The Association between Biomarker-Based Exposure Estimates for Phthalates and Demographic Factors in a Human Reference Population

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Population-based estimates of environmental exposures using biomarkers can be difficult to obtain for a variety of reasons, including problems with limits of detection, undersampling of key strata, time between exposure and sampling, variation across individuals, variation within individuals, and the ability to find and interpret a given biomarker. In this article, we apply statistical likelihoods, weighted sampling, and regression methods for censored data to the analysis of biomarker data. Urinary metabolites for seven phthalates, reported by Blount et al., are analyzed using these methods. In the case of the phthalates data, we assumed the underlying model to be a log-normal distribution with the mean of the distribution defined as a function of a number of demographic variables that might affect phthalate levels in individuals. Included as demographic variables were age, sex, ethnicity, residency, family income, and education level. We conducted two analyses: an unweighted analysis where phthalate distributions were estimated with changes in the means of these distributions as a function of demographic variables, and a weighted prediction for the general population in which weights were assigned for a subset of the population depending on the frequency of their demographic variables in the general U.S. population. We used statistical tests to determine whether any of the demographic variables affected mean phthalate levels. Individuals with only a high school education had higher levels of di-*n*-butyl phthalate than individuals with education beyond high school. Subjects who had family income less than $1,500 in the month before sampling and/or only high school education had higher levels of *n*-butyl benzyl phthalate levels than other groupings. Di(2-ethylhexyl) phthalate was higher in males and/or in urban populations and/or in people who had family income less than $1,500 per month. Our findings suggest that there may be significant demographic variations in exposure and/or metabolism of phthalates and that health-risk assessments for phthalate exposure in humans should consider different potential risk groups. *Key words:* **demographic factors, phthalates, risk assessment.** *Environ Health Perspect* **110:405–410 (2002). [Online 11 March 2002]**
http://ehpnet1.niehs.nih.gov/docs/2002/110p405-410koo/abstract.html

Phthalates are important industrial chemicals used in the manufacture of a wide range of plastic and nonplastic products and can be divided into two basic groups: those used as plasticizers for synthetic polymers that are incorporated into food wrap, medical tubing, and molded toys, and those used primarily in consumers products such as varnishes, perfumes, nail polishes, and insect repellents. It is conceivable that the route of exposure of an organism to phthalates is an important parameter when considering metabolism of these chemicals *in vivo*. Phthalates are readily metabolized in the gut, such that oral exposure would not lead to accumulation of high concentrations of these chemicals (*1*). However, few data are available on the metabolism of this group of chemicals after inhalation or dermal exposure. The primary route of phthalate exposure to the general human population has been presumed to be ingestion. Lower molecular-weight phthalates such as diethyl phthalate (DEP) and di-*n*-butyl phthalate (DBP) can be absorbed percutaneously, and the more volatile congeners can be inhaled. Dermal absorption is important for products applied to skin.

Blount et al. (*2*) reported the concentrations of seven phthalate monoesters [monoethyl phthalate (MEP), monobutyl phthalate (MBP), monobenzyl phthalate (MBzP), monocyclohexyl phthalate (MCHP), mono-2-ethylhexyl phthalate (MEHP), monooctyl phthalate (MOP), monoisononyl phthalate (MINP)] in the urine of 289 people, providing the first systematic compilation of data that address phthalate exposures to the general population from commercially important phthalate diesters. Kohn et al. (*3*) applied a simple pharmacokinetic model to estimate the total daily intake of phthalates that would result in the reported urinary concentrations of monoester metabolites. These intake estimates were used as a measure of total exposure to diethyl phthalate (DEP), di-*n*-butyl phthalate (DBP), *n*-butyl benzyl phthalate (BBP), dicyclohexyl phthalate (DCHP), di-(2-ethylhexyl) phthalate (DEHP), di-*n*-octyl phthalate (DOP), di-*i*-nonyl phthalate (DINP).

