.97	<LOD	
105	Day 1 #4	1326	26.8	160	0.33	53.28	0.02	2.88
105	Day 1 #5	1426	8.5	490	<LOD		<LOD	
105	Day 1 #6	1635	29.7	335	0.32	108.54	0.03	9.05
105	Day 1 #7	1829	17.8	500	0.19	94.50	0.04	19.00
105	Day 1 #8	2027	25.8	360	0.27	97.56	0.04	15.48
105	Day 1 #9	2226	33.6	280	0.23	63.00	0.03	8.96
105	Day 2 #1	0025	70.8	125	0.59	73.25	0.06	7.88
105	Day 2 #2	632	49	550	0.42	230.45	0.06	34.10
102	Day 1 #1	926	227.4	50	1.33	66.45	0.65	32.55
102	Day 1 #2	1048	37.9	210	<LOD		0.10	21.84
102	Day 1 #3	1120	21.9	300	<LOD		0.07	19.50
102	Day 1 #4	1218	41.4	180	0.24	43.02	0.09	16.74
102	Day 1 #5	1311	113.4	60	0.53	31.50	0.18	10.74
102	Day 1 #6	1409	28.4	260	0.18	46.02	0.08	20.02
102	Day 1 #7	1600	49.5	260	0.27	69.16	0.14	36.14
102	Day 1 #8	1811	76.6	180	0.28	50.40	0.22	39.42
102	Day 1 #9	1914	35.8	235	0.14	32.43	0.10	24.44

Subject ID	Specimen #	Time	Creatinine conc. urine mg / dL urine	Urine volume mL	Total BPA in urine ng / mL	Mass BPA in urine ng	Total BPS in urine ng / mL	Mass BPS in urine ng
102	Day 1 #10	1947	13.7	260	<LOD		0.05	11.70
102	Day 1 #11	2045	25.4	244	<LOD		0.06	15.62
102	Day 1 #12	2202	90.7	90	0.30	27.00	0.16	14.49
102	Day 2 #1	103	27.2	500	<LOD		0.07	35.00
102	Day 2 #2	444	49.5	490	0.28	137.69	0.10	49.98
102	Day 2 #3	704	103.2	154	0.31	48.20	0.16	25.26
106	Day 1 #1	754	60.1	310	0.31	95.79	0.82	253.58
106	Day 1 #2	935	22.5	300	0.11	33.00	0.29	87.60
106	Day 1 #3	1042	39.5	172	0.23	39.56	0.34	58.14
106	Day 1 #4	1139	15.8	335	<LOD		0.12	38.86
106	Day 1 #5	1239	13.7	385	<LOD		0.13	49.67
106	Day 1 #6	1449	7.7	550	<LOD		0.10	56.10
106	Day 1 #7	1620	13.3	520	<LOD		0.13	67.60
106	Day 1 #8	1738	22	345	<LOD		0.10	32.78
106	Day 1 #9	1859	67.3	110	0.74	81.73	0.81	89.32
106	Day 1 #10	2047	35.6	270	0.36	97.20	0.40	107.46
106	Day 1 #11	2127	13.7	270	<LOD		0.17	45.36
106	Day 1 #12	2200	10.7	250	<LOD		0.04	11.00
106	Day 2 #1	0010	17.6	520	<LOD		0.15	75.92
106	Day 2 #2	501	50.4	520	0.19	100.88	0.36	189.28

It appears that for some participants, concentrations of both BPA and BPS in urine were still tending to increase by the last urine sample, the first morning void of day 2, which occurred about 21-22 hours after the initial pre-exposure urine sample. This observation is surprising since for the ingestion route of exposure the half-life of BPA is about 4-6 hours, with nearly 100% excreted by 24 hours after the dose. Evidence from at least one other dermal receipt exposure simulation study seems to support our finding; Ehrlich et al. reported peak concentrations of BPA in urine of participants 6-8 hours after handling BPA-coated receipt papers for 2 hours (Ehrlich et al., 2014). In a similar experiment conducted by Porras et al., BPA levels were slightly elevated in those who handled BPA-coated receipts, but were not substantially greater than the intra-individual variability observed. In that study, the peak concentration tended to occur 6-12 hours after the end of the 8-hour exposure period (Porras et al., 2014).

