# Temporal Variability of Urinary Phthalate Metabolite Levels in Men of Reproductive Age

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Phthalates are a family of multifunctional chemicals widely used in personal care and other consumer products. The ubiquitous use of phthalates results in human exposure through multiple sources and routes, including dietary ingestion, dermal absorption, inhalation, and parenteral exposure from medical devices containing phthalates. We explored the temporal variability over 3 months in urinary phthalate metabolite levels among 11 men who collected up to nine urine samples each during this time period. Eight phthalate metabolites were measured by solid-phase extraction–high-performance liquid chromatography–tandem mass spectrometry. Statistical analyses were performed to determine the between- and within-subject variance apportionment, and the sensitivity and specificity of a single urine sample to classify a subject’s 3-month average exposure. Five of the eight phthalates were frequently detected. Monoethyl phthalate (MEP) was detected in 100% of samples; monobutyl phthalate, monononyl phthalate, mono-2-ethylhexyl phthalate (MEHP), and monomethyl phthalate were detected in >90% of samples. Although we found both substantial day-to-day and month-to-month variability in each individual’s urinary phthalate metabolite levels, a single urine sample was moderately predictive of each subject’s exposure over 3 months. The sensitivities ranged from 0.56 to 0.74. Both the degree of between- and within-subject variance and the predictive ability of a single urine sample differed among phthalate metabolites. In particular, a single urine sample was most predictive for MEP and least predictive for MEHP. These results suggest that the most efficient exposure assessment strategy for a particular study may depend on the phthalates of interest. Key words: biomarkers, human, phthalates, reliability, urine. Environ Health Perspect 112:1734–1740 (2004). doi:10.1289/ehp.7212 available via http://dx.doi.org/ [Online 16 August 2004]
patterns, such as time spent in specific microenvironments (i.e., residential, workplace, or other) with ambient phthalate levels. Therefore, characterizing an individual’s phthalate exposure is complex, and exposure may vary considerably over short time periods, such as days. Although phthalate biomarkers in urine are available to accurately measure a person’s exposure at a single point in time, determining exposure over time intervals of weeks or months will require multiple measurements of phthalate metabolites. Therefore, the present study was designed to explore the temporal variability in urinary phthalate metabolite levels. Our design allowed us to determine between- and within-subject variability in urinary phthalate metabolite levels, as well as apportion the within-person variability into monthly and daily variances. We also explored the sensitivity of a single urine measurement to predict an individual’s 3-month average exposure. This information can be used for designing exposure assessment strategies for epidemiologic studies and to adjust for measurement error in phthalate exposure.

Materials and Methods

Eleven men from our ongoing study of the relationship between environmental agents and male reproductive health agreed to participate in the phthalate variability study. Participant recruitment into the environmental agents and male reproductive health study has been previously described (Hauser et al. 2003). Briefly, men who were the partner in couples seeking fertility evaluation for infertility to conceive were recruited to participate. The study site was the Massachusetts General Hospital (MGH) Andrology Laboratory, so most men resided in the New England area. At the clinic visit, each man was asked to produce a single semen sample and to collect a single spot urine sample.

For each of the 11 men in the phthalate temporal variability study, up to nine additional spot urine samples were collected during three cycles over a 92-day period. Ten of these 11 men each contributed a total of 10 urine samples (nine for the variability study and one for the male reproductive study), whereas one of the men provided a total of seven samples (including six for the variability study). Nestled within each of the three cycles were three urine samples, collected on the first 3 consecutive days of each cycle. The first cycle began upon enrollment into the phthalate temporal variability study, and urine samples were collected on days 0, 1, and 2. Cycles 2 and 3 began 30 days into the phthalate temporal variability study, cycle. The first cycle began upon enrollment collected on the first 3 consecutive days of each study, whereas one of the men provided a study and one for the male reproductive study.

