Annals of Work Exposures and Health, 2018, Vol. 62, No. 7, 840–851
doi: 10.1093/annweh/wxy042
Advance Access publication 13 June 2018
Original Article

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An Evaluation of the Relationship among Urine, Air, and Hand Measures of Exposure to Bisphenol A (BPA) in US Manufacturing Workers

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Submitted 1 December 2017; revised 4 April 2018; editorial decision 24 April 2018; revised version accepted 17 May 2018.

Abstract

Background: Exposure to bisphenol A (BPA) can be assessed using external and internal exposure measures. We examined the relationship between two measures of external BPA exposure (air and hand-wipe samples) and one of internal exposure (total BPA in urine) for a group of US manufacturing workers.

Methods: During 2013–2014, we recruited 78 workers from six US companies that made BPA or made products with BPA. We quantified BPA in seven urine samples, two full-shift air samples and in pre- and end-shift hand-wipe samples collected from workers over 2 consecutive days. We examined correlations between creatinine-corrected urinary concentrations of total BPA (total BPA_{CR}) and BPA levels in air and hand wipes using Pearson's correlation coefficient. We also applied mixed-effects regression models to examine the relationship between total BPA_{CR} with BPA in air (*urine~air* model) and with BPA in end-shift hand wipes (*urine~hand* model), separately and together (*urine~air+hand* model), after adjusting for covariates.

Results: End-shift total BPA_{CR} strongly correlated with BPA in air ($r_p = 0.79$, $P < 0.0001$) and nearly as strongly with BPA in end-shift hand wipes ($r_p = 0.75$, $P < 0.0001$). In mixed-effect models, BPA air concentration and end-shift hand-wipe BPA level were significantly and positively associated with end-shift total BPA_{CR} ($P < 0.0001$ each). We found a significant effect of the Day 1 BPA air concentration on Day 2 total BPA_{CR} ($P = 0.0104$). When BPA air concentration and end-shift hand-wipe BPA level were in the same model, the air concentration ($P < 0.0001$) was more significant than the hand-wipe level ($P = 0.0106$).

Conclusion: BPA levels in air and end-shift hand wipes strongly correlated with total $BPA_{CR,}$ suggesting that both inhalation and dermal contract were likely exposure routes; however, inhalation, on

average, appeared to be a more dominant exposure route than dermal contact for these manufacturing workers.

Keywords: air sampling; biological monitoring; bisphenol A; dermal exposure assessment; exposure assessment; exposure assessment – mixed models; manufacturing; urine

Introduction

Bisphenol A (BPA) (CAS 80-05-7, 4,4′-isopropylidenediphenol) is used extensively as a monomer in the production of polycarbonate, epoxy, and phenolic resins (Kopf, 2003; Pham and Marks, 2004; Brunelle, 2014). BPA is also used as a filler in certain investment casting waxes (Carney, 2014) and as a developer in thermal paper although the latter use has declined as substitutes for BPA have been introduced (USEPA, 2014).

After ingestion, BPA is rapidly conjugated in the human liver and gut to mainly BPA glucuronide (BPA-G), a water-soluble compound that is eliminated in the urine with a half-life of 5.4–6.4 h (Völkel *et al.*, 2002; Thayer *et al.*, 2015). Unconjugated BPA (i.e. 'free BPA') can also be detected in urine, but at a much lower percentage than BPA-G, typically <1% of total BPA (Thayer *et al.*, 2015). BPA that is inhaled or absorbed through the skin largely enters the circulatory system without undergoing first-pass metabolism although metabolism of BPA by the skin has been reported in an *ex vivo* model (Zalko *et al.*, 2011; Toner *et al.*, 2018). *In vitro*, the dermal absorbed dose for BPA is generally in the range of 2–13% (Kaddar *et al.*, 2008; Mørck *et al.*, 2010; Demierre *et al.*, 2012; Toner *et al.*, 2018). A few observational studies have suggested a longer elimination half-life for BPA in certain human populations than reported in oral-dosing studies (Stahlhut *et al.*, 2009; Christensen *et al.*, 2012; Hines *et al.*, 2017a). It is unclear, however, if the suggestion of a longer half-life is related to exposure routes, dosing patterns, prolonged elimination of BPA after dermal uptake (Liu and Martin 2017), fat storage, or other factors.

The toxicity of BPA has been extensively investigated in both experimental and observational studies. BPA is weakly estrogenic and has low acute toxicity (Dodds, 1936; European Union, 2008; NTP, 2008). BPA-G, unlike free BPA, does not exhibit estrogenic activity (Snyder *et al.*, 2000; Matthews *et al.*, 2001). In laboratory animals, changes in numerous biological endpoints have been reported after exposure to BPA and a range of health effects have been associated with BPA exposure in epidemiological studies, most of which were cross-sectional in design (as reviewed in WHO, 2011; Cantonwine *et al.*, 2013; Peretz *et al.*, 2014; Mínguez-Alarcon *et al.*, 2016). Endocrine system disruption is hypothesized to underlie many of the effects reported in animal and human studies.

