OPEN

The Association Between Urinary Phthalates and Lung Function

Sabit Cakmak, PhD, Robert E. Dales, MD, MSc, Chris Hebbern, PhD, and Gurusankar Saravanabhavan, PhD

Objective: To investigate the influence of phthalate exposure on lung function in the Canadian population. **Methods:** We tested the association between 1-second forced expiratory volume (FEV_1), forced vital capacity (FVC), and urinary phthalate metabolite levels in a nationally representative sample of 3147, from 6 to 49 years old. **Results:** An interquartile increase in mono-n-butyl phthalate was associated with decreases in percent predicted FEV_1 of 0.8% (95% confidence interval = 0.3 to 1.4) and in FVC of 0.9% (95% confidence interval = 0.3 to 1.5). Results were similar for mono-3-carboxypropyl phthalate, mono-benzyl phthalate, and di(2-ethylhexyl) phthalate metabolites, but significant effects of the latter were only seen in males and those at least 17 years old. **Conclusions:** These results provide evidence that phthalate exposure may adversely affect lung function in the Canadian population. Given that these chemicals are ubiquitous, the population health burden may be significant if the associations were causal.

D iesters of phthalic acid, collectively called "phthalates," are widely used as plasticizers in the manufacture of polyvinyl chloride (PVC) plastics, solvents, clothing, personal care products, and toys.[1] Exposure to phthalates is widespread, with higher concentrations often observed in children than in adults.[2,3] There is evidence that phthalates may increase the risk of allergy and asthma. Greater household dust concentrations of butyl-benzyl phthalate and di(2-ethylhexyl) phthalate (DEHP) were found among Swedish children with rhinitis, eczema, or asthma than in children without allergic symptoms.[4] The amount of PVC plastic flooring and wall coverings has been associated with bronchial obstruction[5] and asthma[6] among Norwegian and Finish children, respectively. House dust concentrations of DEHP are higher in homes with more PVC plastic,[7] suggesting that the observed effect of plastic wall coverings may be mediated by phthalate exposure. There is some evidence of an association between phthalates and respiratory outcomes in adults, as well as differences by sex. In a subgroup of 240 adults who had participated in the US Third National Health and Nutrition Examination Survey between 1988 and 1994 (NHANES III), an interquartile range (IQR) change in urinary monobutyl phthalate (MBP) was associated with a 112-mL (standard error [SE] = 51) decrease in the 1-second forced expiratory volume (FEV_1) among men, but not among women.[8] A more recent study by the same author using data from 2325 participants collected between 2005 and 2006 from NHANES found that a high-molecular-weight phthalate metabolite was positively associated with allergic symptoms in adults but not in

Learning Objectives

- Summarize previous knowledge on population exposure to phthalates and associations with respiratory health.
- Outline the new findings on associations between urinary phthalate levels and lung function measures in the Canadian population.
- Discuss the likely population impact of the observed associations, including observed differences in children compared to adults.

children. This data suggest that there may be complex relations between phthalate exposure and respiratory health, requiring repeated further research.[9]

In this study, we investigate the possible association between phthalate exposure and respiratory outcomes, using objective measures of both biological phthalate dose and physiologic lung function in males and females, in children and adults, obtained from the 2007 to 2009 Canadian Health Measures Survey (CHMS).

RESEARCH METHODS

Study Population

Subject data were obtained from the CHMS, cycle I (2007 to 2009). The methodology for the survey has been described in detail elsewhere.[10] In brief, the CHMS is a general survey in Canada, representative of about 96% of the population aged 6 to 79 years, excluding those in the armed forces, people living on reserves, in institutions, or homeless.[11] Eighteen examination sites were set up to perform physical measurements. They were distributed among five regions across Canada: British Columbia, the Prairies, Ontario, Quebec, and the Atlantic provinces. Using the 2006 Canadian census, households within 100 km of each study site were sampled within 11 age and sex groups. There were approximately 350 respondents per site. This is a direct health measures survey, sampling across Canada, with each subject's results weighted according to the number of people they represent in the general population. The bootstrap method was used to estimate SEs and confidence intervals (CIs).[12,13] For this analysis, subjects were included if both spirometry and phthalate measurements were available (n = 3147).

PHYSIOLOGIC MEASURES

Lung Function

Lung function was tested using a KoKo Spirometer™ (Ferraris CardioRespiratory, Pulmonary Data Services, Inc, Louisville, CO). Spirometry was carried out by trained personnel following standardized criteria for test performance.[14] A maximum of eight trials were permitted to obtain three acceptable and reproducible test results. The greatest values obtained for the FEV_1 and forced vital capacity (FVC) were considered the primary outcome variables. They were expressed as a percentage of predicted accounting for age, height, and sex, using previously developed prediction equations developed from data on an American population.[15] Unless otherwise specified, percentages of predicted FEV_1 and FVC are referred to in the Results and Discussion sections simply as FEV_1 and FVC.