Our collaborator, Dr. Justin Teeguarden, is in the process of refining the kinetic model of dermal absorption and metabolism for BPA and BPS based on our measurements. That data will be available by the time this work is submitted for journal publication.

Although it is difficult to make firm conclusions or generalizations based on such a small study, this experiment has laid the groundwork for future studies that will aim to better understand the similarities and differences between BPA and BPS dermal exposure and toxicokinetics.

Aim 2 (Observational study)

We found a much lower proportion of establishments' receipts tested positive for BPA content than we anticipated. We analyzed 128 store's receipts by GC-MS or LC-MS from area stores and restaurants and found that 30 (23%) of them contained BPA. Based on the literature available at the time we designed and began conducting the study, we expected to see a BPA-positive rate of 40-80% (Geens, Goeyens, Kannan, Neels, & Covaci, 2012; Liao & Kannan, 2011b; Lunder et al., 2010). A more recent survey conducted by two independent labs contracted by a law firm found only 29% of receipts collected between September 2013 and February 2014 (total n=94) contained BPA (Bernstein, 2014). Hormann et al. reported 44% of receipt samples tested (n=50) contained BPA; however it is unclear when those receipts were obtained (Hormann et al., 2014).

Accordingly, 17 of our participants (68%) worked with BPS-coated receipts, 6 participants (24%) handled BPA-coated receipts, 1 participant worked in a library circulation room handling a combination of both BPA- and BPS-containing receipts, and 1 participant handled non-thermally printed receipt paper. We had three participants who were employed at the same store although sampling was not concurrent. One participated early in the study (fall 2013) and the others near the end of the study (spring 2015). We tested a new receipt sample in 2015 and found that the store had been using BPA-coated receipts in 2013 but was using BPS-coated receipts in 2015. Interestingly, we found two stores of the same company whose receipts were clearly labeled "Receipt is BPA free, recycled content;" however, both contained BPA in the same concentration range as the others we tested. Ultimately we did not enroll any participants from these two stores.

Participants ranged in age from 22-49 years (mean=30 years old). Most (84%) were female. 48% of participants were white, 28% were black, 16% were Asian and 8% were multi-racial. Only one participant was Hispanic. Most participants (72%) reported an annual household income between $20,000 – 75,000. 60% of our participants held a bachelor's degree. Participants' height ranged from 61-75 inches (mean=66 inches). Body weights ranged from 123-287 pounds (mean=178 pounds).

Average shift length was 7.6 hours, with a range from 5.3-11.6 hours. Participants averaged 6.4 hours at the register/handling receipts, with a very wide range (3.5-11.25 hours). None of the participants wore gloves while handling receipts. The frequency of cashiers' transactions during their

shift on the day of participation is presented in Figure 1. Most (56%) cashiers handled a receipt about once every 5 or 10 minutes throughout their shift.

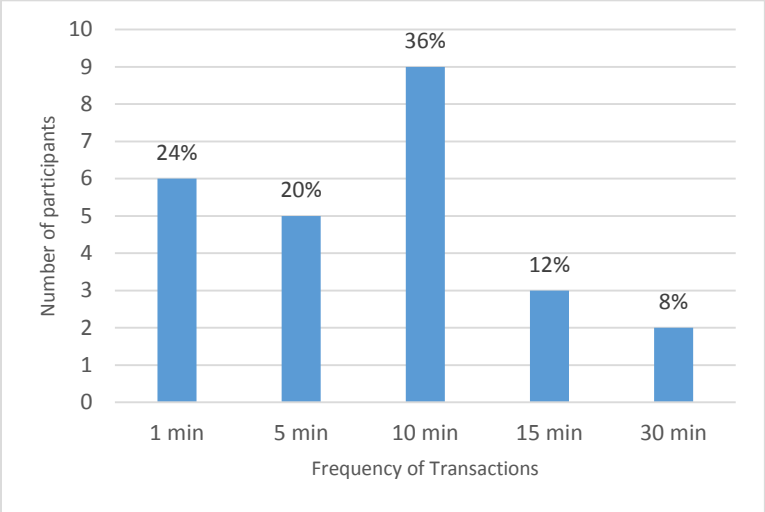

Figure 1. Self-reported average frequency of transactions during shift

Most participants (72%) did not use lotion at all during their shift, and only 16% used lotion more than once during the shift. Similarly, most participants (56%) did not use any hand sanitizer during their shift, but 36% used it at least twice. Nearly all of the participants (92%) washed their hands at least twice during the shift, with 32% washing their hands more than 5 times.