In the USA, BPA (conjugated plus free) has been detected in the urine of more than 92% of individuals ≥6 years of age, an exposure thought to be largely diet-related (Calafat *et al.*, 2008; NTP, 2008). Published reports of occupational BPA exposure are limited. Initial investigations of occupational exposure to BPA were conducted largely among manufacturing workers in Asia (Hanaoka *et al.*, 2002; Xiao *et al.*, 2005, Cha *et al.*, 2008; He *et al.*, 2009; Ren *et al.*, 2012; Wang *et al.*, 2012; Zhuang *et al.*, 2015). More recently, BPA exposures have been reported for cashiers in the USA and France (Ndaw *et al.*, 2016; Thayer *et al.*, 2016), factory workers in Finland (Heinälä *et al.* 2017), and US manufacturing workers (Hines *et al.*, 2017a). Changes in male reproductive health in several functional domains (sexual function, hormone levels, and semen quality) were reported for workers in Chinese factories making BPA or BPA-based epoxy resins in the largest health study of BPA-exposed workers to date (Li et al., 2010a,b, 2011; Zhou *et al.*, 2013; Liu *et al.*, 2015). This study was cross-sectional and its findings have not been confirmed in a similarly exposed population.

While the concentration of BPA in urine provides an estimate of body burden, it does not by itself indicate route(s) of exposure. Understanding exposure routes (i.e. inhalation, dermal, oral) and their relative contributions is important for controlling BPA exposure in the workplace, especially when designing engineering controls, selecting personal protective equipment, and determining the need for workplace cleanliness regimens.

In 2013–2014, the National Institute for Occupational Safety and Health (NIOSH) conducted a study to assess the BPA exposure of US manufacturing workers who made BPA, made products using BPA, or used a BPA-containing product. We previously reported BPA levels in urine, personal air, and hand-wipe samples collected from these workers (Hines *et al.*, 2017a,b). On average, workers had urinary BPA concentrations ~70 times higher than in US adults in the National Health and Nutrition Examination Survey (NHANES)

2013–2014 (Hines *et al.*, 2017a). BPA was detected in 95% of the air samples, and BPA levels in end-shift hand wipes averaged 10 times higher than at pre-shift (Hines *et al.*, 2017b). Our aim in this article is to explore the relationship between BPA levels in personal air and hand-wipe samples, and BPA concentrations in urine. We also evaluate these data for evidence of the relative importance of inhalation and dermal contact as exposure pathways for BPA among these workers.

Methods

Company and participant recruitment

Methods for recruiting companies and participating workers have been described previously (Hines *et al.*, 2017a,b). Relying mainly on the 2010 and 2011 US EPA Toxic Release Inventory (USEPA, 2018), we identified 73 companies potentially making or using BPA. Of these 73 companies, 15 did not respond to inquiries, 15 no longer produced or used BPA, 37 had few workers handling BPA, infrequent BPA use or could not be scheduled within the study period, and six participated in the study. We selected companies that represented a range of BPA manufacturing processes. We visited each company to identify BPA-related jobs and invited workers performing these jobs to participate in the study. The NIOSH Institutional Review Board approved this study. Participants gave written informed consent and were reimbursed $70 for the time and inconvenience of providing samples.

Sample collection

We collected urine, air, and hand-wipe samples from participants over 2 consecutive days (Day 1 and Day 2) (Fig. 1). We scheduled sampling to begin after the participant had been off work for at least 24 h to allow time for BPA to approach baseline concentrations in the urine. Details on sampling methods are provided in Hines *et al.* (2017a,b). Briefly, we asked participants to provide a total of seven urine samples (time points 1–7): pre-shift (baseline), mid-shift (±30 min of the participant's shift mid-point), end-shift, and post-shift (4–6 h after leaving work) urine samples on Day 1 and pre-shift, mid-shift, and end-shift urine samples on Day 2. Participants collected urine samples in sterile polypropylene specimen cups after washing hands with water only (to avoid potential interferences). Participants kept post-shift samples on refrigerant packs between shifts. We aliquoted the urine into polypropylene cryovials followed by immediate freezing on dry ice. We also collected quality control (QC) field blanks and blind duplicates of participants' samples; these samples were aliquoted and handled in the same manner as other participants' samples. Urine samples were shipped and stored frozen (–80°C) until analysis.

We collected a full-shift breathing zone air sample for each participant on each of the 2 days. We used an IOM sampler (SKC, Inc.) with a 25-mm quartz fiber filter in a stainless steel cassette at a nominal flow rate of 2 l min^{-1} to collect inhalable particles. Sampling pumps were pre- and post-calibrated. Upon completion of sampling, filter cassettes were placed in polypropylene containers, and kept cold (4°C) until analysis.