Exclusion criteria included having an acute respiratory tract infection, an inability to understand the instructions, being more than 24 weeks' pregnant, suffering a heart attack in the past 3

months, or having had major chest or abdominal surgery within the past 3 months.

Urinary Phthalate Measurements

Eleven phthalate metabolites—mono-n-butyl phthalate (MnBP), mono-benzyl phthalate (MBzP), mono-cyclohexyl phthalate (MCHP), mono-3-carboxypropyl phthalate (MCPP), mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono-2-ethylhexyl phthalate (MEHP), mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP), mono-ethyl phthalate (MEP), mono-methyl phthalate (MMP), mono-isononyl phthalate (MiNP), and mono-n-octyl phthalate (MnOP)—were measured in urine samples from respondents between 6 and 49 years of age ($n = 3236$). Analyses were conducted at the Centre de Toxicologie du Quebec using ultra-performance liquid chromatography tandem mass-spectrometry, as previously described.[16] Detection rates were lower than 20% for MMP, 13% for MCHP, 6% for MnOP, and 1% for MiNP. These four metabolites were excluded from further analysis. The remaining seven of the metabolites—MEP, MnBP, MBzP, MEHP, MEHHP, MEOHP, and MCPP—were detected in more than 92% of Canadians. Metabolite concentrations that were below the limit of detection (LoD) were assigned a value one half of the LoD.[17] The secondary metabolites MEHHP and MEOHP exhibit longer half-lives of elimination than MEHP alone, and together represent useful parameters for DEHP biomonitoring that may be considered representative of DEHP exposure.[18] Therefore, the DEHP metabolites MEHP, MEHHP, and MEOHP were evaluated as the sum of exposures of all three on a μg/g basis, here denoted "ΣDEHP."

STATISTICAL ANALYSIS

The approach to analysis was performed as previously described,[19] using generalized linear mixed models with sampling weights, to test the association between phthalate exposure and lung function, expressed as a percentage of predicted on the basis of age, height, and sex. Results were adjusted for body mass index, ethnicity (white vs other), greatest household education (no postsecondary education, postsecondary non-university education, university certificate below bachelor level and bachelor's degree, and university degree above bachelor's degree), household income (<$50,000, $50,000 to $60,000, $60,000 to $80,000, $80,000 to $100,000, >$100,000), and passive smoking and current smoking (current, former, never), as smoking is a known risk factor for respiratory illness. Results were also adjusted for ambient environmental conditions on the day of the lung function measurements. Meteorological data—temperature, relative humidity, and barometric temperature—were obtained from the Climate Data and Information Archive.[20] The air pollutants, nitrogen dioxide, ozone, and fine particulates (PM$_{2.5}$) were provided by the National Air Pollution Surveillance Program.[21]

All main effects and first-order interaction products with phthalates were considered. If the Wald chi-squared statistic P value was less than 0.10 for a main effect or interaction product, it was retained. The final model contained the selected variables and covariates if they were significant at $P < 0.05$ or if they confounded the exposure–outcome relationship (ie, a change of 10% in the coefficient for exposure). Previous research has found differences in phthalate concentrations by age group, and this was also the case in this study. Therefore, we segmented the analyses according to age—children (6 to 16 years) and adults (17 to 49 years). The final model variables were PM$_{2.5}$, age, sex, smoking status, fasting, income, and education for all phthalates, with age × phthalates and sex × phthalates interaction terms significant for ΣDEHP. These were selected from the whole sample and used in the subset analysis.

Two modeling approaches were tested to account for creatinine: in the first model, phthalate levels were adjusted by creatinine levels to minimize the effect of urine dilution (μg/g of creatinine); in the second model, lung function was examined with phthalates unadjusted for creatinine in the urine, but with creatinine included as a factor.[22] In both cases the results were very similar; therefore, we present results from the first model only, with phthalate levels adjusted for urinary creatinine. Results were expressed as the percentage change in the physiologic variable for an increase in the phthalate metabolite concentration equivalent to its IQR. Spearman

TABLE 1. Mean (and Standard Deviation) Characteristics of the 3147 Subjects in the CHMS, Cycle I, With Spirometry and Urinary Phthalate Measurements, by Age Group

