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# Urinary excretion and daily intake rates of diethyl phthalate in the general Canadian population

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## HIGHLIGHTS

- Estimated DEP daily intake (DI) in Canadians using CHMS human biomonitoring data
- DI estimates using creatinine correction and urine volume approaches were similar.
- Urinary MEP concentrations correlate well with DI estimates in the overall population.
- Recommend caution when directly using urinary concentrations to compare DI trends.
- DEP DI in Canadians are significantly lower than the US EPA's reference dose.

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## ABSTRACT

We have analyzed the trends in the body-weight-adjusted urinary monoethyl phthalate (MEP) concentrations and the diethyl ethyl phthalate (DEP) daily intake estimates in the general Canadian population (aged 6-49 years) using the Canadian Health Measures Survey 2007–2009 dataset. The creatinine correction approach, as well as the urine volume approach in a simple one compartment model were used to calculate the daily urinary MEP excretion rates and DEP intake rates in individual survey participants. Using multiple regression models, we have estimated least square geometric means (LSGMs) of body-weight-adjusted MEP concentration, daily excretion and intake rates among different age groups and sex. We observed that body weight affects the trends in the MEP concentrations significantly among children (aged 6–11 years), adolescents (aged 12–19 years) and adults (aged 20–49 years). The body-weight-adjusted MEP concentrations in children were significantly higher than those in adults. On the other hand the DEP daily intakes in children were significantly lower than those in adults. We did not observe any differences in the DEP daily intake rates between males and females. Although the urinary MEP concentrations are correlated well with DEP daily intake estimates in the overall population, one should be cautious when directly using the urinary concentrations to compare the intake trends in the sub-populations (e.g. children vs. adults) as these trends are governed by additional physiological factors. The DEP daily intake calculated using the creatinine approach and that using the urine volume approach were similar to each other. The estimated geometric mean and 95th percentile of DEP daily intake in the general Canadian population are 2 and 20 μg/kg-bw/day, respectively. These daily intake estimates are significantly lower than the US Environmental Protection Agency's oral reference dose of 800 μg/kg-bw/day.



## 1. Introduction

Diethyl phthalate (DEP) belongs to the class of synthetic chemicals called “phthalates”. DEP has been widely used as a solvent and fixative in a variety of consumer products such as fragrances, cosmetics, and personal care products (PCPs) such as deodorants, lotions, creams, soaps, and hair care preparations (Houlihan et al., 2000; Hubinger and Havery, 2006; Koniecki et al., 2011; Romero-Franco et al., 2011). For example, Koniecki et al. analyzed 252 cosmetics and PCPs for phthalate diesters and found that DEP is not only present in 103 out of 252 products analyzed, but also at concentrations much higher than other phthalate esters such as dibutyl-, di(2-ethylhexyl)- and dimethyl phthalates (DBP, DEHP and DMP) (Koniecki et al., 2011). In addition to cosmetics, DEP is also used as a plasticizer in cellulose-based plastic films and sheets, consumer articles such as toothbrushes, and automotive parts (WHO, 2003). Moreover, DEP and other phthalate diesters have been identified and quantified in indoor air, and dust samples

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suggesting that the exposure to phthalate in the general population could occur from multiple sources and pathways (Fromme et al., 2004).

Like other phthalates, DEP undergoes rapid metabolism in humans. DEP is hydrolyzed to form the major metabolite monoethyl phthalate (MEP) which further hydrolyzes to phthalic acid or is conjugated to glucoronic acid and excreted (Silva et al., 2004). Pharmacokinetic studies in animals indicate that urinary MEP has been identified as the major metabolite after oral or intravenous administration of DEP (Albro and Moore, 1974; Kao et al., 2012). The MEP could undergo further transformations to form metabolites with aldehyde-, keto-, and carboxylic acid-functional groups (ATSDR, 1995). These oxidative metabolites constitute minor metabolites of DEP which have not been identified/detected in human biomonitoring studies regularly. Consistent with animal studies, MEP has been detected widely in human urine samples in several general population surveys (Becker et al., 2009; Blount et al., 2000; CDC, 2012; Saravanabhavan et al., 2013; Silva et al., 2004). Such biomonitoring data can be used to characterize the body burden (i.e. internal exposure) of synthetic chemicals in the general population (Koch and Calafat, 2009; Thornton et al., 2002). Results from the Canadian Health Measures Survey (CHMS) show that urinary MEP concentration is the highest among the phthalate metabolites measured (Health Canada, 2010) suggesting DEP body burden would be higher compared to that of other phthalates in the general population. Moreover, the urinary MEP concentration in the general population is observed to increase with age (Saravanabhavan et al., 2013). However, as children have relatively lower body weights than adolescents and adults, the urinary excretion expressed per kg body weight basis in children may be higher despite lower urinary MEP concentration. On the other hand, children have lower total daily urine output compared to adults. This fact suggests that for a given exposure dose of DEP, the urinary concentration of MEP in children would be relatively higher than that of adults. Thus, the body weight and the total urine output exert opposing effects in determining the daily intake (μg/kg-bw/day) of DEP using urinary MEP concentrations.