On Day 2, we collected a pre-shift and an end-shift hand-wipe sample from each participant. We collected hand wipes on Day 2 to minimize interference with concurrent biological monitoring. Because of a schedule change, pre- and post-shift hand wipes were collected on Day 1 for one worker. We used four Large Alpha® Swabs (TX715, ITW Texwipe) moistened with 100% high-performance liquid chromatography (HPLC) grade isopropanol (Thermo Fisher Scientific) to systematically

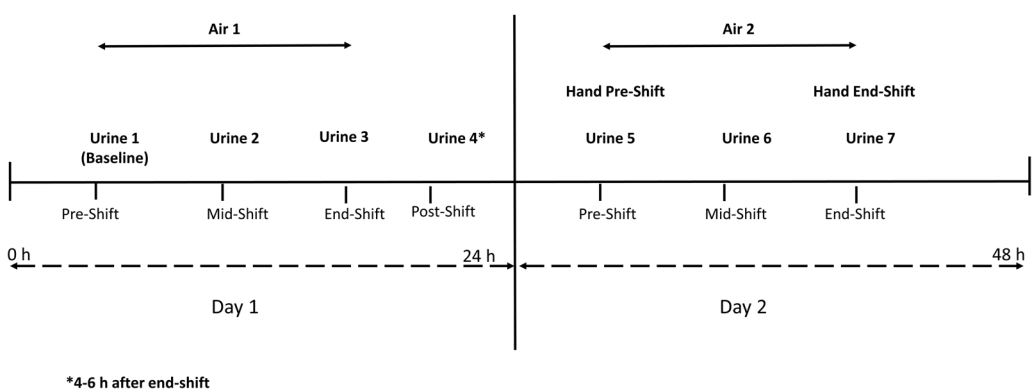

Figure 1. Urine, air, and hand-wipe sample collection over 2 consecutive work days.

wipe the palms, backs and fingers of a participant's hands (two swabs per hand). We instructed participants to delay their final hand washing of the shift until the end-shift hand-wipe sample had been taken; otherwise they could wash their hands as needed. We inserted the four swabs into a polypropylene vial to form a single sample. Field blanks were prepared for both air and hand-wipe samples (10% each) and handled in a manner similar to the participant samples.

Sample analysis

Sample analysis details and QC results are given in Hines *et al.* (2017a,b). Briefly, we quantified urinary concentrations of total (free plus conjugated) BPA by online solid phase extraction-HPLC-isotope dilution tandem mass spectrometry (Zhou *et al.*, 2014). The limit of detection (LOD) was 0.1 μg l^{-1}. We measured urinary creatinine using a Vitros® 250 Chemistry Analyzer (Ortho-Clinical Diagnostics). To adjust for urine dilutions, BPA concentrations were divided by creatinine (units = μg g^{-1} creatinine). The NIOSH contract laboratory Bureau Veritas North America quantified BPA in air and hand-wipe samples. Briefly, air and wipe samples were extracted with acetonitrile and analyzed for BPA by HPLC with ultraviolet detection. The LOD across seven sample batches ranged from 0.03 to 0.1 μg m^{-3} (air) and from 0.05 to 0.3 μg per sample (hand wipe).

Statistical analysis

The distributions of the levels of creatinine-corrected total BPA in urine (total BPA_{CR}), BPA in air, and BPA on hand wipes were each skewed to the right, and a natural log transformation was applied to each variable prior to all statistical analyses. BPA detection was 100% (urine), 95.2% (air), 93.2% (pre-shift hand wipe), and 100% (end-shift hand wipe) (Hines *et al.*, 2017a,b). We assigned LOD/2 to air and hand-wipe samples where BPA was not detected (Hornung and Reed, 1990). All statistical analyses were performed in SAS v. 9.3 (SAS Institute, Inc.).

We initially used Pearson's correlation coefficient to evaluate the relationship between the end-shift total BPA_{CR} and (1) the BPA air concentration and (2) the end-shift BPA hand level. Day 1 and Day 2 BPA air concentrations were paired with the end-shift total BPA_{CR} for the corresponding day. We also averaged the mid-shift and end-shift total BPA_{CR} on each day and re-ran the correlations.

We next applied mixed-effects linear regression models using the PROC MIXED procedure in SAS to evaluate the relationship between total BPA_{CR} and (1) BPA air concentration (*urine~air* model), (2) end-shift hand-wipe BPA level (*urine~hand* model), and (3) BPA air concentration and end-shift hand-wipe BPA level in the same model (*urine~air+hand* model). The base models are summarized in Table 1. In these models, the dependent variable was ln(total BPA_{CR}) at mid- and end-shift on Day 1 (time points 2 and 3) and on Day 2 (time points 6 and 7).

In the *urine~air* model, worker was treated as a random effect; fixed effects included day (Day 1 or 2), shift time (mid-shift or end shift), an interaction term for day and shift time (day × shift time), ln(total BPA_{CR} at baseline), body mass index (BMI) computed from self-reported height and weight, and ln(BPA air concentration). We used a first-order autoregressive AR(1) covariance structure in this model. The air concentration measured on Day 1 was associated with time points 2 and 3; the air concentration on Day 2 with time points 6 and 7. BMI and ln(total BPA_{CR} at baseline) were included in the model based on earlier modeling results with total BPA_{CR} (Hines *et al.*, 2017a).

