HHS Public Access

Author manuscript

Environ Res. Author manuscript; available in PMC 2019 July 01.

Published in final edited form as:

Environ Res. 2018 July ; 164: 580–584. doi:10.1016/j.envres.2018.03.035.

Medications as a Potential Source of Exposure to Parabens in the U.S. Population

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Abstract

INTRODUCTION—Use of paraben-containing medications has been shown to be associated with urinary paraben concentrations among couples undergoing fertility treatment, but it is unknown whether this association is also present among the general population.

METHODS—A list of prescription medications of interest was developed based on their likelihood of containing parabens and the ability to identify users in the National Health and Nutrition Examination Survey (NHANES); alendronate, escitalopram oxalate, fluoxetine, and olanzapine were chosen. Participants reported whether they had used each medication in the past month. Linear regression models were used to compare model-based mean urinary concentrations of each paraben among users and non-users of these four medications.

RESULTS—A total of 10,302 respondents were included in the analysis, 265 (2.6%) of whom had reported using a paraben-containing prescription medication in the previous month. Users of alendronate had mean concentrations of ethyl paraben that were approximately three-fold higher than non-users ($p \geq 0.001$ in unadjusted and adjusted models), which was likely due to three participants with very high concentrations. No other differences in paraben concentrations were found for any of the medications of interest (all $p \geq 0.13$). Compared to non-users, a significantly

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Competing interests

SHD has received unrestricted training grants from, and consulted for, pharmaceutical companies.

greater proportion of alendronate users had butyl and ethyl paraben concentrations above the 95th percentile (17.8% and 12.3%, respectively) compared to non-users (5.0% and 5.0%, respectively; both p≤0.01), despite ethyl paraben not being an expected ingredient in the brand name formulation of alendronate.

CONCLUSION—Despite previous work showing that medications can be an important source of paraben exposure, there was no clear overall evidence of associations between the use of paraben-containing medications and increases in urinary paraben concentrations among participants in NHANES 2005-2012. These results highlight the difficulties inherent in proper assessment of exposures with short half-lives based on a single cross-sectional biologic sample.

Keywords

parabens; environmental health; environmental exposure; medications

INTRODUCTION

Parabens are esters of p-hydroxybenzoic acid that are used as preservatives in a variety of commercial products, including pharmaceutical drugs (Elder, 1984). Paraben exposure is widespread among the U.S. population and is assessed within the National Health and Nutrition Examination Survey (NHANES). NHANES is conducted by the National Center for Health Statistics (NCHS) and periodically surveys a nationally-representative sample of the US population (McDowell et al. 1981; NCHS 1994). Data from NHANES 2005-2006 shows that nearly all subjects had detectable levels of methyl (99.1%) and propyl (92.7%) paraben in their blood/urine (Fourth National Report, 2013), while only 40% of subjects showed detectable levels of butyl paraben (Fourth National Report, 2013).

Parabens have estrogenic activity that is many times weaker than endogenous estradiol. In rats, some forms of parabens have been found to adversely affect testosterone production and male reproductive functions (Oishi, 2002; Tavares, 2009). In humans, paraben residues have been detected in breast cancer tumor cells (Darbre et al., 2004) and associated with sperm DNA damage in men (Meeker, 2010), and while no causal association has been shown, health practitioners and researchers have begun to question whether ubiquitous paraben exposure may have unintended health effects. In humans, paraben exposure has been found to be associated with sperm DNA damage (Meeker et al. 2011), and there may be a relationship between paraben exposure and oxidative stress (Kang et al. 2013). Additionally, serum thyroid hormone concentration has been found to be inversely associated with urinary paraben levels, especially among adult women (Koeppe et al. 2013).

Parabens are glucuronidated by liver enzymes and excreted in the urine, and evidence suggests that they do not accumulate in normal human tissue (Abbas et al. 2010). However, there is some evidence that parabens can accumulate in human breast tumors (Dagher et al. 2012). Their short half-lives are on the order of hours (Janjua et al. 2008).

Previous research on paraben exposure has largely focused on personal care products such as creams and lotions, which are the main route of dermal exposure (CIR Expert Panel, 2008). In addition to personal care products, ingestion of parabens that are included as non-active

ingredients in commercialized medications and drugs may be a source of unrecognized intense paraben exposure. We have previously shown that use of paraben-containing medications is associated with higher urinary paraben concentrations within hours of use (Dodge, 2015). However, this was a small sample restricted to participants attending a fertility treatment center. The association between use of paraben-containing medications and urinary paraben concentrations has not been explored in a large national dataset, and it is unknown whether such datasets can be used to detect paraben exposure from sources such as medications. Our aim was to determine whether NHANES can detect paraben exposure from medications by evaluating whether users of paraben-containing medications have higher urinary concentrations of parabens than non-users of these medications.