All the urine samples were collected in a sterile specimen cup. The urine sample on day 0 was collected at the MGH Andrology laboratory. All other samples were collected at the subject’s home and frozen before overnight shipment to the Harvard School of Public Health (HSPH) on blue ice. All urine samples were then shipped frozen on dry ice from HSPH to CDC. Eight phthalate monoesters—MBzP, MBP, MEP, MEHP, monomethyl phthalate (MMP), mono-n-octyl phthalate (MOP), mono-3-methyl-5-dimethylhexyl phthalate (MINP), and monocyclohexyl phthalate (MCHP)—were measured in each spot urine sample using an analytical approach developed at the CDC (Silva et al. 2003). Briefly, the determination of phthalate metabolites in urine involved enzymatic deconjugation of the glucuronidated metabolites, solid-phase extraction, separation with high-performance liquid chromatography, and detection by tandem mass spectrometry. Detection limits were in the low micrograms per liter range. Reagent blanks and $\text{^{13}C}_2$-labeled internal standards were used along with conjugated internal standards to increase the precision of the measurements. One method blank, two quality control samples (human urine spiked with phthalates), and two sets of standards were analyzed along with every 21 unknown urine samples. Analysts at the CDC were blind to all information concerning subjects.

Several methods adjust for urine volume (Boeniger et al. 1993; Teass et al. 1998). Although creatinine is a frequently used form of adjustment, if a compound is excreted primarily by tubular secretion it is not appropriate to adjust for creatinine level (Teass et al. 1998). Although the methods of excretion of the phthalate monoesters measured in this study are unknown, terephthalic acid was found to be actively secreted by renal tubules and actively reabsorbed by the kidney (Tremaine and Quebbemann 1985). Furthermore, because organic compounds that are glucuronidated in the liver, like the phthalates, are eliminated by active tubular secretion (Boeniger et al. 1993), creatinine adjustment may not be appropriate for phthalates. Additionally, creatinine levels may be confounded by muscularity, physical activity, urine flow, time of day, diet, and disease states (Boeniger et al. 1993; Teass et al. 1998). For these reasons, specific gravity, rather than creatinine, was used to normalize phthalate levels.

Urinary phthalate levels were normalized for dilution by specific gravity adjustment using the formula $P' = P \times (1.024 – 1)/(SG – 1)$, where $P$ is the specific-gravity–corrected phthalate concentration (micrograms per liter), $P'$ is the observed phthalate concentration (micrograms per liter), and SG is the specific gravity of the urine sample (Boeniger et al. 1993; Teass et al. 1998). Specific gravity was measured using a handheld refractometer (National Instrument Company, Inc., Baltimore, MD), which was calibrated with deionized water before each measurement.

Statistical analyses. We performed the statistical analyses using the Statistical Analysis Software (SAS), version 8.1 (SAS Institute, Cary, NC). Both unadjusted and specific-gravity–adjusted values were used. For values below the limit of detection (LOD), corresponding to 1.2 (MEP), 0.94 (MBP), 0.47 (MBzP), 0.86 (MEHP), 0.70 (MMP), 0.77 (MOP), 0.79 (MINP), and 0.93 µg/L (MCHP), we used an imputed value equal to one-half the LOD.

We constructed graphs to compare metabolite levels within and between subjects, and calculated Spearman correlation coefficients to investigate correlations between samples collected at different time points.

To assess between- and within-person variability of metabolite levels, we calculated ICCs for each metabolite based on output from a random effects model fit using PROC MIXED (Rosner 1999). ICC, defined as the ratio of between-person variance to total variance, is a measure of reliability of repeated measures over time. ICC ranges from 0 to 1, with values near 1 indicating high reliability and values near 0 indicating poor reliability. ICC can also be used in an internal validity study to account for measurement error in epidemiology effect estimates (Carroll et al. 1995; Rosner et al. 1992).

To apportion variances among nested components, we fit a hierarchical model (using PROC MIXED). For a more robust estimate of between-subject variability, we used the results of the single urine samples collected from all 369 men enrolled so far in the ongoing environmental agents and male reproductive health study in the variance apportionment analysis. Because the 11 men in this variability study were also enrolled in the male reproductive health study, their single urine sample collected for the reproductive study contributed additional information on variability. Within-subject variance was further apportioned into cycle-to-cycle variance and day-to-day variance (Box et al. 1978). Day-to-day variance was defined as the variance in phthalate metabolite levels between samples 1 or 2 days apart, regardless of whether they were collected in cycle 1, 2, or 3. Cycle-to-cycle variance was defined as the variance between the three cycles minus the day-to-day variances within the cycles. Because day is nested within cycle, the cycle-to-cycle variance uses information from the three nested daily samples in cycles 1, 2, and 3.