Blount et al. (*2*) reported a considerable number of observations in which the analyte levels in urine were below the limit of detection (LOD) for the procedure being used. This analysis excluded analytes for which more than 25% of the studied individuals were below the LOD and discarded individuals below the LOD for analytes they did analyze. This represents a substantial loss of information. Maximum likelihood methods for censored observations (*4*–*7*) have been used for many years to analyze survival data and data for which some observations cannot be seen, but it is known that the observation is beyond some critical point. For urinary metabolite data, an observation below the LOD can be assumed to have a metabolite concentration less than the LOD. Methods have been developed for analyzing biomarkers of exposure—including observations below the LOD—by using statistical likelihoods and regression methods for censored data (*8*). Using a likelihood for censored data, these fractional pieces of information contribute to the overall interpretation of the data and can be used in a natural framework to estimate parameters and test for population differences. To account for strata differences of demographic factors, we estimated population-based exposures to phthalates using a weighted analysis in which weights were assigned for each individual group depending on the frequency of their demographic variables in the general U.S. population.

The aim of this study was to present methods for the analysis of exposure estimates based on urinary biomarker data accounting for strata differences and problems with LOD and to investigate the association between biomarker-based exposure estimates for phthalates and demographic factors in a human reference population.

Materials and Methods

Phthalates data. The data for this study were collected from adults during 1988–1994 as part of the Third National Health and Nutritional Examination Survey (NHANES III) (*9*). NHANES III analyzed urine

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Received 24 August 2001; accepted 7 November 2001.

samples from 289 subjects for 7 phthalate monoesters (MEP, MBP, MBzP, MCHP, MEHP, MOP, MINP). Urine samples were collected at different times throughout the day and were not first-morning voids. This sampling of the NHANES III population was not designed to be representative of the U.S. population but rather to serve as a reference range for a demographically described group. The population studied comprised noninstitutionalized adults ages 20–60 years (mean ± SD, 37.4 ± 10.6 years). The sex distribution (56% female) was similar across age groups. Racial distribution was weighted toward minority groups (Caucasian, 39%; African American, 30%; Mexican American, 23%; and other, 8%). The residency distribution was urban 57%, rural 43%. The family income was categorized by two groups (≥ $1,500 in the month before sampling, 56%; < $1,500 in the month before sampling, 44%), and the education level was categorized by two groups (high school diploma or less, 69%; education beyond high school, 31%).

Estimating intake levels from urinary metabolites. Kohn et al. (*3*) calculated the intake for each individual in the reference population as follows: The daily exposure can be estimated by using a linear two-compartment model. The normalized integrated rate equations are

$$FE = 1 - \exp(-k_{total}\, t) \quad [1]$$

$$FU = \frac{k_u}{k_{total}}\left[1 - \exp\left(-k_{total} t\right)\right], \quad [2]$$

where FE and FU are the total and urinary fractions of the dose eliminated in time t, and k_{total} and k_u are the apparent first-order rate constants for total elimination and elimination of urinary monoester, respectively. We calculated the two rate constants from the excreted fractions observed during the 24 hr after a single oral dose of diester, using Equations 1 and 2.

Assuming steady-state intake and metabolic clearance of the diester, the internal exposure rate for an individual was approximated by Equation 3 to be:

$$\text{intake}\left(\mu g/kg/day\right) = \frac{ME\left(\mu g/g\right) \times CE\left(mg/kg/day\right)}{f \times 1{,}000\left(mg/g\right)} \times \frac{MW_d}{MW_m}, \quad [3]$$

where ME is the urinary concentration of monoester per g creatinine, CE is the creatinine excretion rate normalized by body weight, f is the ratio of urinary excretion to total elimination (k_u/k_{total}), and MW_d and MW_m are the molecular weights of the di- and monoesters, respectively.

Table 1 shows total fractional excretion (FE) and fractional urinary excretion of monoester (FU) during 24 hr after a single oral dose of diester.

Statistical methods. Linear models are a common means of analyzing data to detect statistically significant differences between groups or for significant trends in the data as a function of some continuous variable. Let X denote the random variable associated with the daily intake level calculated using Equation 3 in a given individuals. For the analysis presented here, we assume that

$$Y = ln\,(X) = f_\mu(\theta) + \varepsilon, \quad [4]$$

where ln denotes the natural log of X, $f_\mu(\theta)$ is a function of a set of covariates denoted θ, and, depending on a set of parameters, μ, and ε is a random variable for which

$$\varepsilon \sim N(0, \sigma^2) \quad [5]$$

—that is, ε is normally distributed with mean 0 and variance σ^2. From Equation 4, it follows that

$$E[Y] = f_\mu(\theta). \quad [6]$$

In the analysis that follows, we use a linear model to analyze the impact of age, sex, ethnicity, residence, family income, and education on the daily intake of phthalates in the sampled population. The largest model used was of the form

$$f_\mu(\theta) = \mu_0 + \sum_{i=1}^{6} \mu_i \theta_i, \quad [7]$$

where μ_0 is the overall mean of the entire sample, μ_i is an adjustment to this mean for the ith demographic indicator θ_i. Six demographic indicators were included: $\mu_1\theta_1$ for age, $\mu_2\theta_2$ for sex, $\mu_3\theta_3$ for ethnicity, $\mu_4\theta_4$ for residence, $\mu_5\theta_5$ for family income, and $\mu_6\theta_6$ for education.