MATERIALS AND METHODS

Data Sources

For the present analysis, we used the following three files from NHANES 2005-2012: a) sample demographics file, which provides selected demographic variables such as age and sex; b) the prescription medication section of the Sample Person Questionnaire; and c) the environmental phenols laboratory file, which includes data on urinary concentrations of specific parabens. These files were linked using unique survey participant identification numbers. Because only survey participants who were ≥6 years of age were eligible for the laboratory subsections, we restricted our analyses to individuals who were ≥6 years of age.

Exposure Assessment

Participants were asked whether, in the past month, they had taken a medication for which they needed a prescription. The interviewer entered the medication name and selected the best match from a computerized list of prescription drugs. All reported medications were converted to their standard generic ingredient name for public data release (i.e., no specific brand names or formulations are available). Individuals who were unable to report the name of the drug were excluded from the analysis. The analgesics sub-section did assess use of non-prescription pain relief medicines, but the specific analgesic brand names were not recorded. No other information regarding the use of non-prescription medications was recorded.

For each survey cycle, urine samples were collected from a sub-sample of one third of the participants who were ≥6 years of age. Samples were collected at any time of day, and all samples were stored frozen until analysis. Since 2005, the urinary concentrations of several parabens have been measured at the National Center for Environmental Health using solid-phase extraction (SPE) coupled to high-performance liquid chromatography (HPLC)–isotope dilution tandem mass spectrometry (MS/MS), as described previously (Ye et al. 2006). Briefly, the conjugated phenol species are hydrolyzed using β-glucuronidase/sulfatase, though the deconjugation step is not used for the measurement of free species. Following hydrolysis, samples are acidified with 0.1 M formic acid. Phenols are preconcentrated by online SPE, separated by reversed-phase HPLC, and detected by atmospheric pressure chemical ionization– MS/MS. Urinary concentrations of methyl (MPB), ethyl (EPB), propyl (PPB), and butyl (BPB) paraben are available starting in 2005.

In NHANES, concentrations below the limit of detection (LOD) are assigned an imputed value equal to the LOD divided by the square root of two (Hornung and Reed 1990).

A list of medications that might contain parabens as inactive ingredients was developed *a priori* using publically available sources such as Dailymed, from the National Library of Medicine, as described previously (Dodge et al. 2015). Briefly, we first created a list of medications of interest based on their likelihood of containing parabens and then obtained more detailed information on their formulations using information from FDA websites. Available drug product labeling was screened for paraben content, and if a product was found to contain a paraben, then other common formulations of the same active ingredient were researched. Given the limited data available in NHANES, we restricted the scope of the analysis to paraben-containing *prescription* medications for which we were able to identify users in the study population. Further, because NHANES codes medication use by the active ingredient and not by the brand, we selected medications (and their respective active ingredients) for which paraben-containing brand(s) were likely to account for a high proportion of use (based on tables of the most commonly prescribed drugs for 2005-2012). In addition, we focused on active ingredients that were likely to have a high prevalence of use, e.g., used to treat common chronic health conditions in the general population. Based on these criteria, from a list of 79 medications that may contain parabens, we selected the following four *a priori* for evaluation: 1) alendronate, which is used to treat osteoporosis and contains PPB and BPB; 2) olanzapine, which is used to treat psychotic disorders and contains PPB and BPB; 3) escitalopram oxalate, which is used to treat depression and generalized anxiety disorder and contains MPB and PPB; and 4) fluoxetine, which is used to treat depression, obsessive compulsive disorder, eating disorders, and panic disorders and contains MPB, PPB, and BPB. Non-users were defined as individuals who did not report using any of these four medications.

While we do not know the precise concentrations of parabens included in any of these medications of interest, as this information is proprietary and may change over time, the FDA stipulated maximum potencies of inactive ingredients included in drug products. These are currently 0.04 mg of butyl paraben, 0.17 mg of methyl paraben, and 0.12 mg of propyl paraben for sustained action tablet formulations; no maximum is listed for ethyl paraben in this formulation, though the maximum for other listed formulations was 2 mg/5 ml for a suspension formulation (Federal Drug Administration).

Statistical Analysis

We compared model-based mean urinary concentrations of each paraben among users and non- users of these four medications using linear regression models. Models are presented as unadjusted and adjusted for sex, age, race/ethnicity, and NHANES survey cycle. Sampling weights were not used, as we were not trying to make conclusions about the distribution of use of these drugs in the U.S. population. Proportions of respondents with urinary paraben concentrations above the 95th percentile were compared between users and non-users of paraben-containing medications using chi square tests. All analyses were performed using SAS for Windows, version 9.4 (SAS Institute Inc., Cary, NC).

