Prenatal Exposures to Phthalates among Women in New York City and Krakow, Poland

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Experimental evidence has shown that certain phthalates can disrupt endocrine function and induce reproductive and developmental toxicity. However, few data are available on the extent of human exposure to phthalates during pregnancy. As part of the research being conducted by the Columbia Center for Children's Environmental Health, we have measured levels of phthalates in 48-hr personal air samples collected from parallel cohorts of pregnant women in New York, New York, (n = 30) and in Krakow, Poland (n = 30). Spot urine samples were collected during the same 48-hr period from the New York women (n = 25). The following four phthalates or their metabolites were measured in both personal air and urine: diethyl phthalate (DEP), dibutyl phthalate (DBP), diethylhexyl phthalate (DEHP), and butyl benzyl phthalate (BBzP). All were present in 100% of the air and urine samples. Ranges in personal air samples were as follows: DEP (0.26–7.12 μg/m^3), DBP (0.11–14.76 μg/m^3), DEHP (0.05–1.08 μg/m^3), and BBzP (0.00–0.63 μg/m^3). The mean personal air concentrations of DBP, di-isobutyl phthalate, and DEHP are higher in Krakow, whereas the mean personal air concentration of DEP is higher in New York. Statistically significant correlations between personal air and urinary levels were found for DEP and monoethyl phthalate (r = 0.42, p < 0.05), DBP and monobutyl phthalate (r = 0.58, p < 0.01), and BBzP and monobenzyl phthalate (r = 0.65, p < 0.01). These results demonstrate considerable phthalate exposures during pregnancy among women in these two cohorts and indicate that inhalation is an important route of exposure. *Key words:* **endocrine disruption, exposure assessment, internal dose, personal air monitoring, phthalates, prenatal exposures, urban, urinary metabolites.** *Environ Health Perspect* **111:1719–1722 (2003). doi:10.1289/ehp.6235 available via *http://dx.doi.org/* [Online 7 July 2003]**

Recent surveys have revealed that phthalate exposures are widespread in the general U.S. population [Blount et al. 2000b; Centers for Disease Control and Prevention (CDC) 2003]. Based on one survey, women of reproductive age (20–40 years of age) appear to be more exposed to dibutyl phthalate (DBP) than are other age groups (Blount et al. 2000b; Kohn et al. 2000), possibly due to the volatilization and inhalation of phthalates from a variety of commonly used cosmetics and household products. These findings prompted an investigation to characterize phthalate exposures in two cohorts of pregnant women in New York, New York, and in Krakow, Poland, as part of the research being conducted by the Columbia Center for Children's Environmental Health. We used 48-hr personal air samples to measure external exposures in all 60 subjects. Urinary metabolites were used as a measure of internal dose for 25 of the New York subjects.

Phthalates are a class of high production volume chemicals (> 1 million tons produced or exported into the United States per year) that are commonly present in the home environment. Phthalates have widespread uses as plasticizers, emollients (skin softeners), humectants (skin moisturizers), antifoaming agents in aerosols, agents to prevent brittleness and cracking in nail polishes, and sealants [Agency for Toxic Substances and Disease Registry (ATSDR) 1999; Center for the Evaluation of Risks to Human Reproduction (CERHR) 2000a, 2000b, 2000c; Houlihan and Wiles 2000]. As of October 2000, the U.S. Patent and Trademark Office had 309 patents registered for DBP use in cosmetics (Houlihan and Wiles 2000). This includes 120 nail base coats, polishes, and enamels and 27 manicuring preparations (DiGangi et al. 2002). Phthalates are used in insect repellants, shower curtains, hair sprays, and building products (ATSDR 1999; CERHR 2000c). In 1995, diethyl phthalate (DEP) was reported to be in 67 formulations as a solvent and as a vehicle for fragrance and cosmetic ingredients at concentrations ranging from 0.1% to 50% (Scientific Committee on Cosmetic Products and Non-food Products Intended for Consumers 2002). Diethylhexyl phthalate (DEHP) has been the primary plasticizer used in polyvinyl chloride since the 1930s (Woodward 1988).