The parameters μ_0, μ_1, … μ_6, and σ were estimated via maximum likelihood estimation using the log-likelihood

$$L_\mu(Y) = \sum_{i=1}^{N} \left\{ ln\, \phi\left(y_i; f_\mu(\theta_i), \sigma^2\right) I_{>LOD} + \left(1 - I_{>LOD}\right) ln\, \Phi\left(LOD; f_\mu(\theta_i), \sigma^2\right) \right\}, \quad [8]$$

where n is the sample size (n = 289 for the phthalates example), $\phi(z; \mu, \sigma_2)$ is the density function for the normal distribution with mean μ and variance σ^2 evaluated at z, $\Phi(z; \mu, \sigma_2)$ is the cumulative density function for the normal distribution with mean μ and variance σ^2 evaluated at z—i.e., $\phi(z; \mu, \sigma^2)$ is $\Pr[Z < z]$ where Z is a normal random variable with mean μ and variance σ^2, $I_{>\mathrm{LOD}}$ is an indicator function such that $I_{>\mathrm{LOD}} = 1$ if the observed urinary metabolite can be quantified, and $I_{>\mathrm{LOD}} = 0$ if it is below the limit of detection, y_i is the log of the daily intake level for the ith individual and LOD_i is the log of the limit of detection for the ith individual calculated as daily intake level.

We performed the regression analysis using the LIFEREG procedure in SAS 8.0 for Windows (SAS Institute, Cary, NC) to test for significant differences in mean phthalate levels as a function of age, sex, ethnicity, residency, family income, and education level to phthalate exposure data. The parameters are estimated by maximum likelihood in LIFEREG procedure, and probability density function is used if the observed urinary metabolite can be quantified, or cumulative density function is used if it is below the limit of detection (*8*). We conducted this analysis using an unweighted analysis where phthalate distributions were estimated with changes in the means of these distribution as a function of demographic variables. We estimate phthalates exposures using a weighted prediction for the general population in which weights were assigned for subset of the population depending on the frequency of their demographic variables in the general U.S. population. In this analysis, a composite distribution is formed by resampling from individual distributions for each significant demographic variable.

Results

As an initial step, we calculated correlations across phthalates and demographic factors. Within exposure estimates for phthalates,

Table 1. Total fractional excretion (FE) and fractional urinary excretion of monoester (FU) during 24 hr after a single oral dose of diester.

Monoester	Diester	FE	FU
Ethyl (MEP)	Diethyl (DEP)	0.94[a]	0.52[a]
n-Butyl (MBP)	Di-*n*-butyl (DBP)	0.94	0.52 (*10,11*)
Benzyl (MBzP)	*n*-Butyl benzyl (BBP)	0.70	0.36 (*12–14*)
Cyclohexyl (MCHP)	Dicyclohexyl (DCHP)	0.65[b]	0.069[b]
2-Ethylhexyl (MEHP)	Di(2-ethylhexyl) (DEHP)	0.65	0.069 (*15,16*)
n-Octyl (MOP)	Di-*n*-octyl (DOP)	0.65[b]	0.043 (*17*)
i-Nonyl (MINP)	Di-*i*-nonyl (DINP)	0.65[b]	0.069[b]

[a]Assumed to be the same as di-*n*-butyl phthalate. [b]Assumed to be the same as di(2-ethylhexyl) phthalate.