Characteristics	All Ages	Age 6–16 ($n = 1642$)	Age 17–49 ($n = 1505$)
Sociodemographic			
Age, yr	20.7 (13.3)	10.7 (3)	31.5 (10.9)
Sex—male, %	49.4	51.4	46.9
Ethnicity—white, %	86.0	84.0	87.5
Highest household education—greater than high school, %	77.2	81.1	75.1
Total household income, $	84,598.0 (62,598.8)	88,892.0 (64,061.0)	78,646.0 (59,005.0)
Daily cigarette smoking, %	15.6	2.5	17.1
Physical and physiologic			
Height, cm	158.1 (18.5)	147.7 (18.0)	170.1 (9.3)
Weight, kg	58.5 (23.8)	43.1 (17.7)	75.1 (17.8)
Asthma, %	10.5	11.1	10.1
Wheezing—in the past, %	5.5	5.6	5.4
Wheezing—in the last 12 mo, %	1.7	1.9	1.5
Resting heart rate, per min	73.6 (11.6)	77.5 (11.0)	69.5 (11.1)
Resting systolic blood pressure, mm Hg	100.3 (11.6)	94.8 (8.3)	106.2 (11.8)
Resting diastolic blood pressure, mm Hg	64.9 (9.3)	61.0 (7.1)	69.3 (9.4)
FEV$_1$—predicted, %	97.9 (12.4)	99.2 (12.3)	96.6 (12.3)
FVC—predicted, %	96.7 (7.6)	97.1 (7.2)	96.3 (8.5)
FEV$_1$/FVC—predicted, %	99.8 (12.0)	100.0 (12)	99.5 (12.1)

FEV$_1$, 1-second forced expiratory volume; FVC, forced vital capacity.

pairwise correlation coefficients were calculated between the phthalate compounds. All data management and regression modeling was completed in SAS, v9.1 (Cary, NC).

RESULTS

Of the 5604 subjects in the CHMS, spirometry was measured in 5011, and phthalates in 3236, all aged between 6 and 49 years. A total of 3147 subjects had measurements available for both spirometry and phthalates and were included in this analysis. The average age of our study population was 20.7 years, almost half were male, and the majority of subjects were white, with better than a high school education and an average household income of $84,598 (Table 1). Mean physical and physiologic characteristics were unremarkable.

The highest urinary phthalate geometric mean concentrations fell between 41 and 63 μg/g of creatinine, for MEP (Table 2), with the lowest concentrations measured for MCPP, at 1.7 μg/g of creatinine (95% CI = 1.62 to 1.78). Concentrations of six of the seven phthalates measured were greater in children between 6 to 16 years old than in the older age group. Mono-n-butyl phthalate was 40.49 (95% CI = 39.01 to 42.02) among children compared with 22.59 (95% CI = 21.77 to 23.44) among adults. Only MEP was greater in the older age group (63.16; 95% CI = 59.32 to 67.25) than in children (41.15; 95% CI = 39.18 to 43.22). Compared with males, females had greater concentrations of MnBP, MCPP, and MEP. The majority of Spearman pairwise correlations between compounds were less than 0.1; the range was from −0.015, between MBzP and MEP, to 0.983, between MEHHP and MEOHP (data not shown).

Reductions of approximately 1% in FEV_1 or FVC were significantly associated with an IQR increase in the geometric means of MnBP, MBZP, MCPP, and ΣDEHP for the population as a whole (Table 3). A greater reduction in FEV_1 than FVC significantly lowered the FEV_1/FVC ratio for MBzP.

Among children between 6 and 16 years old, an IQR increase in MCPP was associated with reductions of 3.9% (95% CI = 1.4 to 6.3) in FEV_1 and 3% (95% CI = 1.4 to 4.7) in FEV_1/FVC (Table 4). Among adults aged 17 to 49 years, FEV_1 and FVC were approximately −0.9% (95% CI = 0.2 to 1.6) lower for ΣDEHP. Among adults, an IQR increase in MBzP and ΣDEHP was negatively associated with the FEV_1/FVC ratio, with a magnitude of the observed effect of approximately 1%. Decrements in all three parameters were significant for an IQR change in ΣDEHP in adults.

Increases in MnBP, MCPP, MEP, and ΣDEHP were significantly associated with reductions in FEV_1 or FVC in men, compared with only MnBP in women (Table 5). The observed effect sizes were approximately 1% for IQR increases in phthalate metabolites. For ΣDEHP all three lung function parameters were significantly reduced by an IQR change in urinary phthalate.

To further explore the observed differences in sex in Table 5, the changes in predicted spirometry values were evaluated for both age and sex for an IQR change in ΣDEHP (Table 6). For males younger than 16 years, FVC and FEV_1/FVC were significantly reduced, whereas all three parameters were significantly reduced in male adults. There was no significant change for females in either age group for any parameter, suggesting a higher susceptibility for males in the study population.