We also evaluated alternate *urine~air* models. Specifically, the model was re-run with the dependent variable ln(total BPA_{CR}) including only end-shift urine samples (time points 3 and 7), with all post-baseline urine samples (time points 2–7), and with post-baseline Day 1 through pre-shift Day 2 urine samples (time points 2–5) to capture mostly Day 1 exposure. We also re-ran the air model with the dependent variable restricted to mid- and end-shift urine samples on Day 2 only (time points 6 and 7), but with the Day 1 and Day 2 air concentrations included as separate covariates, then re-ran this model after removing the Day 1 air concentration (all other terms remained) in order to assess if BPA air concentrations on Day 1 had an effect on total BPA_{CR} on Day 2. Optimum covariance structures for these alternate models varied by model. We used Akaike's Information Criterion (AIC) to compare models. A lower AIC indicated better model fit.

In the *urine~hand* model, worker was treated as a random effect. Fixed effects included shift time (mid-shift or end shift), ln(total BPA_{CR} at baseline), BMI, ln(BPA hand at pre-shift), and ln(BPA hand at end shift). We used a compound symmetric (CS) covariance structure as each worker in this model had only two urine samples. We re-ran the *urine~hand* model excluding two participants with particularly high end-shift hand-wipe BPA levels (19 000 and 12 000 μg per sample, 76- and 48-times higher, respectively, than the 95th percentile of 250 μg per sample for 148 hand-wipe samples). We also re-ran the *urine~hand* model restricting the dependent variable to end-shift urine samples [time points 3

Table 1. Parameters of base models.

Dependent variable	Base model[a]		
	Urine ~air	Urine~hand	Urine~air+hand
	ln(total BPA_{CR}) at time points 2, 3, 6, 7	ln(total BPA_{CR}) at time points 2, 3 (for hand wipes on Day 1), 6, 7 (for hand wipes on Day 2)	ln(total BPA_{CR}) at time points 2, 3, 6, 7
Random effect	Worker	Worker	Worker
Covariance structure	AR(1)	CS	CS
Fixed effects			
Day	X		
Shift time	X	X	X
Day × shift time	X		
ln(total BPA_{CR}) at baseline	X	X	X
BMI	X	X	X
ln(BPA air)	X		X
ln(BPA hand at pre-shift)		X	X
ln(BPA hand at end shift)		X	X

AR(1), first-order autoregressive.
[a]Model variations explained in Methods.

(participant with Day 1 hand wipes) and 7 (all other participants)].

In the *urine~air+hand* model, we treated worker as a random effect, included shift time (mid-shift or end shift), ln(urinary total BPA_{CR} at baseline), BMI, ln(BPA air concentration), ln(BPA hand at pre-shift) and ln(BPA hand at end shift) as fixed effects, and used a CS covariance structure. We then ran the model without the BPA air concentration, then re-ran the model after restoring the BPA air concentration but excluding the pre- and end-shift hand-wipe BPA levels. This latter analysis allowed us to evaluate the relative effect of the air and hand-wipe data on model fit using AIC to compare models.

Results

A total of 78 workers participated in the study. One worker was excluded from all analyses because of possible urine sample contamination with BPA; 77 workers remained after exclusion (Fig. 2). Demographic characteristics of these 77 workers are described in Hines *et al.* (2017a). Briefly, the workers were predominately male (98.7%) and white (89.6%), with a median age of 44 years. Median BMI was 29.8 kg m^{-2} (range 21.0–44.3 kg m^{-2}). Most workers (84.4%) had been off work at least 24 h before collecting the first urine sample. Seven of the 12 workers with less than 24 h off work were maintenance workers.

We found a strong correlation between the BPA concentration in air and end-shift total BPA_{CR} (r_p = 0.79, P < 0.0001, Fig. 3). The correlation was nearly as strong when the average of mid- and end-shift total BPA_{CR} was used (r_p = 0.77, P < 0.0001). A strong correlation was also found between the end-shift hand-wipe BPA level and end-shift total BPA_{CR} (r_p = 0.75, P < 0.0001, Fig. 4), as well as with the average of mid- and end-shift total BPA_{CR} (r_p = 0.76, P < 0.0001).

In the *urine~air* model, after adjusting for day (P < 0.0001), shift time (P < 0.0001), the interaction of day and shift time (P = 0.0121), total BPA_{CR} at baseline (P < 0.0001), and BMI (0.0268), the BPA air concentration was significantly and positively associated with total BPA_{CR} at end shift (P < 0.0001, Table 2). The association remained significant when the dependent variable consisted only of end-shift urine samples (time points 3 and 7) (Table S1, Supplementary data, available at *Annals of Occupational Hygiene* online), all post-baseline urine samples (time points 2–7) (Table S2, Supplementary data, available at *Annals of Occupational Hygiene* online), or urine samples thought to be most associated with exposure to BPA on Day 1 (time points 2–5) (Table S3, Supplementary data, available at *Annals of Occupational Hygiene* online). When we included Day 1 and Day 2 BPA air concentrations in the model as separate independent variables and restricted the total BPA_{CR} to Day 2 mid- and end-shift samples, we saw a significant effect of Day 1 air concentrations on Day 2 total

