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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 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 $p \leq 0.01$), 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.

1. 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 U.S. 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

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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 et al., 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.

2. Materials and methods

2.1. 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.

2.2. 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 subsample 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 (DailyMed Current Medication Information, 2014), 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, 2018).

2.3. 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,