DISCUSSION

In this large population-based national study, we found associations between the body burden of specific phthalates and small but significant reductions in physiologic lung function. For six of the seven phthalates, levels were greater in children than in adults. Significant observed effects were seen between lung function among children for MnBP and MCPP, whereas for adults associations were seen for MBzP and MEP and DEHP metabolites. Observed effects in males were greater than in females. For males, associations were

TABLE 2. Urinary Phthalate Metabolite (μg/g) Geometric Means by Age and Sex

Urinary Phthalate	All (95% CI) {Interquartile Range}	Age 6–16, n = 1642 (95% CI) {Interquartile Range}	Age 17–49, n = 1505 (95% CI) {Interquartile Range}	Male, n = 1555 (95% CI) {Interquartile Range}	Female, n = 1592 (95% CI) {Interquartile Range}
MnBP* (100% > LoD)	30.65 (29.8–31.52) {29.62}	40.49 (39.01–42.02) {35.05}	22.59 (21.77–23.44) {17.75}	26.74 (25.75–27.77) {27.54}	35.19 (33.79–36.64) {30.87}
MBzP (100% > LoD)	16.40 (15.84–16.98) {23.43}	24.23 (23.18–25.34) {29.66}	10.70 (10.22–11.20) {13.81}	15.71 (14.95–16.52) {22.95}	17.13 (16.31–17.98) {24.16}
MCPP (93% > LoD)	2.42 (2.34–2.51) {3.01}	3.27 (3.13–3.41) {3.78}	1.70 (1.62–1.78) {1.80}	2.25 (2.15–2.36) {2.92}	2.61 (2.49–2.74) {3.29}
MEHHP (100% > LoD)	30.47 (29.47–31.50) {35.87}	37.84 (36.26–39.49) {42.88}	24.04 (22.89–25.24) {24.65}	29.18 (27.82–30.60) {36.49}	31.83 (30.40–33.33) {35.40}
MEHP (99.7% > LoD)	4.08 (3.94–4.22) {5}	4.12 (3.94–4.32) {4.92}	4.03 (3.82–4.25) {5.08}	3.90 (3.71–4.09) {4.91}	4.27 (4.07–4.48) {5.12}
MEOHP (99.7% > LoD)	18.71 (18.1–19.34) {22.1}	23.66 (22.69–24.68) {26.29}	14.47 (13.79–15.19) {14.35}	17.37 (16.55–18.22) {21.88}	20.18 (19.29–21.10) {21.68}
MEP (100% > LoD)	50.49 (48.51–52.56) {75.52}	41.15 (39.18–43.22) {45.74}	63.16 (59.32–67.25) {107.24}	45.66 (43.04–48.43) {66.49}	55.91 (52.98–59.00) {80.21}

*Detection limits for each analyte: MnBP, 0.2 ng/L; MBzP, 0.2 ng/L; MCPP, 0.2 ng/L; MEHHP, 0.4 ng/L; MEHP, 0.2 ng/L; MEOHP, 0.2 ng/L; MEP, 0.5 ng/L.
CI, confidence interval; LoD, limit of detection; MBzP, mono-benzyl phthalate; MCPP, mono-3-carboxypropyl phthalate; MEHHP, mono-(2-ethyl-5-hydroxyhexyl) phthalate; MEHP, mono-2-ethylhexyl phthalate; MEOHP, mono-(2-ethyl-5-oxohexyl) phthalate; MEP, mono-ethyl phthalate; MnBP, mono-n-butyl phthalate.

TABLE 3. Change in Percent Predicted Spirometry Parameters for an Interquartile Change in Urinary Phthalate Metabolite Concentrations ($n = 3071$)*

Urinary Phthalate	FEV_1	FVC	FEV_1/FVC
MnBP	*− 0.8 (−1.4, −0.3)*	*− 0.9 (−1.5, −0.3)*	− 0.1 (−0.7, 0.5)
MBzP	*− 0.9 (−1.6, −0.2)*	− 0.6 (−1.2, 0.1)	*− 0.5 (−0.9, −0.1)*
MCPP	*− 1.1 (−1.6, −0.5)*	*− 1.1 (−1.6, −0.5)*	− 0.3 (−0.9, 0.3)
MEP	− 0.7 (−0.8, 0.3)	− 0.6 (−1.3, 0.1)	0.0 (−0.4, 0.5)
ΣDEHP	*− 0.7 (−1.3, −0.1)*	*− 0.8 (−1.4, −0.3)*	0.1 (−0.4, 0.6)

*Results are adjusted for $PM_{2.5}$, age, sex, smoking (current, occasional, and nonsmokers), fasting, income, and education. Italicized data show results considered statistically significant if 95% confidence limits do not encompass 0.

DEHP, di(2-ethylhexyl) phthalate; FEV_1, 1-second forced expiratory volume; FVC, forced vital capacity; MBzP, mono-benzyl phthalate; MCPP, mono-3-carboxypropyl phthalate; MEP, mono-ethyl phthalate; MnBP, mono-n-butyl phthalate.