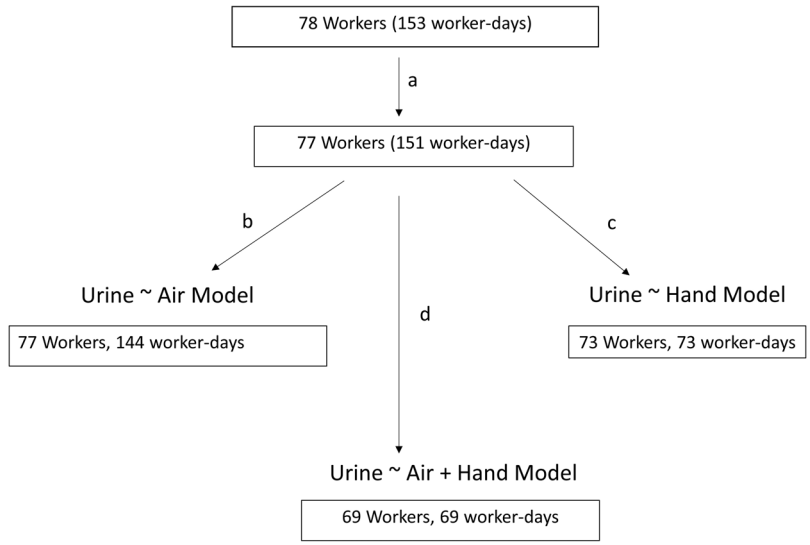

Figure 2. Participants included in regression models with urine, air, and/or hand BPA exposure data. [a]Exclude 1 worker (2 worker-days) with possible BPA urine contamination. [b]Exclude 7 worker-days on 7 different workers with a missing air sample; each worker had an air sample on the non-missing day. [c]Exclude 4 workers (6 worker-days) missing one or both hand samples; exclude 72 worker-days because hand samples collected on only 1 day. [d]Exclude 4 workers (6 worker-days) missing one or both hand samples; exclude 4 additional workers (4 worker-days) missing an air sample on the day hand samples were collected; exclude 72 worker-days because hand samples collected on only 1 day.

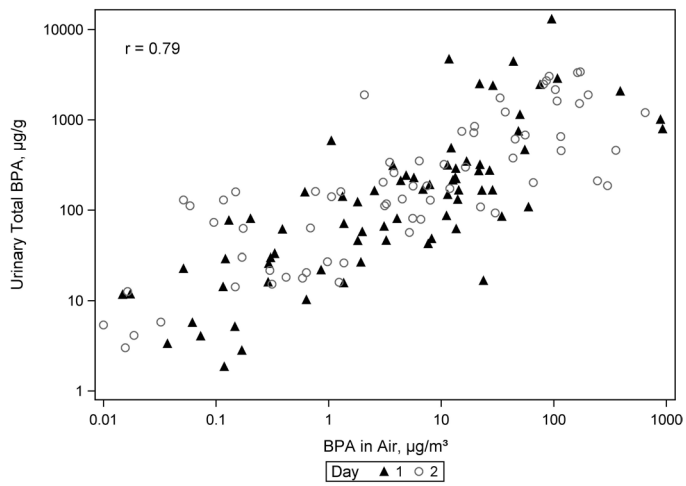

Figure 3. Scatter plot of urinary total BPA_{CR} (µg g^{-1}) at end shift versus BPA air concentration (µg m^{-3}) stratified by Day. Pearson's $r = 0.79$ (on natural log-transformed data), $P < 0.0001$.

BPA_{CR} ($P = 0.0104$); Day 2 BPA air concentration was, as expected, highly significant ($P < 0.0001$) in this model (Table S4, Supplementary data, available at *Annals of Occupational Hygiene* online). The negative interaction between day and shift time indicated that the change in total BPA_{CR} from mid-shift to end shift on Day 1 was greater than on Day 2.

In the *urine~hand* model, after adjusting for shift time ($P < 0.0001$), total BPA_{CR} at baseline ($P < 0.0027$), BMI ($P = 0.1932$), and the pre-shift BPA hand-wipe level ($P = 0.5703$), the end-shift hand-wipe BPA level was significantly and positively associated with total BPA_{CR} at end shift on the day the hand-wipe sample was collected (Table 3). When we excluded the two participants with the particularly high end-shift hand-wipe BPA levels

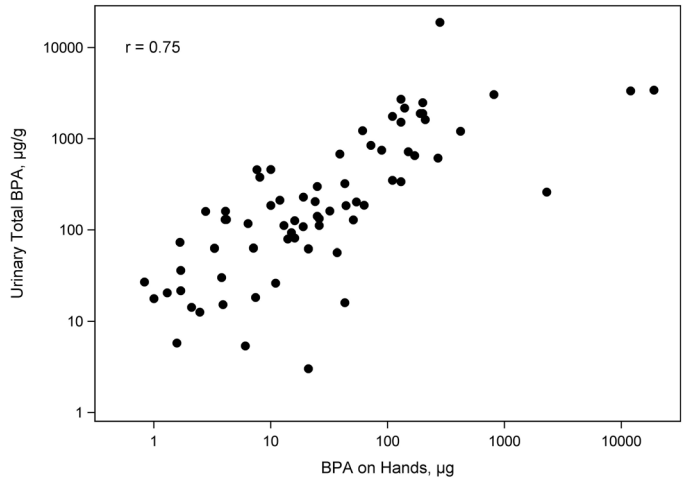

Figure 4. Scatter plot of urinary total BPA_{CR} (µg g^{-1}) at end shift on day of hand-wipe collection versus end-shift hand-wipe BPA level (µg per sample). $n = 73$ ($n = 1$ on Day 1; $n = 72$ on Day 2). Pearson's $r = 0.75$ (on natural log-transformed data), $P < 0.0001$.