DBP was highly correlated with BBP (r = 0.52, p < 0.01). We noticed relatively low correlation between BBP and DEHP (r = 0.28, p < 0.01). DBP showed a slight correlation with DCHP (r = 0.13, p = 0.02), DEHP (r = 0.19, p < 0.01), and DOP (r = 0.13, p = 0.02); BBP with DCHP (r = 0.12, p = 0.02) and DOP (r = 0.13, p = 0.01); and DCHP with DEHP (r = 0.11, p = 0.04), DOP (r = –0.14, p = 0.01), and DINP (r = 0.19, p < 0.01). Also, we noticed a slight correlation between DEP and DBP (r = 0.18) and between DOP and DINP (r = 0.15). BBP showed slightly significant correlation coefficients with age (r = –0.11, p = 0.04), family income (r = 0.17, p < 0.01), and education level (r = –0.16, p < 0.01); DCHP with education level (r = 0.12, p = 0.03); DEHP with sex (r = –0.13, p = 0.02), Mexican ethnicity (r = 0.11, p = 0.04), residency (r = –0.13, p = 0.01), and family income (r = 0.14, p = 0.01). There was a similar magnitude of correlation between DINP and education level (r = –0.12, p = 0.04), and DBP and education level (r = –0.13, p = 0.02). The reference values are male in sex, non-black in black ethnicity, non-Mexican in Mexican ethnicity, urban in residency, more than $1,500 in the month before sampling in family income, and high school diploma or less in education level.

Table 2 shows the results of the regression analysis using maximum likelihood methods as described in "Materials and Methods." Individuals with only a high school education had higher levels of DBP than individuals with education beyond high school (p < 0.05). Subjects who had family income less than $1,500 in the month before sampling and/or only high school education had higher levels of BBP than other groupings (p < 0.05). DEHP was higher in males and/or in urban populations and/or in people who had family income less than $1,500 per month ($p$ < 0.05).

Figure 1 demonstrates the differences between estimates of DBP in subjects who had only a high school education or less versus subjects with education beyond high school. The fitted normal curve of log DBP in subjects who had a high school education or less was significantly shifted to right (p = 0.02). There were no censored observations in these samples, and the results indicate fairly close agreement between the observed data and the fitted normal distribution. Figure 2 illustrates the fit of the normal curve of log DEHP by residency; here the distribution was significantly shifted to the right in subjects who lived in the urban areas (p = 0.01). The proportion below the LOD is less in urban (17.7%) than in rural (27.2%), and both graphs show a considerable difference between the observed histogram and the plotted density due to the data points below the LOD.

Table 3 shows estimated phthalates exposure weighted using demographic characteristics in the general U.S. population. The mean of estimated exposure is 10.1 µg/kg/day for DEP, 1.66 µg/kg/day for DBP, 0.84 µg/kg/day for BBP, 1.26×10^{-5} µg/kg/day for DCHP, 0.41 µg/kg/day for DEHP, 6.16×10^{-5} µg/kg/day for DOP, and 8.99×10^{-7} µg/kg/day for DINP.

Discussion

Population-based estimates of environmental exposures using biomarkers can be difficult to obtain for a variety of reasons, including problems with limit of detection, under-sampling of key strata, time between exposure and sampling, variation across individuals, variation within individuals, and the ability to find and interpret a given biomarker. In this article, we present methods for analyzing biomarkers of exposure using statistical likelihoods, weighted sampling, and regression methods for censored data. Determination of normal ranges using biomonitoring data where measurements are below the LOD is a frequently encountered problem. Data sets in which concentrations below a fixed value are undetectable usually fit a normal or log normal distribution, and more adequate statistical methods can be used to determine their normal range. Maximum-likelihood estimation is a more appropriate statistical

Table 2. Results of the regression analysis using maximum likelihood methods of the relation between the log of exposure estimates for phthalates and demographic factors.[a]

Phthalate, covariate	Estimate	SE	χ^2	p-Value
DBP				
Intercept	7.51	0.07	10555.43	< 0.001
Education[b]	–0.29	0.13	4.99	0.02
BBP				
Intercept	6.81	0.09	5281.21	< 0.001
Family income[c]	0.23	0.11	4.07	0.04
Education	–0.25	0.12	4.21	0.04
DEHP				
Intercept	6.32	0.24	691.17	< 0.001
Sex[d]	–0.61	0.25	5.91	0.01
Residency[e]	–0.65	0.25	6.54	0.01
Family income	0.68	0.25	7.26	0.007

[a]These models include demographic factors such as age (continuous), sex (male, female), ethnicity: black (no, yes), ethnicity: Mexican (no, yes), residency (urban, rural), family income (≥ $1,500 in the month before sampling, < $1,500 in the month before sampling), and education level (high school diploma or less, beyond high school). [b]Reference is high school diploma or less. [c]Reference is ≥ $1,500 in the month. [d]Reference is male. [e]Reference is urban.