Mean urinary concentrations for BPA in both groups were within the typical range for adults in the U.S. population, mostly in the 50^{th}-75^{th} percentile range, except for a couple of pre-shift outlier values (LaKind & Naiman, 2015) (Table 4). However, it is important to note that we would have expected BPA levels to be quite a bit lower than average since our study protocol was designed to minimize dietary exposure, which is generally presumed to be the dominant source of exposure in both the general population and cashiers (Geens, Aerts, et al., 2012).

Table 4. Urinary BPA and BPS concentrations by group (ng/mL)

BPA and BPS Means By Group

Note: 1 subject is in both groups (receipts had both BPA and BPS), and 1 subject is in neither group (receipts had neither BPA nor BPS)

All subjects

	BPA Group						BPS Group					
Outcome	N	Mean	(SD)	Min	Max	Cohen's d	N	Mean	(SD)	Min	Max	Cohen's d
BPA (ng/mL)						-0.30						-0.44
Pre	7	3.8	(5.0)	0.61	14.3		18	2.3	(3.2)	0.10	13.6	
Post	7	2.4	(1.7)	0.1	5.5		18	1.0	(1.2)	0.086	4.8	
Difference	7	-1.4	(4.7)	-11.7	2.2		18	-1.3	(2.9)	-12.1	1.6	
Percent Change	7	9.6	(92)	-83.6	186		18	-18.3	(102)	-89.0	281	
BPS (ng/mL)						-0.15						0.16
Pre	7	1.2	(1.7)	0.13	5.0		18	1.6	(2.1)	0.12	9.1	
Post	7	1.0	(0.8)	0.015	1.9		18	1.7	(2.1)	0.091	8.1	
Difference	7	-0.2	(1.4)	-3.2	1.1		18	0.15	(0.9)	-1.0	2.5	
Percent Change	7	11.3	(87)	-91.4	139		18	25.8	(95)	-85.3	221	

Removing 2 subjects with large BPA (>10) at Pre-shift sample (1 in BPA group, 1 in BPS group) and 1 subject with large BPS (>9) at Pre-shift sample (in BPS group)

	BPA Group						BPS Group					
Outcome	N	Mean	(SD)	Min	Max	Cohen's d	N	Mean	(SD)	Min	Max	Cohen's d
BPA (ng/mL)						0.32						-0.59
Pre	6	2.1	(2.0)	0.61	6.1		16	1.6	(1.5)	0.10	5.6	
Post	6	2.4	(1.9)	0.1	5.5		16	1.0	(1.2)	0.086	4.8	
Difference	6	0.3	(1.1)	-0.6	2.2		16	-0.6	(1.0)	-2.3	1.6	
Percent Change	6	24.9	(91)	-83.6	186		16	-10.5	(106)	-88.8	281	
BPS (ng/mL)						0.50						0.24
Pre	6	0.6	(0.3)	0.13	0.8		16	1.1	(1.0)	0.12	3.9	
Post	6	0.9	(0.8)	0.015	1.9		16	1.3	(1.4)	0.091	5.1	
Difference	6	0.3	(0.6)	-0.2	1.1		16	0.22	(0.9)	-1.0	2.5	
Percent Change	6	24.0	(87)	-91.4	139		16	29.3	(100)	-85.3	221	

On average the concentration of BPA and/or BPS in urine tended to be ~30% higher post-shift relative to pre-shift, however, this difference did not achieve statistical significance (N=21 excluding outliers and non-thermal-paper-exposed, p=0.18) (Table 5). Accordingly, given the limitations of our sample size, we are not able to discern a work place related increase in urinary BPA or BPS levels.