Table 2. *Urine~air* model. Multiple regression results for creatinine-adjusted total BPA (µg g^{-1}) at time points 2, 3, 6, and 7 regressed on BPA air concentration (µg m^{-3}) and including covariates (144 worker-days, 77 workers).

Dependent variable: ln(total BPA_{CR}, µg g^{-1})[a,b] $n = 286$	β (SE)	*P*-value	Factor[c]
Intercept	0.7702 (0.5376)	0.1559	
Day			
1	Ref.		
2	0.6276 (0.1163)	<0.0001	1.87
Shift time			
Mid-shift	Ref.		
End shift	0.6486 (0.08804)	<0.0001	1.91
Day × shift time	−0.3379 (0.1333)	0.0121	0.71
ln(total BPA_{CR} at baseline, µg g^{-1})	0.5890 (0.05498)	<0.0001	1.80
BMI, kg m^{-2}	0.03514 (0.01556)	0.0268	1.04
ln(BPA air concentration, µg m^{-3})	0.2614 (0.02821)	<0.0001	1.30

Ref, referent group.

[a]First-order autoregressive covariance structure, AR(1), AIC = 665.7.

[b]Regression equation: total BPA_{CR}, µg g^{-1} = ($e^{0.7702 + 0.6276\ (\text{if Day=2}) + 0.6486\ (\text{if Shift time=End shift}) - 0.3379\ (\text{if End shift on Day 2}) + 0.3514 \times \text{BMI}}$) × (total BPA_{CR} at baseline, µg g^{-1})$^{0.5890}$ × (BPA air concentration, µg m^{-3})$^{0.2614}$.

[c]e^{β}.

from the *urine~hand* model, the end-shift hand-wipe BPA level remained significant (Table S5, Supplementary data, available at *Annals of Occupational Hygiene* online). When the *urine~hand* model was restricted to urinary total BPA_{CR} at end shift only, the end-shift hand-wipe BPA level remained significant with a slightly higher effect estimate (β = 0.4340, Table S6, Supplementary data, available at *Annals of Occupational Hygiene* online) than in the *urine~hand* model with both mid- and end-shift total BPA_{CR} concentrations (β = 0.4036, Table 3).

When both the BPA air concentration and the end-shift hand-wipe BPA level were in the same model (*urine~air+hand*) and after adjusting for covariates, the BPA air concentration was significant at $P < 0.0001$, and the end-shift hand-wipe BPA level at $P = 0.0106$ (Table 4). When we re-ran this model with either the BPA air concentration or the end-shift hand-wipe BPA level in the model but not both, the AIC was lower for the model with the air concentration (AIC = 337.4) than the model with the end-shift hand wipe (AIC = 357.5) (Table 4).

Discussion

Table 3. *Urine~hand* model. Multiple regression results for creatinine-adjusted total BPA (μg g^{-1}) at time points 2 and 3 (for hand wipes collected on Day 1) and 6 and 7 (for hand wipes collected on Day 2) regressed on BPA hand levels (μg per sample) and including covariates (73 worker-days, 73 workers).

Dependent variable: ln(total BPA_{CR}, μg g^{-1})[a,b] n = 144	β (SE)	*P*-value	Factor[c]
Intercept	1.3698 (0.8294)	0.0968	
Shift time			
Mid-shift	Ref.		
End shift	0.3481 (0.07898)	<0.0001	1.42
ln(total BPA_{CR} at baseline, μg g^{-1})	0.3438 (0.1106)	0.0027	1.41
BMI, kg m^{-2}	0.03019 (0.02298)	0.1932	1.03
ln (BPA hand, μg per sample at pre-shift)	0.05962 (0.1045)	0.5703	1.06
ln (BPA hand, μg per sample at end shift)	0.4036 (0.09127)	<0.0001	1.50

Ref, referent group.

[a]Compound symmetric covariance structure. AIC = 376.1.

[b]Regression equation: total BPA_{CR}, μg g^{-1} = $(e^{1.3698 + 0.3481\ (\text{if Shift time=End shift}) + 0.03019 \times BMI})$ × (total BPA_{CR} at baseline, μg $g^{-1})^{0.3438}$ × (BPA pre-shift hand level, μg per sample)$^{0.05962}$ × (BPA end-shift hand level, μg per sample)$^{0.4036}$.

[c]e^{β}.

In the general population, diet is thought to be the main source of BPA exposure (NTP, 2008). In this study, however, manufacturing workers were likely exposed to BPA mainly by inhalation and/or dermal contact with diet contributing minimally to their overall BPA exposure (Hines *et al.*, 2017a,b). Measuring BPA in urine captures exposure by all routes, but does not provide direct information on exposure routes. In this analysis, we evaluated the relationship between total BPA_{CR} in urine and measures of exposure via inhalation (air samples) and dermal contact (hand wipes). We then constructed models to estimate total BPA_{CR} from air and hand-wipe data in order to explore the relative importance of inhalation and dermal exposure routes among workers in our study.