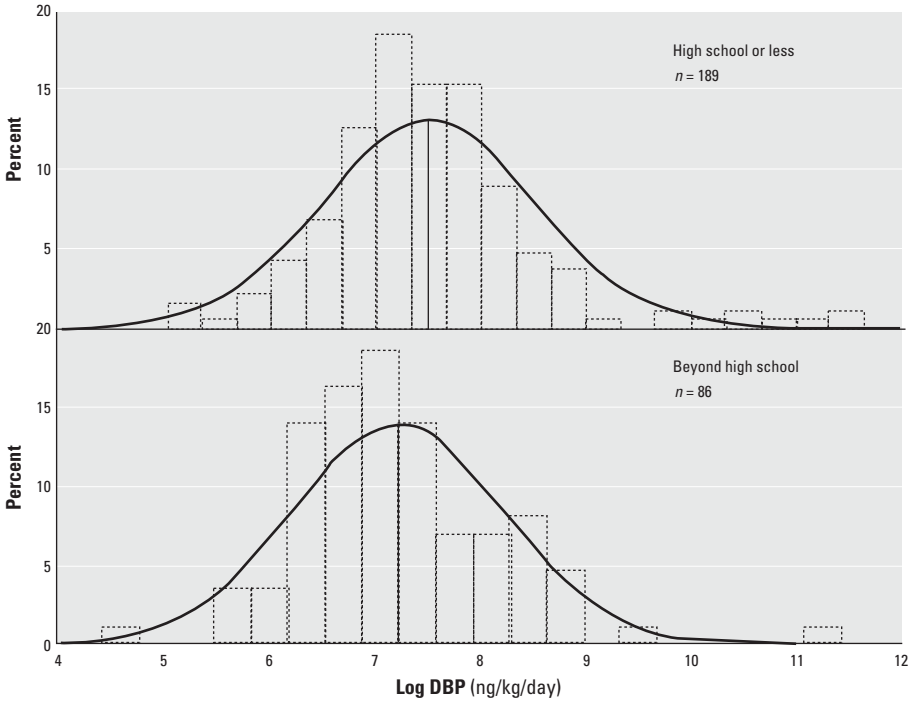

Figure 1. The fit of the normal curve to log DBP data by education; the means of these two distributions are significantly different (p = 0.02). Data were analyzed using a linear regression model with maximum likelihood methods that account for censoring; see equations in text.

method for the determination of normal range from left-censored data (*4–7*). Any statistical analysis depends on the assumption that the data can reasonably be regarded as a random sample from some underlying distribution. For the present case, data sets are available that are not left-censored. These data sets can be used to suggest suitable distributions for the censored samples, and techniques for estimation of parameters from such samples are straightforward. The log-normal distribution adequately fit these data (Figure 1) and were used for all of the biomarkers. In the case of our left-censored data, we used the corresponding cumulative probability distributions so that the likelihood functions for models involving censored data can easily be constructed and maximized.

Phthalates are used in the manufacture of a wide range of plastic and nonplastic products. Most of a phthalate dose is cleared in 24 hr and completely eliminated in 3–5 days (*13,19–22*). Because phthalates are lipophilic (*23*), it might be predicted that these compounds would accumulate in fat. However, with other lipophilic compounds, such as polychlorinated biphenyls, deposition of the compound into fat may not occur until several hours or several months after dosing (*24–26*). Because of the rapid metabolism of phthalates to more polar metabolites, these compounds are not sequestered in fat. Phthalates are widely distributed in the body, with the liver being the major, initial repository organ. Clearance from the body is rapid, and there is only a slight cumulative potential (*16*). Even though there is only a slight cumulative potential, phthalates are found in a wide variety of extensively used products, have been identified in all environmental compartments, and are a serious concern for the possibility of adverse effects. The acute toxicity of phthalates is low, with LD_{50} values ranging from 0.7 to > 20 g/kg (*27*); however, changes in lipid metabolism (*28–30*), testicular atrophy (*31,32*), alterations in xenobiotic metabolism (*33,34*), liver peroxisome proliferation (*35*), and carcinogenicity (*36,37*) have been observed. Regarding reproductive and developmental effects, phthalates vary in potency, with DEHP being the most potent and DBP and BBP roughly an order of magnitude less potent (*38–45*).