Ethical Approval

The NCHS obtained institutional review board approval to conduct the NHANES survey, and all respondents provided informed consent. NHANES is supported by the U.S. government, and public-use data files and their documentation are available from the NHANES website (NHANES 2017).

RESULTS

Of the 31,034 individuals who completed the demographic questionnaire, 10,390 (33.5%) had information on urinary paraben concentrations. Sixty-nine respondents (0.7%) were excluded due to missing prescription medication names, and in order to isolate the effects of single medications on urinary paraben concentrations, one participant who reported using two paraben-containing medications (fluoxetine and olanzapine) was excluded, leaving an analytic dataset of 10,320 individuals. Of these, 265 (2.6%) reported using one of the paraben-containing medications chosen *a priori* (Table 1). Compared to non-users of paraben-containing medications, users were more likely to be older and of non-Hispanic white race.

Among users of paraben-containing drugs, 35.1% reported using fluoxetine, 33.2% reported using escitalopram oxalate, 27.5% reported using alendronate, and 4.2% reported using olanzapine (Table 2). Users of alendronate tended to be older than users of the other medications. Users of olanzapine and fluoxetine were more likely to be female, and users of olanzapine were more likely to be of non-Hispanic black race than users of the other medications.

Users of alendronate had higher mean concentrations of all parabens compared to non-users (Table 3), with significantly higher mean urinary concentration of ethyl paraben in both the unadjusted ($p<0.001$) and adjusted ($p=0.001$) models. Further examination showed that of the 73 users of alendronate, three users had very high urinary concentrations of ethyl paraben (range: 405–1,510 ng/ml) compared to the remaining users (range: <LOD–138 ng/ml). The mean urinary paraben concentrations among users and non-users of escitalopram, fluoxetine, and olanzapine did not differ significantly in either the unadjusted or adjusted models (all $p\geq0.13$), though interestingly, users of olanzapine tended to have notably lower concentrations than non-users. Eighteen percent of alendronate users had urinary concentrations of butyl paraben that were above the 95^{th} percentile ($p<0.001$), and 12.3% had urinary concentrations of ethyl paraben that were above the 95^{th} percentile ($p=0.01$); no other differences were found in the proportions of respondents whose concentrations were above the 95^{th} percentile (all $p\geq0.33$; Table 4).

CONCLUSION

There was no widespread evidence of associations between the use of paraben-containing medications and increases in urinary paraben concentrations among participants in NHANES 2005-2012. We expected to find elevated urinary concentrations of propyl paraben in users of all four medications, elevated urinary concentrations of butyl paraben in users of alendronate, olanzapine, and fluoxetine, and elevated urinary concentrations of

methyl paraben in users of escitalopram and fluoxetine. Among these four drugs, only alendronate showed any significant association with urinary paraben concentrations; users had significantly higher mean urinary concentrations of ethyl paraben, and a significantly greater proportion of users had concentrations of ethyl and butyl paraben that were above the 95th percentile. However, this is likely driven by three participants with very high urinary concentrations of ethyl paraben. Notably, ethyl paraben was not an expected ingredient in the brand-name version of alendronate, and was therefore not expected to be elevated in alendronate users. This underscores the difficulty in identifying inactive ingredients in pharmaceutical products, which may make it impossible for researchers to identify exposure sources and for consumers to avoid environmental chemical exposure.

This study raises issues surrounding the analysis of pharmaceutical product use within large national databases such as NHANES. While it is possible that there is no association between the use of paraben-containing pharmaceutical products and urinary paraben concentrations, it is also possible that we were unable to detect true differences between users and non-users due to exposure misclassification. Misclassification could arise from users taking a brand or specific product formulation of medication that does not contain parabens (e.g., only the oral solution of name-brand alendronate was identified as containing parabens [Drugs@FDA]). The timing of medication use and sample collection might be another source of misclassification. The questionnaire used in NHANES asked whether respondents had taken prescription medications at any time in the past month. Some “exposed” users may have used a single dose of a medication weeks before urine collection, while others may have taken multiple daily doses in the past month. For example, alendronate is prescribed for once-weekly use, while olanzapine, escitalopram, and fluoxetine are used once or twice daily (Drugs@FDA). Therefore, the use may had been before the relevant pharmacokinetic window for paraben concentrations to be elevated in the urine, which is on the order of hours due to short half-lives (Janjua et al. 2008). We previously found that individuals who reported taking a paraben-containing medication on the day of their urine sample had higher urinary paraben concentrations than non-exposed individuals (Dodge et al. 2015).