We found that both air and hand-wipe measures of BPA exposure strongly correlated with total BPA_{CR}. Further exploration using mixed-effects regression modeling indicated that model fit improved when the model included the BPA air concentration compared with when the model had only the BPA hand-wipe level (holding all other terms constant). This result suggests that inhalation was a more important exposure route, on average, than dermal contact for this group of workers although we note that both measures were statistically significant in all models. This observation is also consistent with higher BPA intake estimates based on inhalation than on dermal exposure in these workers (Hines *et al.*, 2017b). At the BPA air concentrations measured in this study, we also found that worker exposure to BPA in air is reflected in total BPA_{CR} on both the day the air sample was taken and the following day. This finding indicates that information on the prior day's BPA air concentration should be collected in order to better model total BPA_{CR} in exposed workers.

We did not have direct measures of workers' oral exposure to BPA; however we had information on behaviors at work that could have contributed to oral exposure such as smoking, eating, chewing gum, and chewing tobacco and hand washing frequency. In our previous analyses (Hines *et al.*, 2017a), these factors were not associated with increased total BPA_{CR} although the study may not have had sufficient power to detect such effects.

Using the BPA air concentration to predict total BPA_{CR} at various time points improved by having information on a worker's BMI and total BPA_{CR} at baseline (pre-shift Day 1). With these two pieces of information, the *urine~air* model (Table 2) can be used to estimate total BPA_{CR} at select time points. For example, at a concentration of 6 μg m^{-3} (median air concentration for study workers), a baseline total BPA_{CR} of 25 μg g^{-1} (~ median for study workers), and a BMI of 30 kg m^{-2} (~median for study workers), the predicted end-shift total BPA_{CR} was 126 μg g^{-1} (Day 1) and 168 μg g^{-1} (Day 2). At the maximum air concentration measured, 920 μg m^{-3}, the predicted end-shift total BPA_{CR} was 470 μg g^{-1} (Day 1) and 628 μg g^{-1} (Day 2).

Likewise, BMI and total BPA_{CR} at baseline were important factors in estimating end-shift total BPA_{CR} from end-shift hand-wipe BPA levels. Pre-shift hand-wipe BPA levels had essentially no effect on end-shift total BPA_{CR} (Table 3). For example, at a BMI of 30, a baseline total BPA_{CR} of 25 μg g^{-1}, a pre-shift hand-wipe

Table 4. *Urine~air+hand* model. Multiple regression results for creatinine-adjusted total BPA (μg g^{-1}) at time points 2, 3, 6, and 7 regressed on BPA air concentration (μg m^{-3}) and BPA hand level (μg per sample) and including covariates. Model 1: BPA air concentration and BPA levels on hand wipes both in model; Model 2: BPA air concentration excluded from model; Model 3: BPA levels on hand wipes excluded model (69 worker-days, 69 workers).

Dependent variable: ln(total BPA_{CR}, μg g^{-1})[a] n = 136	β(SE)	*P*-value	Factor[c]
Model 1 (AIC = 336.7)[b]			
Intercept	2.0137 (0.7013)	0.0055	
Shift time			
Mid-shift	Ref.		
End shift	0.3417 (0.08305)	0.0001	1.41
ln(total BPA_{CR} at baseline, μg g^{-1})	0.3022 (0.09162)	0.0016	1.35
BMI, kg m^{-2}	0.02279 (0.01970)	0.2518	1.02
ln (BPA air concentration, μg m^{-3})	0.2725 (0.04977)	<0.0001	1.31
ln (BPA hand, μg per sample at pre-shift)	–0.04015 (0.08851)	0.6516	0.96
ln (BPA hand, μg per sample at end shift)	0.2205 (0.08374)	0.0106	1.25
Model 2 (AIC = 357.5)			
Intercept	1.5486 (0.8384)	0.0693	
Shift time			
Mid-shift	Ref.		
End shift	0.3424 (0.08317)	0.0001	1.41
ln(total BPA_{CR} at baseline, μg g^{-1})	0.3231 (0.1103)	0.0047	1.38
BMI, kg m^{-2}	0.02705 (0.02372)	0.2584	1.03
ln (BPA hand, μg per sample at pre-shift)	0.04822 (0.1049)	0.6472	1.05
ln (BPA hand, μg per sample at end shift)	0.4034 (0.09250)	<0.0001	1.50
Model 3 (AIC = 337.4)			
Intercept	2.0897 (0.6994)	0.0040	
Shift time			
Mid-shift	Ref.		
End shift	0.3438 (0.08309)	0.0001	1.41
ln(total BPA_{CR} at baseline, μg g^{-1})	0.4015 (0.07412)	<0.0001	1.49
BMI, kg m^{-2}	0.02890 (0.02021)	0.1575	1.03
ln (BPA air concentration, μg m^{-3})	0.3320 (0.04418)	<0.0001	1.39

Ref, referent group.

[a]Compound symmetric covariance structure.