TABLE 4. Change in Percent Predicted Spirometry Parameters for an Interquartile Change in Urinary Phthalate Metabolite Concentrations by Age*

	Age 6–16 ($n = 1642$)			Age 17–49 ($n = 1505$)		
Urinary Phthalate	FEV_1	FVC	FEV_1/FVC	FEV_1	FVC	FEV_1/FVC
MnBP	− 0.5 (−1.3, 0.3)	*− 0.9 (−1.6, −0.1)*	0.9 (−0.7, 2.6)	− 0.8 (−1.7, 0.2)	− 0.6 (−1.5, 0.2)	− 0.3 (−1.0, 0.4)
MBzP	− 0.6 (−1.5, 0.3)	− 0.7 (−1.6, 0.2)	0.0 (−0.5, 0.5)	− 0.5 (−1.5, 0.6)	0.4 (−0.6, 1.4)	*− 0.8 (−1.4, −0.2)*
MCPP	*− 3.9 (−6.3, −1.4)*	*− 1.0 (−1.8, −0.2)*	*− 3.0 (−4.7, −1.4)*	− 0.8 (−1.7, 0.1)	− 0.7 (−1.6, 0.2)	− 0.2 (−0.8, 0.4)
MEP	− 0.6 (−2.5, 1.3)	− 0.8 (−2.1, 1.8)	− 0.3 (−0.9, 0.3)	− 0.7 (−1.5, 0.1)	*− 1.0 (−1.7, −0.3)*	0.2 (−0.4, 0.8)
ΣDEHP	− 0.3 (−1.2,0.6)	0.4 (−0.2, 0.9)	− 0.7 (−1.6, 0.1)	*− 0.9 (−1.6, −0.2)*	*− 0.8 (−1.5, −0.1)*	*− 1.0 (−1.8, −0.2)*

*Results are adjusted for $PM_{2.5}$, sex, smoking (current, occasional, and nonsmokers), fasting, income, and education. Italicized data show results considered statistically significant if 95% confidence limits do not encompass 0.

DEHP, di(2-ethylhexyl) phthalate; FEV_1, 1-second forced expiratory volume; FVC, forced vital capacity; MBzP, mono-benzyl phthalate; MCPP, mono-3-carboxypropyl phthalate; MEP, mono-ethyl phthalate; MnBP, mono-n-butyl phthalate.

TABLE 5. Change in Percent Predicted Spirometry Parameters for an Interquartile Change in Urinary Phthalate Metabolite Concentrations by Sex*

	Male ($n = 1555$)			Female ($n = 1592$)		
Urinary Phthalate	FEV_1	FVC	FEV_1/FVC	FEV_1	FVC	FEV_1/FVC
MnBP	*− 1.1 (−2.0, −0.2)*	*− 1.0 (−1.8, −0.2)*	− 0.2 (−0.8, 0.4)	− 1.0 (−2.0, 0.1)	*− 0.9 (−1.6, −0.2)*	− 0.3 (−1.0, 0.4)
MBzP	0.8 (−1.5, 3.1)	0.6 (−2.6, 3.6)	− 0.1 (−1.3, 1.1)	− 0.3 (−2.1, 1.5)	− 0.6 (−2.4, 1.2)	0.1 (−0.8, 1.0)
MCPP	*− 1.6 (−2.5, −0.7)*	*− 1.4 (−2.3, −0.5)*	− 0.2 (−0.8, 0.4)	− 0.6 (−1.4, 0.2)	− 0.7 (−1.5, 0.1)	− 0.5 (−1.2, 0.2)
MEP	− 0.9 (−1.9, 0.1)	*− 1.1 (−2.0, −0.2)*	0.1 (−0.5, 0.7)	− 0.1 (−0.9, 0.6)	− 0.3 (−1.1, 0.5)	− 0.0 (−0.6, 0.6)
ΣDEHP	*− 0.9 (−1.7, −0.1)*	*− 1.1 (−2.1,−0.1)*	*− 1.1 (−2.2, −0.0)*	− 0.6 (−1.4, 0.2)	− 0.7 (−1.7, 0.3)	0.2 (−0.3, 0.7)

*Results are adjusted for $PM_{2.5}$, age, smoking status (current, occasional, and nonsmokers), fasting, income, and education. Italicized data show results considered statistically significant if 95% confidence limits do not encompass 0.

DEHP, di(2-ethylhexyl) phthalate; FEV_1, 1-second forced expiratory volume; FVC, forced vital capacity; MBzP, mono-benzyl phthalate; MCPP, mono-3-carboxypropyl phthalate; MEP, mono-ethyl phthalate; MnBP, mono-n-butyl phthalate.

found with MnBP, MCPP, MEP, and DEHP metabolites, whereas for women the only significant relation was between FVC and MnBP.