Table 5. Percent change in thermal developer (by exposure group), outliers and participant unexposed to thermal paper removed (n=4)

Outcome	N	Mean	(SD)	Min	Max	Paired t-Test P-value	Signed Rank P-value
Percent Change							
BPA only	5	30.8	(100)	-83.6	185.9	--	--
BPS only	15	31.3	(103)	-85.3	220.7	--	--
BPA & BPS	1	-3.9	--	--	--	--	--
Combined	21	29.5	(98)	-85.3	220.7	0.18	0.51

Figures 2 and 3 show that results for individual participants were quite mixed.

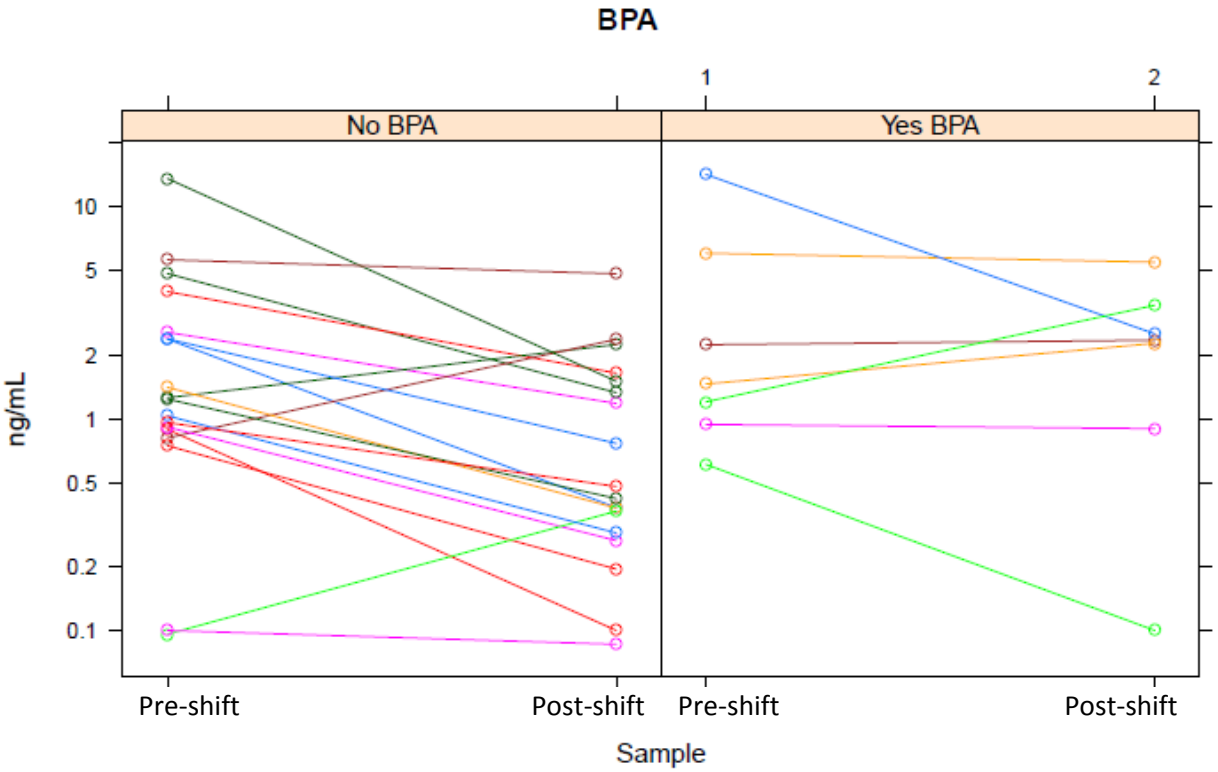

Figure 2. Bisphenol A (BPA) concentrations (ng/mL) in pre- and post-shift urine samples for each participant, by receipt group