Another difficulty in estimating the environmental hazard posed by phthalates is the lack of sufficient data documenting the human and wildlife exposure. Furtmann (*46*) has suggested that the main source of phthalates is consumer products, and that as a result of disposal of these products, there are considerable phthalate emissions into the environment. The estimated total loss to the environment of phthalates in Western Europe has been estimated as 7,740 tons/annum, or approximately 1% of total consumption (*47*). However, the use of such data in the assessment of environmental hazards for individual chemicals is problematic because the data are generalized, and estimates refer to total phthalates. Other more rigorous deterministic approaches based on measured or estimated levels in environmental media (food, soil, water, air) and human activity/consumption patterns have been used for estimating individual phthalate exposure (*48*). Recently, the intake of several phthalates was estimated from measured individual urinary phthalate by Kohn et al. (*3*) and were found to agree quite well with previous deterministic exposure estimates (*3*). Kohn et al. described in detail how the different metabolites can be derived from common precursor compounds or can arise from different parent compounds. For MBzP, the presumed parent compound is BBP; however, MBP has two parent compounds, BBP and DBP. For the other monoesters, the presumed parent compound is the diester with two of the same substituents as in the monoester. Estimates of exposure from biomarker data are based on real, not potential, dose, provide information on individual variation in exposure, and allow for a more rigorous evaluation of factors contributing to exposure. In this study, we investigated the association between biomarker-based exposure estimates for phthalates and demographic factors in a human reference population.

Exposure data for phthalates are critical for scientifically sound human risk assessments,

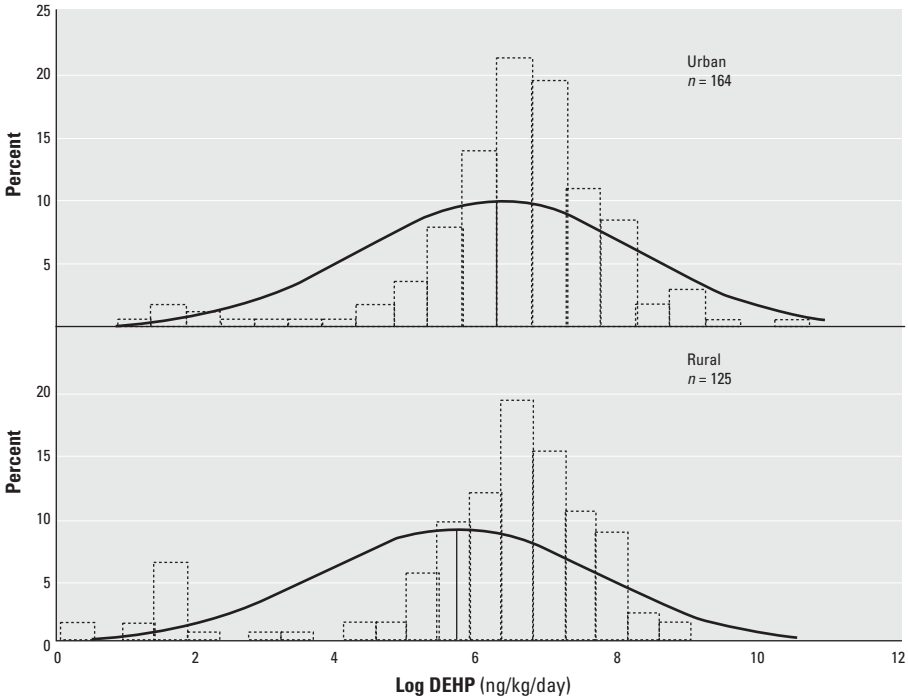

Figure 2. The fit of the normal curve to log DEHP data by residency; the means of these two distributions are significantly different ($p = 0.01$). Data were analyzed using a linear regression model with maximum likelihood methods that account for censoring; see equations in text.