Although ICC is an indicator of reliability for continuous measures, it does not measure...
the extent of exposure misclassification that may occur if exposure is categorized into ter-
	
tiles of low, medium, and high exposure. To explore categorical exposure misclassification,
	
to perform sensitivity and specificity analy-
	
ses and surrogate category analyses. In both
	
analyses, tertiles were created using the mean of the nine repeat urine samples for each of
	
the 10 subjects in the variability study. The
	
subject with only six repeat urine samples was not included in these analyses because he did
	
not have complete data. Tertiles based on the
	
369 single urine samples from subjects in the
	
male reproductive health study produced an
	
unbalanced and unstable design because some
	
of these tertiles contained zero subjects from
	
the variability study. This led to nonidentifi-
	
able results for that tertile. Therefore, analyses
	
using tertiles based on the 369 single urine
	
samples are not presented.

In the surrogate category analysis, we cal-
	
culated actual values for surrogate categories
	
to show the quantitative differences in phtha-
	
late metabolite levels that correspond to the
	
relative categories defined by a single urine
	
sample from the 10 variability subjects
	
(Willett 1998). We grouped variability sub-
	
jects first into tertiles by treating each of
	
the nine repeat urine samples as a single spot
	
urine sample (i.e., the surrogate method). For
	
instance, for each of the nine repeat urine
	
samples, the 10 subjects were categorized into
	
high, medium, or low tertiles. The “true value”
	
for these same subjects based on their
	
3-month average phthalate metabolite levels
	
(using all the nine replicate samples) was then
	
assigned to the tertiles defined by the single
	
(surrogate) sample. Each of the nine samples
	
was used as the surrogate sample in separate
	
calculations to check for consistency. Each
	
subject’s 10th sample from the male repro-
	
ductive health study was not used in this
	
analysis because this sample could have been
	
collected up to 12 months earlier.

We also evaluated sensitivity and speci-
	
ficity of a single urine sample as a predictor of
	
high and low tertiles of 3-month average phthalate metabolite levels by comparing the
distribution of predicted and observed levels
for agreement. For observed or “true” exposure,
we calculated 3-month average metabolite levels (using all the nine replicate samples)
for each subject and divided the 10 subjects
into tertiles. The distribution of 96 individual
samples (10 subjects providing nine replicate samples, one subject providing six) was then
also divided into tertiles, with each sample
representing a predicted value based on a sin-
gle spot urine sample. For each sample time
days 0–92), agreement between predicted
and observed “true” tertile categorization was
scored across all subjects, resulting in nine
separate contingency tables. All nine tables
were then combined into a single table, where
overall sensitivity and specificity were calcu-

lated (Peck et al. 2003). The same method was
used to assess the sensitivity and specificity if
two samples, and then additionally if three
samples were taken for each subject at least one
cycle apart within a 92-day time period. When
evaluating the sensitivity of two and three sam-

dles, all possible combinations of sample pair-
ings from the nine repeated samples, excluding
samples from the same cycle, were used in the
analysis. The goal was to simulate and compare
the ability of exposure assessments that involve
one, two, or three urine samples to predict a
subject’s “true” 3-month average exposure ter-
tile classification.

Results
We measured eight phthalate metabolites in
urine. However, because > 75% of the sam-
ple had nondetectable levels of MCHP, MOP,
and MINP, the results for these three
metabolites were not informative and were

| Table 1. Distribution of phthalate metabolite levels (µg/L) measured in a single spot urine sample from 369 men. |