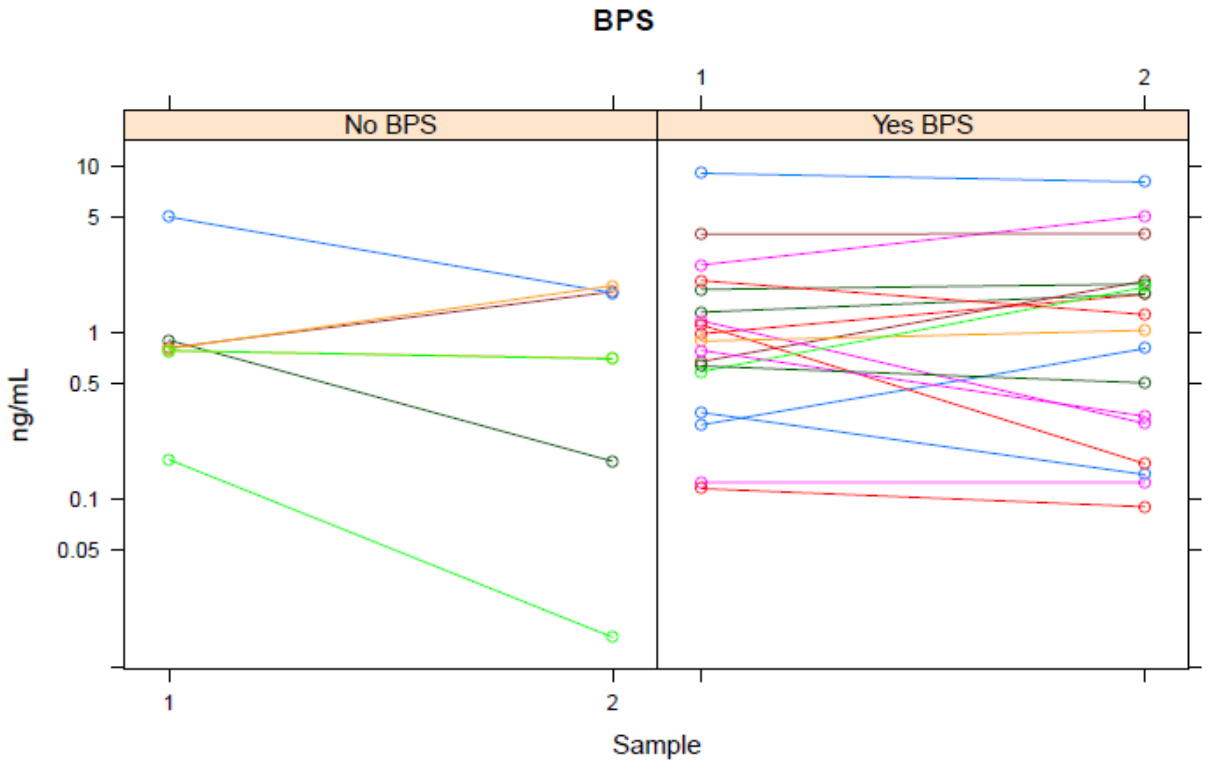

Figure 3. Bisphenol S (BPS) concentrations (ng/mL) in pre- and post-shift urine samples for each participant, by receipt group

It is possible that the timing of our post-shift sampling was too soon following the exposure to capture the peak concentration of BPA (or BPS) in urine. A cashier simulation study recently reported that the maximum urinary BPA after handling BPA-coated receipts for 2 hours occurred around 8 hours after the beginning of the exposure period (6 hours after the end of exposure) (Ehrlich et al., 2014). As such, any substantial increase in urinary levels of BPA (or BPS) may be occurring overnight following the work shift, when we did not have access to participants for urine sample collection. In fact, some of the higher observed pre-shift thermal developer concentrations we observed may actually be an artifact of cashier work the day prior to study participation. Unfortunately, it was not practical to arrange study days that were more than 24 hours following a previous shift, and our survey did not obtain information on the previous day's work. Thayer et al. (2015) reported a similar challenge, although their study design allowed for some compensation for this issue (Thayer et al., 2015).

Our results are similar, especially with regard to differences between BPA and BPS exposures among cashiers, to those reported last month in a study of cashiers with a slightly different design (Thayer et al., 2015). Thayer et al (2015) reported a significant increase in geometric mean urinary BPS concentration pre-shift to post-shift; however, BPA levels in urine increased in some and decreased in other participants. They also found that the post-shift urinary BPA in cashiers was higher than non-cashiers (Thayer et al., 2015). However, our study attempted (and we think succeeded fairly well) in minimizing dietary exposure to BPA (and possibly BPS due to similar sources/products); therefore, we are likely to have less exposure misclassification and our observations are more likely linked with dermal receipt exposure than other sources.