Table 3. Estimated phthalates exposure (μg/kg/day) weighted using demographic characteristics in the general US population and using regression parameters which are significant ($p < 0.15$) from the LIFEREG procedure.[a]

Phthalates	Variable[b]	Mean	Median	5th percentile	95th percentile
DEP	Ethnicity (black)	10.1	10.2	0.43	229
DBP	Education, ethnicity (Mexican)	1.66	1.66	0.31	8.78
BBP	Family income, education	0.84	0.85	0.19	3.65
DCHP	Family income	1.26×10^{-5}	1.30×10^{-5}	1.18×10^{-9}	0.14
DEHP	Sex, residence, family income	0.41	0.41	0.015	11.3
DOP	Residence, education	6.16×10^{-5}	6.26×10^{-5}	2.19×10^{-9}	1.56
DINP	None	8.99×10^{-7}	9.28×10^{-7}	4.25×10^{-13}	1.67

[a]Data from U.S. Census Bureau (*18*). [b]Below 0.15 significant level.

especially with respect to potentially susceptible populations. Our analysis suggests that people with a high school education or less have higher urinary output of DBP and BBP metabolites; individuals with a family income less than $1,500 in the month before sampling have higher urinary output of BBP and DEHP metabolites; and males and urban populations have higher urinary output of DEHP metabolites. The analysis used assumed that the pharmacokinetics of these compounds is the same in all individuals; this may not be true because genetic polymorphisms in the genes controlling the metabolism and elimination of phthalates may exist and could have an impact on levels of these metabolites in the urine. Hence, our findings may derive from differences in actual exposures, differences in metabolism, or a combination of these. Further study is needed to determine which of these may drive the observed differences.

Our sampled data have strata differences in demographic factors compared with the general U.S. population. We found significant variables in the regression model using the LIFEREG procedure weighted toward minority ethnicity, rural residency, low family income, and low education level. We estimated distributions with changes in the means of these distributions as a function of the demographic variables. We estimated phthalate exposures using a weighted prediction for the general population in which weights were assigned for each subset of the population depending on the frequency of their demographic variables in the general U.S. population. This approach yielded phthalate exposure estimates for the general U.S. population, but because the study sample consisted of 289 noninstitutionalized adults and was not designed to be representative of the U.S. population, some bias might be present in our study. Our calculated human daily intake estimates are in good agreement with estimates of Kohn et al. (*3*) and exposures for the general population estimated by the National Toxicology Program Center for the Evaluation of Risks to Human Reproduction (*48*). Therefore, we suggest that estimating phthalates exposure for the general U.S. population using weights of demographic characteristics from a small, nonrepresentative sample as demonstrated here can be a useful approach for evaluating human exposures, but should be interpreted with caution. We can calculate the mean and fifth percentile of phthalate intake estimates using this approach, even though in some cases 75% of the data is below the LOD.

The correlation matrix of the log of exposure estimates for phthalates showed a high correlation between DBP and BBP (r = 0.52), indicating potential common sources of exposure or interacting metabolic pathways. Blount et al. (*2*) reported that MBP and MBzP were present predominantly as the glucuronide form in urine, so individual differences in glucuronidation capacity might affect elimination of these compounds. This example illustrates one limitation of biomarkers: It is not possible to attribute differences in individual biomarker levels to differences in actual exposure or to metabolic differences. Also, BBP was moderately correlated with DEHP (r = 0.28). DEHP, DBP, and BBP are of particular concern because of their developmental and reproductive toxicity in animals (*38–45*). Therefore, assessments of phthalate health risks should consider cumulative adverse effects of DEHP, DBP, and BBP.

Recently, the urinary concentration of the same seven phthalate monoesters in the urine analyzed here was reported from 1,029 people as part of the National Health and Nutritional Examination Survey (NHANES) (*49*). Measurement of these metabolites will be repeated in future NHANES, leading to larger cumulative sample sizes to be used for deriving national estimates of both current exposure levels and exposure trends. The data available to date show that urinary levels of MEP, MBzP, MBP from NHANES 1999 are lower than those from NHANES III. Further efforts will focus on evaluating the association between biomarker-based exposure estimates for phthalates and demographic factors in this larger human reference population.

In summary, we developed methods for analyzing biomarkers of exposure using statistical likelihoods, weighted sampling, and regression methods for censored data and analyzed the association between biomarker-based exposure estimates for phthalates and demographic factors in a human reference population. Our findings suggest that there may be significant demographic variations in exposure and/or metabolism of phthalates, and that health-risk assessments for phthalate exposure in humans should consider different potential risk groups. These findings support and extend previous information on human phthalate exposure and should prove useful in accurately quantifying human risk of exposure to these compounds, identifying factors contributing to higher exposures and opportunities for reducing those exposures, and stimulating additional research on sources of exposure to phthalates.

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