<table>
<thead>
<tr>
<th>Phthalate metabolite</th>
<th>Geometric mean</th>
<th>10th</th>
<th>25th</th>
<th>50th</th>
<th>75th</th>
<th>90th</th>
<th>95th</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted MEHP</td>
<td>5.7</td>
<td>0.5</td>
<td>1.9</td>
<td>5.2</td>
<td>17.2</td>
<td>63.6</td>
<td>110</td>
</tr>
<tr>
<td>MBzP</td>
<td>5.6</td>
<td>1.1</td>
<td>2.4</td>
<td>6.0</td>
<td>13.7</td>
<td>25.3</td>
<td>34.7</td>
</tr>
<tr>
<td>MEP</td>
<td>149</td>
<td>22.7</td>
<td>46.1</td>
<td>128</td>
<td>444</td>
<td>1,144</td>
<td>1,879</td>
</tr>
<tr>
<td>MBF</td>
<td>13.3</td>
<td>2.9</td>
<td>7.0</td>
<td>13.6</td>
<td>29.3</td>
<td>50.4</td>
<td>73.1</td>
</tr>
<tr>
<td>MMP</td>
<td>3.8</td>
<td>0.4</td>
<td>1.7</td>
<td>4.4</td>
<td>9.6</td>
<td>21.5</td>
<td>29.9</td>
</tr>
<tr>
<td>Specific-gravity adjusted MEHP</td>
<td>6.8</td>
<td>0.8</td>
<td>2.4</td>
<td>6.5</td>
<td>19.5</td>
<td>64.5</td>
<td>120</td>
</tr>
<tr>
<td>MBzP</td>
<td>6.6</td>
<td>1.8</td>
<td>3.8</td>
<td>7.2</td>
<td>14.0</td>
<td>22.8</td>
<td>36.2</td>
</tr>
<tr>
<td>MEP</td>
<td>175</td>
<td>30.7</td>
<td>58.7</td>
<td>153</td>
<td>495</td>
<td>1,145</td>
<td>1,897</td>
</tr>
<tr>
<td>MBF</td>
<td>15.8</td>
<td>4.8</td>
<td>9.8</td>
<td>16</td>
<td>29.2</td>
<td>45.9</td>
<td>66.7</td>
</tr>
<tr>
<td>MMP</td>
<td>4.5</td>
<td>0.6</td>
<td>2.2</td>
<td>4.9</td>
<td>11.7</td>
<td>22.4</td>
<td>30.4</td>
</tr>
</tbody>
</table>

Figure 1. Nine repeated urine samples collected from 10 men over a 3-month period: MEHP. (A) Unadjusted. (B) Specific-gravity adjusted.

Figure 2. Nine repeated urine samples collected from 10 men over a 3-month period: MBzP. (A) Unadjusted. (B) Specific-gravity adjusted.

Figure 3. Nine repeated urine samples collected from 10 men over a 3-month period: MEP. (A) Unadjusted. (B) Specific-gravity adjusted.
Variance apportionment for specific-gravity–adjusted phthalate levels in urine.

Table 2. Variance apportionment for specific-gravity–adjusted phthalate levels in urine.

<table>
<thead>
<tr>
<th>Variability subjects only (N = 11, n = 96)</th>
<th>All subjects (N = 369, n = 465)</th>
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<tbody>
<tr>
<td></td>
<td>Variance estimate ± SE</td>
</tr>
<tr>
<td>ln(MEHP) Subject^{a}</td>
<td>0.49 ± 0.32</td>
</tr>
<tr>
<td>ln(MBzP) Subject</td>
<td>0.47 ± 0.25</td>
</tr>
<tr>
<td>ln(MEP) Subject</td>
<td>1.08 ± 0.59</td>
</tr>
<tr>
<td>ln(MBP) Subject</td>
<td>0.30 ± 0.20</td>
</tr>
<tr>
<td>ln(MBP) Day</td>
<td>0.97 ± 0.17</td>
</tr>
<tr>
<td>ln(MBP) Cycle</td>
<td>0.075 ± 0.086</td>
</tr>
<tr>
<td>ln(MBP) Day</td>
<td>0.54 ± 0.096</td>
</tr>
<tr>
<td>ln(MEP) Subject</td>
<td>0.33 ± 0.20</td>
</tr>
<tr>
<td>ln(MEP) Day</td>
<td>0.89 ± 0.16</td>
</tr>
<tr>
<td>ln(MEP) Subject</td>
<td>0.14 ± 0.085</td>
</tr>
<tr>
<td>ln(MEP) Day</td>
<td>0.025 ± 0.046</td>
</tr>
<tr>
<td>ln(MEP) Day</td>
<td>0.33 ± 0.058</td>
</tr>
<tr>
<td>ln(MMP) Subject</td>
<td>1.11 ± 0.55</td>
</tr>
<tr>
<td>ln(MMP) Day</td>
<td>0.011 ± 0.012</td>
</tr>
<tr>
<td>ln(MMP) Day</td>
<td>1.09 ± 0.18</td>
</tr>
</tbody>
</table>

Abbreviations: N, number of subjects; n, number of samples.