In this study, phthalate metabolites were associated with reductions of approximately 1% in lung function in adults, and in the case of MCPP, a 3% to 4% decrement in children in FEV_1 and FEV_1/FVC. A reduced ratio is commonly seen with an airflow obstruction, whereas the more frequently seen reduction in FEV_1 and FVC in this study, rather than the ratio between the two, is consistent with a mild restrictive respiratory condition.[23] Although the reduction is small at an individual level, the size of reduction that we report may be of public health importance when exposure affects the entire population.

Similar age differences in exposure levels have been found elsewhere, for example, in Denmark where younger children had a higher phthalate burden than older children and adolescents,[24] and in Germany.[18]

Levels of phthalates were higher in females than in males, as previously found.[17] Nevertheless, among males, phthalate metabolites were more often significantly associated with decreased lung function. This finding may be the result of subgroup analysis, although sex differences in health outcomes related to phthalate exposure have been previously reported; among 240 adults who participated in NHANES III, an MBP level of 31.53 ng/g creatinine was significantly associated with decrements in three measures of

TABLE 6. Change in Percent Predicted Spirometry Parameters for an Interquartile Change in Urinary Phthalate Metabolite Concentrations by Sex and Age, for ΣDEHP*

	Parameter	Change in Percent Predicted
Male, age 6–16 (n = 795)	FEV_1	− 0.6 (−1.8, 0.6)
	FVC	*− 1.3 (−2.5, −0.1)*
	FEV_1/FVC	*− 0.7 (−1.3, −0.1)*
Female, age 6–16 (n = 847)	FEV_1	− 0.2 (−1.3, 0.9)
	FVC	− 0.3 (−1.4, 0.8)
	FEV_1/FVC	− 0.0 (0.7, 0.7)
Male, age 17–49 (n = 760)	FEV_1	*− 1.2 (−2.0,−0.4)*
	FVC	*− 1.2 (−2.0, −0.4)*
	FEV_1/FVC	*− 1.2 (−2.1, −0.2)*
Female, age 17–49 (n = 745)	FEV_1	− 0.1 (−1.6, 1.4)
	FVC	− 0.1 (−1.4, 1.2)
	FEV_1/FVC	− 0.2 (−1.0, 0.6)

*Results are adjusted for $PM_{2.5}$, age, sex, smoking status (current, occasional, and nonsmokers), fasting, income, and education. Italicized data show results considered statistically significant if 95% confidence limits do not encompass 0.

DEHP, di(2-ethylhexyl) phthalate; FEV_1, 1-second forced expiratory volume; FVC, forced vital capacity.

pulmonary function (FVC, FEV_1, and PEF) in males, but not in females. For an IQR change in MBP levels among males, FEV_1 decreased 112 mL (SE = 51; $P = 0.03$). For an average FEV_1 of 3.5 L, this would be equivalent to a 2% to 3% change. Monoethyl phthalate was associated with lower FVC and FEV_1 values in men.[8]

Human Studies

There is uncertainty about the role of phthalates in causing pulmonary toxicity. One systematic literature review concluded that, in humans, occupational exposure to PVC-containing fumes, and residential exposure to PVC-containing dust are associated with an increased risk of respiratory symptoms.[25] DEHP, a parent compound of MEHP, is a major component of PVC. Hsu et al[26] reported an association between levels of phthalates in settled house dust and allergy and asthma in children, whereas a birth cohort study found log-unit increases in urinary concentrations of DEP and butyl-benzyl phthalate were associated with 6.6% and 8.7% increases in exhaled nitric oxide, respectively.[27] This study adds to the evidence for phthalates being risk factors for respiratory health in the home environment. Oxidative stress may be one mechanism to explain the association between respiratory health and phthalates. Among 418 elderly Korean subjects, the association between MEHHP phthalate and MEOHP on FEV_1/FVC was significant in subjects with certain genetic polymorphisms of oxidative stress-related genes.[28] Nevertheless, one comprehensive review of animal and human studies concluded that there is insufficient evidence to prove that phthalate exposure is a risk factor for allergic sensitization or asthma in humans at levels of exposure outside the occupational setting.[29] Since this review was published, Hoppin et al[9] reported that concentration of a high-molecular-weight phthalate metabolite, MBzP, was positively associated with allergic symptoms in adults but not in children.