Additionally, both users of non-users of paraben-containing drugs could have been exposed to other sources of parabens, such as other over the counter drugs or personal care products. However, these sources of baseline paraben urinary levels in the U.S. population are expected to be balanced in exposed and unexposed groups. More directly, we previously found that controlling for the number of personal care products used only slightly attenuated the associations between urinary paraben concentration and use of paraben-containing medications (Dodge et al. 2015).

Only 2.6% of respondents had used a paraben-containing medication in the past month, which limited the sample size for analysis. While we did not find widespread evidence of associations between the use of paraben-containing medications and increases in urinary paraben concentrations among participants in NHANES 2005-2012, individuals who regularly consume paraben-containing medications may experience continuous paraben exposure and thus may be at higher risk of health effects from these exposures; we were unable to assess regular use in this study. This continual exposure is of particular concern for

populations such as children and pregnant women, as data indicates that parabens can cross the placenta (Towers et al. 2015) and be transferred to the fetus (Kang et al. 2013).

The present analysis highlights the difficulties inherent in proper assessment of pharmaceutical product use within a large and generally comprehensive health study. Future research should increase power by targeting participants exposed to selected medications, try to minimize exposure misclassification, and ensure that the time of urinary biomarker measurement occurs at the relevant time window with respect to use of the medication. Further exploration and consideration of the contribution of medications to paraben exposure are warranted due to the potential for high delivered doses of parabens to certain segments of the population, such as children, adolescents, and pregnant women.

Acknowledgments

This work was supported by National Institute of Environmental Health Sciences training grant T32 ES 07069, which supported LED.

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Highlights

- Paraben-containing medications may an important source of paraben exposure
- No clear evidence of paraben exposure from medications in a national dataset
- Assessment of exposures with short half-lives difficult in cross-sectional samples
- Assessing paraben exposure within the correct pharmacokinetic window is crucial

Table 1

Demographic characteristics of users and non-users of select paraben-containing medications, NHANES 2005-2012

Characteristic	Total N=10,320	Users n=265	Non-users n=10,055
Age (years)			
<16	2,509 (24.3)	8 (3.0)	2,501 (24.9)
16-30	2,330 (22.6)	22 (8.3)	2,308 (23.0)
31-50	2,340 (22.7)	68 (25.7)	2,272 (22.6)
51-<65	1,670 (16.2)	73 (27.6)	1,597 (15.9)
>65	1,471 (14.3)	94 (35.5)	1,377 (13.7)
Body mass index			
Underweight	1,153 (11.2)	16 (6.0)	1,137 (11.3)
Normal weight	3,487 (33.8)	69 (26.0)	3,418 (34.0)
Overweight	2,784 (27.0)	75 (28.3)	2,709 (26.9)
Obese	2,896 (28.1)	105 (39.6)	2,791 (27.8)
Sex			
Female	5,005 (48.5)	137 (51.7)	4,868 (48.4)
Male	5,313 (51.5)	128 (48.3)	5,187 (51.6)
Race			
Non-Hispanic White	4,112 (39.8)	183 (69.1)	3,929 (39.1)
Non-Hispanic Black	2,436 (23.6)	23 (8.7)	2,413 (24.0)
Mexican American	2,039 (19.8)	28 (10.6)	2,011 (20.0)
Other Hispanic	913 (8.9)	19 (7.2)	894 (8.9)
Other	820 (8.0)	12 (4.5)	808 (8.0)

Data are shown as n (%)

Table 2

Demographic characteristics of users of select paraben-containing medications, NHANES 2005-2012

Characteristic	Alendronate n=73	Escitalopram n=88	Fluoxetine n=93	Olanzapine n=11
Age (years)				
<16	0 (0.0)	0 (0.0)	7 (7.5)	1 (9.1)
16-30	0 (0.0)	12 (13.6)	10 (10.8)	0 (0.0)
31-50	2 (2.7)	27 (30.7)	35 (37.6)	4 (36.4)
51-65	22 (30.1)	27 (30.7)	20 (21.5)	4 (36.4)
>65	49 (67.1)	22 (25.0)	21 (22.6)	2 (18.2)
Body mass index				
Underweight	3 (4.1)	4 (4.6)	8 (8.6)	1 (9.1)
Normal weight	23 (31.5)	29 (33.0)	14 (15.1)	3 (27.3)
Overweight	24 (32.9)	18 (20.5)	32 (34.4)	1 (9.1)
Obese	23 (31.5)	37 (42.0)	39 (41.9)	6 (54.6)
Sex				
Female	36 (49.3)	40 (45.5)	54 (58.1)	7 (63.6)
Male	37 (50.7)	48 (54.6)	39 (41.9)	4 (36.4)
Race				
Non-Hispanic White	48 (65.8)	62 (70.5)	69 (74.2)	4 (36.4)
Non-Hispanic Black	5 (6.9)	9 (10.3)	6 (6.5)	3 (27.3)
Mexican	10 (13.7)	7 (8.0)	9 (9.7)	2 (18.2)
Other Hispanic	5 (6.9)	5 (5.7)	8 (8.6)	1 (9.1)
Other	5 (6.9)	5 (5.7)	1 (1.1)	1 (9.1)