\(^{a}\)Includes 10 variability subjects who provided 10 samples each, 1 subject who provided 7 samples, plus 358 subjects who provided a single sample. \(^{b}\)Between-subject variance. \(^{c}\)Variance between three cycles after accounting for nested day-to-day variance. \(^{d}\)Variance between 3 consecutive days within a cycle.
exposure, to 22.8 µg/L in the medium-exposure group, although single spot urine samples were generally predictive, there were differences in the predictive ability of a single urine sample for different phthalate monoesters. A single urine sample was least predictive for MEHP, where only five of the nine spot urine samples produced a monotonic increasing geometric mean. In contrast, eight of the nine spot urine samples produced monotonic increasing geometric means for MBzP, MBP, MEP, and MMP. As expected, MEP, with the widest range in exposure levels, showed the largest difference in geometric means between low-, medium-, and high-exposure categories.

For a more quantitative assessment of how well a single urine sample predicts a subject’s exposure category based on 3-month average metabolite levels, we conducted sensitivity and specificity analyses, using only the results from the 10 subjects who provided nine urine samples each (Table 4). The proportion of men who truly had the highest 3-month average exposure (top 33%) that would be identified as such using single urine samples anytime throughout that 3-month period (i.e., sensitivity) ranged from 0.56 for MEHP to 0.74 for MMP. The proportion of men with truly the lowest 3-month average exposure (bottom 33%) that would be identified as such using single urine samples anytime throughout that 3-month period (i.e., specificity) ranged from 0.67 for MBzP to 0.90 for MMP.

Table 4. Sensitivity and specificity for predicting men with the highest 3-month average phthalate metabolite levels (top 33%) with one, two, or three urine samples

<table>
<thead>
<tr>
<th>No. of samples</th>
<th>MEHP</th>
<th>MBzP</th>
<th>MEP</th>
<th>MBP</th>
<th>MMP</th>
</tr>
</thead>
<tbody>
<tr>
<td>One sample</td>
<td>0.56</td>
<td>0.63</td>
<td>0.83</td>
<td>0.63</td>
<td>0.84</td>
</tr>
<tr>
<td>Two samples</td>
<td>0.60 (0.67)</td>
<td>0.87 (0.98)</td>
<td>0.67 (0.90)</td>
<td>0.87 (0.90)</td>
<td>0.74 (0.90)</td>
</tr>
<tr>
<td>Three samples</td>
<td>0.70 (0.70)</td>
<td>0.88 (0.87)</td>
<td>0.88 (0.87)</td>
<td>0.88 (0.87)</td>
<td>0.88 (0.87)</td>
</tr>
</tbody>
</table>

Only values from the 10 subjects who provided nine urine samples each were used in this analysis.

*Values in parentheses are sensitivity and specificity using geometric mean ranks instead of arithmetic mean ranks for observed tertile classification; for the other four phthalates these values were identical.
spot urine sample to predict 3-month average phthalate exposure was moderate to high. As expected, because phthalates are rapidly metabolized and do not bioaccumulate, the collection of additional urine samples 1–3 months apart improves the prediction of a subject’s 3-month average exposure. The levels of urinary metabolite levels found in the present study were similar to reference ranges measured in U.S. males for NHANES 1999–2000 (CDC 2003; Silva et al. 2004).