Not surprisingly, the concentrations of BPA in observed in our study were much lower than those observed by Hormann et al. (2014) in a simulation study where participants' hands were coated with alcohol-based hand sanitizer to increase dermal penetration, and where hand-to-mouth exposure was also simulated (Hormann et al., 2014).

Conclusions

The findings from this research hold great significance for worker health and safety. The substantial U.S. retail workforce is made up of a large fraction of women who are of reproductive age and therefore particularly vulnerable to the possible reproductive and endocrine disruptive effects of BPA or BPS. Although these data and their analysis are preliminary, it appears that exposure to BPA or BPS from receipt tape is subtle and perhaps not detectable given the limitations of our study design. However, we cannot conclude that cashier exposure to receipt tape is unimportant, since uncertainty remains about the long-term effects of low-level chronic exposure to endocrine disrupting compounds like BPA and BPS. Future research should focus primarily on BPS exposure and other alternative thermal developers that arrive on the market, since much less is known about their potential adverse health effects and exposure sources and levels in the general population.

Our data also suggest that we need to shift our focus to the potential health impacts of workers' exposure to BPS, since the market has substantially changed with regard to thermal developers in the last 2-3 years. While BPA has been studied extensively, with some questions about exposure and health effects yet to be settled, BPS has seen much less scientific and public scrutiny.

There is some indication that BPA and BPS may remain in the body longer when exposed through the dermal rather than ingestion route, which is another area for future study, since BPA has long been assumed unlikely to cause widespread adverse effects due to its quick first-pass metabolism and short residence time in the body. This assumption may not hold for those cashiers and other workers who are dermally exposed.

Our evaluation of blood collection devices and conclusion that contamination was nearly impossible to avoid contributes important information to the field of BPA exposure research as a whole, since contamination from laboratory and clinical environments has long been suspected but sources and causes not fully elucidated.

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Publications & presentations

Teeguarden JG, Twaddle N, Churchwell MI, Yang X, Fisher JW, Seryak LM, Doerge DR. 24-Hour Human Urine and Serum Profiles of Bisphenol A: Evidence against Sublingual Absorption Following Ingestion in Soup. 54th Annual Meeting of the Society of Toxicology. March 23, 2015; San Diego, CA.

Seryak LM, Doerge DR, Churchwell MI, Andridge RR, Savage Jr. RE, Wilkins III JR, Buckley TJ. Cashiers' Exposure to BPA from Occupational Receipt Handling. Oral Presentation. 24th Annual Meeting of the International Society of Exposure Science. October 13, 2014; Cincinnati, OH.

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**The primary journal articles reporting the results of each aim of this study are currently in preparation, with intent to submit to high impact peer-reviewed journals.

Cumulative Inclusion Enrollment Report

Study Title: Evaluation of Bisphenol A Dermal Exposure and Toxicokinetics among Cashiers
Comments: This table covers both aims of the study.

Racial Categories	Ethnic Categories									Total
	Not Hispanic or Latino			Hispanic or Latino			Unknown/Not Reported Ethnicity			
	Female	Male	Unknown/Not Reported	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/Not Reported	
American Indian/ Alaska Native	0	0	0	0	0	0	0	0	0	0
Asian	5	1	0	0	0	0	0	0	0	6
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0	0	0	0	0
Black or African American	5	1	0	1	0	0	0	0	0	7
White	12	3	0	0	1	0	0	0	0	16
More Than One Race	1	1	0	0	0	0	0	0	0	2
Unknown or Not Reported	0	0	0	0	0	0	0	0	0	0
Total	23	6	0	1	1	0	0	0	0	31

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Inclusion of children

Children (ages <21) were excluded from this research because insufficient data were available in adults to judge potential risk in children of the prescribed exposure regimen for Specific Aim 1. Furthermore, children are unlikely to work full shifts as cashiers, and thus their exposure scenario in the workplace would be different from that which was the target of this study.