Animal Studies

Little is known about mechanisms whereby phthalates could potentially cause pulmonary toxicity. One study reported that MEHP induced bronchial hyperreactivity in rats, and the increased rat tracheal smooth muscle response to methacholine, and postulated that the observed effect may be mediated by inhibition of protein ki-

nase C, which relaxes smooth muscle.[30] In humans, increased airway responsiveness to methacholine is highly predictive of clinical asthma and used as a diagnostic test. Oie et al[31] postulated that MEHP may cause airway inflammation similar to the effects of certain prostaglandins and thromboxanes. Larsen et al[32] demonstrated that in mice, subcutaneous injection of MEHP and MOP increased the IgE response to ovalbumin, suggesting that these compounds could modify allergic sensitization in humans. Hansen et al[33] could not replicate the effect on IgE when MEHP was inhaled, but did observe an increase in IgG_1 and inflammatory cells in bronchial lavage fluid, and increased IL-5 and IL-10 in single-cell suspensions of lymph nodes. These observations lead to the hypothesis that inhaled MEHP enhanced Th2 responses. A comprehensive review of the literature stated: "the data . . . support an adjuvant effect on Th2 differentiation and Th2 promoted IgG1 and IgE by several of the phthalates . . . ."[34]

Strengths and Limitations of This Study

This study benefited from the use of objective measures of both phthalate exposure and of lung function in a nonbiased large population-based sample. The information gained from spirometry is clinically important. It is used to determine the degree of impairment from respiratory disease, and to diagnose chronic obstructive lung disease and acute asthma exacerbations. Although the changes in spirometry-derived variables were relatively small, levels of ambient air pollution, which are associated with changes of this magnitude, are also associated with a similar percentage increase in hospitalizations for respiratory disease among certain sociodemographic subgroups.[35]

Confounding of the observed association between urinary phthalate and lung function is a possibility, but it would require a factor that is associated with the exposure and is also a risk factor for the outcome. Given the short half-life of phthalates such as DHEP,[36] the urinary concentrations represent current exposure. If the study participants' lifestyle and environment has not changed, then it would be expected that the current concentration may also reflect longer term exposure but this cannot be assumed. Cross-sectional study designs do not normally allow us to distinguish acute from chronic pulmonary effects. We can only say that reduced lung function is associated with elevated levels of urinary phthalates.

CONCLUSIONS

Our findings suggest that phthalates at concentrations experienced by the general population may have adverse physiologic effects, and that males might be at a higher risk. The observed effect sizes are for the most part relatively small, but given that phthalates are ubiquitous in our society, exposure is near universal and therefore the population-attributable risk of reduced lung function may be significant if the observed effects were causal. Understanding the health-related effects of phthalates has a practical application given that modification of phthalate exposure is possible through changes in manufacturing and consumer choices.

REFERENCES

1. U.S. EPA. Phthalates: TEACH Chemical Summary. Available at http://www.epa.gov/teach./ Published 2007. Accessed January 21, 2014.
2. Wittassek M, Angerer J. Phthalates: metabolism and exposure. *Int J Androl.* 2008;31:131–138.
3. Silva MJ, Barr DB, Reidy JA, et al. Urinary levels of seven phthalate metabolites in the U.S. population from the National Health and Nutrition Examination Survey (NHANES) 1999–2000. *Environ Health Perspect.* 2003;112:331–338.
4. Bornehag C-G, Sundell J, Weschler CJ, et al. The association between asthma and allergic symptoms in children and phthalates in house dust: a nested case-control study. *Environ Health Perspect.* 2004;112:1393–1397.

5. Jaakkola JJ, Oie L, Nafstad P, Botten G, Samuelsen SO, Magnus P. Interior surface materials in the home and the development of bronchial obstruction in young children in Oslo, Norway. *Am J Public Health.* 1999;89:188–192.

6. Jaakkola JJ, Verkasalo PK, Jaakkola N. Plastic wall materials in the home and respiratory health in young children. *Am J Public Health.* 2000;90:797–799.

7. Bornehag C-G, Lundgren B, Weschler CJ, Sigsgaard T, Hagerhed-Engman L, Sundell J. Phthalates in indoor dust and their association with building characteristics. *Environ Health Perspect.* 2005;113:1399–1404.

8. Hoppin JA, Ulmer R, London SJ. Phthalate exposure and pulmonary function. *Environ Health Perspect.* 2004;112:571–574.

9. Hoppin JA, Jaramillo R, London SJ, et al. Phthalate exposure and allergy in the U.S. Population: results from NHANES 2005–2006. *Environ Health Perspect.* 2013;121:1129–1134.

10. Giroux S. Canadian Health Measures Survey: sampling strategy overview. *Heal Rep Stat Can.* 2007;18:31–36.

11. Tremblay MS, Gorber SC. Canadian health measures survey. *Can J Public Health.* 2007;98:453–456.

12. Rao NK, Wu CFJ, Yue K. Some recent work on resampling methods for complex surveys. *Surv Methodol.* 1992;18:209–217.

13. Rust K, Rao J. Variance estimation for complex surveys using replication techniques. *Stat Methods Med Res.* 1996;5:283–310.

14. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J.* 2005;26:319–338.

15. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. *Am J Respir Crit Care Med.* 1999;159:179–187.

16. Langlois É, Leblanc A, Simard Y, Thellen C. Accuracy investigation of phthalate metabolite standards. *J Anal Toxicol.* 2012;36:270–279.

17. Saravanabhavan G, Guay M, Langlois E, Giroux S, Murray J, Haines D. Biomonitoring of phthalate metabolites in the Canadian population through the Canadian Health Measures Survey (2007–2009). *Int J Hyg Environ Health.* 2013;1–10.

18. Koch HM, Preuss R, Angerer J. Di(2-ethylhexyl)phthalate (DEHP): human metabolism and internal exposure—an update and latest results. *Int J Androl.* 2006;29:155–165; discussion 181–185.

19. Cakmak S, Dales R, Leech J, Liu L. The influence of air pollution on cardiovascular and pulmonary function and exercise capacity: Canadian Health Measures Survey (CHMS). *Environ Res.* 2011;111:1309–1312.

20. Environment Canada. Climate Data and Information Archive. Available at http://climate.weather.gc.ca./ Accessed January 21, 2014.

21. Environment Canada. National Air Pollution Surveillance Program (NAPS). Available at http://www.ec.gc.ca/rnspa-naps/Default.asp?lang=En&n=5C0D33CF-1. Accessed January 21, 2014.

22. Barr DB, Wilder LC, Caudill SP, Gonzalez AJ, Needham LL, Pirkle JL. Urinary creatinine concentrations in the U.S. population: implications for urinary biologic monitoring measurements. *Environ Health Perspect.* 2004;113:192–200.

23. Pellegrino R, Viegi G, Brusasco V, et al. Interpretative strategies for lung function tests. *Eur Respir J.* 2005;26:948–968.

24. Frederiksen H, Aksglaede L, Sorensen K, Skakkebaek NE, Juul A, Andersson A-M. Urinary excretion of phthalate metabolites in 129 healthy Danish children and adolescents: estimation of daily phthalate intake. *Environ Res.* 2011;111:656–663.

25. Jaakkola JJK, Knight TL. The role of exposure to phthalates from polyvinyl chloride products in the development of asthma and allergies: a systematic review and meta-analysis. *Environ Health Perspect.* 2008;116:845–853.

26. Hsu N-Y, Lee C-C, Wang J-Y, et al. Predicted risk of childhood allergy, asthma, and reported symptoms using measured phthalate exposure in dust and urine. *Indoor Air.* 2012;22:186–199.

27. Just ACA, Whyatt RRM, Miller RLR, et al. Children's urinary phthalate metabolites and fractional exhaled nitric oxide in an urban cohort. *Am J Respir Crit Care Med.* 2012;186:830–837.

28. Park HY, Kim JH, Lim Y-H, Bae S, Hong Y-C. Influence of genetic polymorphisms on the association between phthalate exposure and pulmonary function in the elderly. *Environ Res.* 2013;122:18–24.

29. Kimber I, Dearman RJ. An assessment of the ability of phthalates to influence immune and allergic responses. *Toxicology.* 2010;271:73–82.

30. Doelman C, Borm P, Bast A. Plasticisers and bronchial hyperreactivity. *Lancet.* 1990;335:725.

31. Oie L, Hersoug LG, Madsen JO. Residential exposure to plasticizers and its possible role in the pathogenesis of asthma. *Environ Health Perspect.* 1997;105:972–978.

32. Larsen ST, Hansen JS, Thygesen P, Begtrup M, Poulsen OM, Nielsen GD. Adjuvant and immuno-suppressive effect of six monophthalates in a subcutaneous injection model with BALB/c mice. *Toxicology.* 2001;169:37–51.

33. Hansen JS, Larsen ST, Poulsen LK, Nielsen GD. Adjuvant effects of inhaled mono-2-ethylhexyl phthalate in BALB/cJ mice. *Toxicology.* 2007;232:79–88.

34. Bornehag CG, Nanberg E. Phthalate exposure and asthma in children. *Int J Androl.* 2010;33:333–345.

35. Cakmak S, Dales RE, Rubio MA, Vidal CB. The risk of dying on days of higher air pollution among the socially disadvantaged elderly. *Environ Res.* 2011;111:388–393.

36. Koch HM, Bolt HM, Angerer J. Di(2-ethylhexyl)phthalate (DEHP) metabolites in human urine and serum after a single oral dose of deuterium-labelled DEHP. *Arch Toxicol.* 2004;78:123–130.