The predictive ability of a single urine sample to determine a subject’s 3-month average exposure varied across phthalates. For MEHP, a single urine sample was least predictive of the tertile categorization and had the lowest sensitivity (Table 4). This implies that in statistical analyses in which only a single urine sample is available to categorize a subject’s 3-month exposure to MEHP, there is likely exposure measure misclassification resulting in bias toward the null hypothesis for exposure–response relationships. MEHP has been associated with developmental reproductive toxicity in laboratory studies (Oishi 1986; Park et al. 2002; Soborg et al. 1986). However, in our previously published study, we did not find an association between MEHP and semen parameters among adult men (Dury et al. 2003). In contrast, we did find associations of MBP and MBEP with semen parameters. Although our study differed from the animal studies because we measured adult and not gestational exposure, our findings suggesting that a single urine sample, used to categorize a subject’s exposure, did not adequately measure 3-month average exposure to MEHP. This may partially explain our inability to detect associations between semen parameters with MEHP. To improve upon our exposure classification of MEHP, we are currently collecting two urine samples 1 month apart from all subjects. This will allow us to use measurement error correction methods to adjust for exposure misclassification of phthalate exposure (Carroll et al. 1995).

It is possible the calculated sensitivities and specificities may be slightly overestimated to a small degree because we included predicted values in the calculation of the observed values. Therefore, the errors of predicted and observed values are not totally independent, which can lead to an overestimation of sensitivity and specificity (Willett 1998). Similarly, a portion of the increased sensitivity and specificity observed when taking two or three samples per subject instead of a single sample may be caused partly by the increased dependence between the errors of the predicted and observed values.

Apportioning the sources of variability in urinary phthalate metabolite levels can be used to design more valid and efficient exposure assessments. As expected, the urinary phthalate metabolite concentrations in samples collected close together in time, separated by 1–2 days, were more correlated than those in samples collected farther apart in time, separated by 1–3 months. Two samples collected a month or more apart include variability in urinary phthalate metabolite levels contributed to both by day-to-day changes in exposure and by monthly trends in phthalate exposure, such as seasonal changes in diet, personal product use, or activity patterns, as well as other environmental or biologic factors.

For each health end point of interest in an epidemiologic study, the relevant time window over which exposure is measured needs to be defined. For acute responses after acute exposures, a single urine sample may be adequate to define phthalate exposure. However, we are generally interested in health end points that have exposure windows of months, if not years. To this end, accurate exposure assessment depends on a strategy whereby we accurately measure exposure over these time windows. The simplest approach is to collect multiple urine samples from all subjects over the time interval of interest. However, it is not always feasible to collect multiple urine samples because of both cost constraints and limitations imposed by the subject’s commitments to multiple collections. Based on the results of this phthalate variability study, for male reproductive health end points, we recommend collecting at least two urine samples 1–3 months apart. This will provide an estimate of the within-person variability taking into account both month-to-month and day-to-day variance. Nevertheless, if the study design only permitted collecting two samples 1–2 days apart, this, too, would provide a reasonable estimate of within-subject variance contributed to by day-to-day variance. After collection of the replicate urine samples in either sampling scheme, measurement error models could then be used to adjust for measurement error in exposure (Carroll et al. 1995). A discussion of this is beyond the scope of this report.

In conclusion, although a single urine sample was moderately predictive of 3-month exposure to phthalates, the predictive ability varied across phthalate monooesters. A single urine sample was more predictive for MEP and less predictive for MEHP. The single sample performed well in classifying a subject’s exposure into tertiles, and the amount of non-differential random exposure misclassification is likely to be moderate or small for most phthalate metabolites of interest. The variance apportionment analysis suggests that two urine samples, the second collected 1–3 months after the first sample, is the minimum number of samples necessary to account for the within subject day-to-day and cycle-to-cycle variability in urinary phthalate metabolite levels. Because the degree of between- and within-subject variance and thus the predictive ability of a single urine sample differ among phthalate metabolites, the most efficient exposure assessment strategy for a particular study depends on the phthalates of interest. The results from the present study will be used in our ongoing environmental agents and male reproductive health study to correct for measurement error in the effect estimates of exposure–response relationships between phthalates and sperm function. The findings from this variability study may also be pertinent to other end points with relevant exposure periods of several months. However, if the study population is not adult men of reproductive age, such as studies involving children or pregnant women, we recommend that a variability study be conducted to determine population-specific exposure assessment strategies.

References


Correction

The values in Tables 1 and 3 have been rounded from those in the manuscript published online to reflect laboratory sensitivities. In Table 2, for all subjects the SE for ln(MBzP) day is 0.10, and that for percent of total variance ln(MEP) day is 40.9. The errors have been corrected here.