In this paper, we first illustrate the effect of body weight on the urinary MEP concentration by analyzing the MEP data from the CHMS 2007–2009. We have used the creatinine correction approach as well as urine volume approach in a simple one compartment model to calculate the daily urinary MEP excretion rates and DEP intake rates in individual survey participants. Using multiple regression models, we have estimated least square geometric means (LSGMs) of body-weight-adjusted MEP concentration, daily excretion and intake rates among different age groups and sex.

## 2. Materials and methods

### 2.1. Data source

The CHMS 2007–2009 collected biological specimens from 5604 Canadians representing 96.1% of overall Canadian population aged 6 to 79 years. MEP and other urinary phthalate metabolites were measured in a subsample of 3237 participants between 6 and 49 years of age. All children and youths aged 6 to 19 years at the time of the household interview were selected for this measure. Adults aged 20 to 49 years old were selected if there were no youths 6 to 11 years old in their household.

MEP and other phthalate metabolites were measured in urine using a previously published analytical method (Langlois et al., 2012) at Centre de Toxicologie du Québec (CTQ).

### 2.2. Statistical analysis

The data were analyzed with SAS 9.2 (SAS Institute Inc., USA), SUDAAN 10.0.1 software (RTI International, USA) and R (R Core Team, 2013). Variance estimates were produced using bootstrap weights, taking into account the 11 degrees of freedom as suggested in CHMS data user guide (Health Canada, 2010). All analyses were weighted using the CHMS cycle 1 survey weights (phthalates subsample) in order to be representative of the Canadian population. MEP concentrations that were below the limit of detection (LOD) were assigned a value of LOD/2.

### 2.3. Regression models

Urinary MEP excretion rate and DEP daily intake rate were calculated as described below for each CHMS study participant. Least squares geometric means (LSGMs) and associated 95% confidence intervals were computed using multiple regression models via SUDAAN's proc REGRESS. Since the MEP excretion rate and DEP daily intakes distributions were skewed, their log transformations were used in the regression models. Geometric means and 95% confidence intervals were back transformed to the original scale by exponentiation. The models included age group (children 6–11 years, adolescents 12–19 years and adults 20–49 years), and sex, as well as the interaction term age × sex in order to obtain LSGM estimates for each age group by sex. This model provided comparisons of LSGM for selected groups (e.g. males vs. females) that were adjusted statistically so that participants had comparable levels of all other covariates. Satterthwaite-adjusted statistics were used to test the significance of the regression coefficients. *T*-tests were used to compare LSGMs between categories. Statistical significance was evaluated at $p < 0.05$, but was Bonferroni-adjusted depending on the number of comparisons. The model assumptions of normality and homoscedasticity were tested by visual examination of the residuals from the regression equations and satisfied for all the models considered.

### 2.4. Estimation of creatinine excretion rate (CER)

Urinary creatinine concentration was measured in all participants in CHMS 2007–2009. As CHMS did not measure urine flow rate, we have estimated daily creatinine excretion rate in all participants using the Mage equations (from Huber et al., 2010). The Mage equations use age, height, and weight of individual participants to estimate their daily creatinine excretion rate. The adiposity adjustment (discussed in the supplemental information (Huber et al., 2010)) was applied to all participants and the body surface area adjustment was applied to children under the age of 18 years. Median body mass index (BMI) by age for the adiposity adjustment was computed using the entire CHMS sample ($n = 3224$). The CHMS phthalates subsample dataset had 174 children who exceeded the height limits in the Mage equations (186 cm for males and 172 cm for females). The Mage equations were applied directly to the observed heights in order to extrapolate creatinine excretion rates for these participants. The predicted excretion rates for these individuals appeared to be reasonable despite the extrapolation.

### 2.5. Estimation of urinary flow rate

Since participant's urinary flow rate (mL/min) was not measured in CHMS, values from NHANES (available online at http://wwwn.cdc.gov/nchs/nhanes/search/datapage.aspx?Component=Laboratory&CycleBeginYear=2009) were randomly assigned to the CHMS participants. Three urinary flow variables were available on the NHANES data file, and the first non-missing value was chosen in order to represent a single spot sample protocol. The imputation was carried out in two ways — one matching CHMS and NHANES participants by age and sex, and another matching age, sex and BMI. To match BMI, both NHANES and CHMS participants were separated into BMI quartiles within each age and sex group. For example, CHMS participants falling into the first CHMS BMI quartile for a given age and sex were matched to NHANES participants in the first NHANES BMI quartile for the same age and sex. The urinary flow rate data was used to calculate the total