[b]Regression equation model 1: Total BPA_{CR} in μg g^{-1} = $(e^{2.0137 + 0.3417\ (\text{if Shit-time=End shift}) + 0.02279 \times BMI})$ × (total BPA_{CR} at baseline, μg $g^{-1})^{0.3022}$ × (BPA air concentration, μg $m^{-3})^{0.2725}$ × (BPA pre-shift hand level, μg per sample)$^{-0.04015}$ × (BPA end-shift hand level, μg per sample)$^{0.2205}$.

[c]e^{β}.

BPA level of 0.3 μg per sample (highest reported LOD), and an end-shift hand-wipe level of 2 μg per sample (median for study workers), the predicted end-shift total BPA_{CR} was 140 μg g^{-1}. At the highest end-shift hand-wipe level, 19 000 μg per sample, the predicted end-shift total BPA_{CR} was 2100 μg g^{-1}.

Workers in this study had, on average, BPA concentrations in their Day 1 pre-shift urine 20 times higher than in NHANES 2013–2014, despite 84% of the workers having been away from work for at least 24 h and 71% for at least 48 h (CDC 2017; Hines *et al.*, 2017a). Consequently, regression models estimating post-baseline total BPA_{CR} from air and hand-wipe data were adjusted for these relatively high baseline concentrations. Moreover, because the range of baseline total BPA_{CR} for workers in our study was quite wide, 0.78–1580 μg g^{-1}, and variable (geometric standard deviation of 5.74), baseline urine samples would be critical to include in future studies of similarly exposed workers.

We collected the inhalable aerosol fraction anticipating mostly large particles when handling raw BPA. Workers in jobs involving molten BPA-filled wax may have inhaled respirable-sized particles if BPA vaporized with heat and then condensed to small particles with

cooling. While the inhalable fraction includes small particles, we do not know the partitioning of the sample between large and small particles. Particle size affects deposition in the respiratory tract, and therefore, may affect uptake and possibly the correlation between BPA concentrations in air and in urine.

Results from this analysis may have implications for workplace controls. As a first step, controls should reduce inhalation exposure, initially through use of engineering or process controls, and then respirators. These efforts should be followed by reducing opportunities for dermal contact with BPA. Wipe sampling of work surfaces in this study that workers touched with ungloved hands indicated, not surprisingly, that objects and surfaces in production areas had higher BPA levels, on average, than eating areas and offices/control rooms (Hines *et al.*, 2017b).

To our knowledge, this is the first analysis in a single study of the relationship among three measures of BPA exposure, urine, air, and hand wipes in either an occupational or a non-occupational population. He *et al.* (2009) examined the correlation between BPA concentrations in personal air samples and in pre- and post-shift urine samples from 131 epoxy resin- and BPA-manufacturing workers in China. They found Spearman coefficients of 0.525 (air with pre-shift urine) and 0.726 (air with post-shift urine) although air and urine samples were not always collected on the same day. We found a slightly higher correlation between BPA air concentration and end-shift total BPA_{CR} (r_p = 0.79). Concentrations of BPA in urine and in air among workers in our study were similar to those of manufacturing workers in China for whom male reproductive health effects were reported (He *et al.* 2009; Li *et al.*, 2010b). Additional health studies of similarly exposed workers are needed.

Strengths of this analysis include its well-defined temporality around the collection of urine, air, and hand-wipe samples, a detailed time course of BPA concentrations in urine over 2 consecutive days, and a sufficient sample size to both identify exposure determinants and to examine the correlation among BPA in urine, air, and on workers' hands. Possible study limitations should also be noted. Participants in our study may not be representative off all manufacturing workers exposed to BPA. In addition, we may not have captured all important exposure determinants, which could affect estimates of urinary BPA concentrations derived from air and hand-wipe data, and we did not have direct measures of oral BPA exposure. The apparent weaker correlation of hand-wipe BPA levels with total BPA_{CR} might be due to a delayed appearance of BPA in urine after dermal uptake. Hand wipes were collected at end shift on the last day of urine sampling and if the elimination of BPA into the urine is slower after dermal contact than after inhalation or ingestion, then we may have not have captured all dermal-related exposure in the urine.

Conclusion

External measures of BPA exposure by inhalation (air samples) and dermal contact (end-shift hand wipes) were highly correlated with mid- and end-shift total BPA_{CR}. Although both inhalation and dermal contact likely contributed to exposure, our analyses suggest that inhalation, on average, appeared to be a more dominant exposure route than dermal contact for this group of manufacturing workers. This finding has implications for setting priorities for exposure control measures in manufacturing workplaces where BPA is handled.

Supplementary Data

Supplementary data are available at *Annals of Work Exposures and Health* online.

Disclaimer

The findings and conclusions in this report are those of the author(s) and do not necessarily represent the official position of the National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention.

Funding

This study was supported in part by an interagency agreement between the National Institute for Occupational Safety and Health and the National Institute of Environmental Health Sciences (AES12009) as a collaborative National Toxicology Program research activity. The authors declare they have no conflict of interest.

Acknowledgments

We gratefully acknowledge the contributions of participating workers, companies, and unions to this study.

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