* Data are reported as n (%)

Table 3

Urinary paraben concentrations (ng/ml) among users and non-users of select paraben-containing medications, NHANES 2005-2012

Medication	Users	Non-users	Unadjusted model			Adjusted model*		
			Users	Non-users	P	Users	Non-users	P
			Methyl paraben (ng/ml)					
Alendronate	73	10,055	337 (80.1)	266 (6.8)	0.38	382 (81.6)	260 (13.7)	0.13
Escitalopram	88	10,055	201 (72.8)	266 (6.8)	0.37	255 (73.4)	261 (13.7)	0.94
Fluoxetine	93	10,055	249 (71.0)	266 (6.8)	0.82	313 (71.4)	260 (13.7)	0.44
Olanzapine	11	10,055	102 (206)	266 (6.8)	0.43	61.9 (203)	261 (13.7)	0.33
			Propyl paraben (ng/ml)					
Alendronate	73	10,055	84.5 (23.4)	63.5 (2.0)	0.37	82.5 (24.1)	56.1 (4.0)	0.26
Escitalopram	88	10,055	49.5 (21.3)	63.5 (2.0)	0.51	52.5 (21.7)	55.9 (4.0)	0.87
Fluoxetine	93	10,055	52.5 (20.7)	63.5 (2.0)	0.60	58.9 (21.0)	55.9 (4.0)	0.88
Olanzapine	11	10,055	10.7 (60.3)	63.5 (2.0)	0.38	−4.8 (60.0)	56.1 (4.1)	0.31
			Butyl paraben (ng/ml)					
Alendronate	73	10,055	9.1 (3.0)	3.9 (0.3)	0.08	6.6 (3.1)	2.7 (0.5)	0.20
Escitalopram	88	10,055	2.9 (2.7)	3.9 (0.3)	0.71	1.3 (2.8)	2.7 (0.5)	0.63
Fluoxetine	93	10,055	3.6 (2.7)	3.9 (0.3)	0.93	2.5 (2.7)	2.7 (0.5)	0.95
Olanzapine	11	10,055	0.14 (7.8)	3.9 (0.3)	0.63	−1.5 (7.8)	2.7 (0.5)	0.60
			Ethyl paraben (ng/ml)					
Alendronate	73	10,055	51.1 (9.9)	16.6 (0.8)	<0.001	44.4 (10.2)	12.0 (1.7)	0.001
Escitalopram	88	10,055	14.4 (8.8)	16.6 (0.8)	0.80	10.1 (9.0)	11.8 (1.7)	0.85
Fluoxetine	93	10,055	17.9 (8.6)	16.6 (0.8)	0.89	13.6 (8.8)	11.6 (1.7)	0.82
Olanzapine	11	10,055	2.5 (25.0)	16.6 (0.8)	0.57	−3.2 (25.0)	11.8 (1.7)	0.55

Data are presented as the mean and standard error

Table 4

Proportion of users and non-users of select paraben-containing medications with urinary paraben concentrations above the 95th percentile, NHANES 2005-2012

Medication	Users	Non-users	P
	Methyl paraben		
Alendronate	6.9	5.0	0.41
Escitalopram	2.3	5.0	0.33
Fluoxetine	4.3	5.0	1.00
Olanzapine	0.0	5.0	1.00
	Propyl paraben		
Alendronate	6.9	5.0	0.41
Escitalopram	3.4	5.0	0.80
Fluoxetine	3.2	5.0	0.63
Olanzapine	0.0	5.0	1.00
	Butyl paraben		
Alendronate	17.8	5.0	<0.001
Escitalopram	4.6	5.0	1.00
Fluoxetine	6.5	5.0	0.47
Olanzapine	0.0	5.0	1.00
	Ethyl paraben		
Alendronate	12.3	5.0	0.01
Escitalopram	5.7	5.0	0.63
Fluoxetine	4.3	5.0	1.00
Olanzapine	0.0	5.0	1.00

Data are presented as %