Phthalates are released into the environment throughout the cycle of their production, use, and disposal. The principal route of exposure is assumed to be the ingestion of contaminated food products (CERHR 2000a, 2000b, 2000c). Phthalates are taken up into the food chain and are present in meat, fish, and dairy products (Petersen and Breindahl 2000). They can migrate from plastic containers and wraps into the fat layer of packaged foods (Sharman et al. 1994). Off-gassing of phthalates from products in the home can contribute to ambient air levels. Because of their lipophilicity, phthalates are readily absorbed through the skin. Inhalation and dermal absorption are considered important direct routes of exposure, although this is not well documented or understood (Blount et al. 2000b; CERHR 2000b, 2000c).

Phthalate congeners with more than two and fewer than eight carbon atoms are reproductive and developmental toxicants of varying potencies (Gray et al. 2000; Heindel et al. 1989). Based on experimental evidence, DBP and DEHP have been characterized as endocrine disruptors acting through complex pathways that generally do not involve the androgen and estrogen receptors (Corton et al. 1997; Davis et al. 1994a; Gray et al. 2000; Lovekamp-Swan and Davis 2003; Mylchreest et al. 1998). Experimental evidence indicates that DEHP suppresses ovarian estradiol production in adult females by inhibiting the transcription of the enzyme aromatase (Davis et al. 1994a, 1994b; Lovekamp and Davis 2001). This has negative effects on estrogen-dependent processes such as ovulation and fertility (Ema et al. 2000; Lovekamp-Swan and Davis 2003). It is not clear how this estrogen effect may interfere in the development of the fetus or a woman's ability to sustain a healthy pregnancy. In male animals, DBP, DEHP, and butyl benzyl phthalate (BBzP) act as antiandrogens, causing decreased testosterone production in the male fetus, which can result in malformations in the external genitalia, degeneration of the seminiferous tubules, and reduced sperm production (Gray et al. 2000; Sharpe 2001). DEP has not been shown to be

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a reproductive or developmental toxicant (Gray et al. 2000; Lamb et al. 1987).

Phthalate monoester levels in the urine have recently been validated as a reliable and accurate biomarker of internal dose (Anderson et al. 2001; Blount et al. 2000a). The objective of the present study was to characterize phthalate exposures in pregnant women using personal air and urine measures (urine in a subset of 25 women) collected within a 48-hr period. Although these samples represent a snapshot of exposures over a 9-month period, they provide important information that will guide future research to better understand the effects of phthalates on pregnancy. This is the first study to report statistical correlations between phthalate diester levels measured in personal air and urinary monoester metabolite levels.

Materials and Methods

Enrollment. Study protocols including eligibility requirements and comparability between women who agreed to participate and those who refused have been described in detail previously (Whyatt et al. 2002). Women 18–35 years of age were enrolled during pregnancy at prenatal clinics in New York and Krakow. In New York, recruitment was restricted to women who were self-identified as African American or Dominican and had resided in northern Manhattan or the South Bronx for ≥ 1 year before pregnancy. In Krakow, because the central aims of the study were to evaluate the effects of ambient air pollution, the study was restricted to women who had resided in Krakow for at least 1 year within a 0.5-km radius of two ambient air monitoring stations with the highest and lowest pollution levels. To control for known risk factors of adverse birth outcomes, women were excluded if they smoked cigarettes or used other tobacco products during pregnancy; used illicit drugs; had diabetes, hypertension, or known HIV (human immunodeficiency virus) infection; or had had their first prenatal visit after the 20th week of pregnancy. The institutional review boards of Columbia University and Jagiellonian University in Krakow approved the study. The 60 personal air samples selected for analysis as part of the present study represent two separate batches of air samples received by the laboratory and analyzed *a posteriori* for phthalates. The New York batch was analyzed in October 2000, and the Krakow batch in June 2001.

Personal ambient air monitoring. The 48-hr personal air monitoring was undertaken during the second trimester of pregnancy for Krakow and during the third trimester for New York subjects. The women wore a small backpack holding a personal ambient air monitor during the daytime hours for 2 consecutive days and kept the monitor near the bed at night. The backpack was designed so that the sampling inlet was positioned in the woman's breathing zone. Pumps operated continuously at 2 L/min among Krakow subjects and 4 L/min among New York subjects, collecting particles of ≤ 2.5 μm in diameter on a precleaned quartz microfiber filter, and semivolatile vapors and aerosols on a polyurethane foam (PUF) cartridge backup. In New York, the women were monitored between March and July 2000. In Krakow, they were monitored between November 2000 and March 2001.

Phthalates in air monitoring samples. The air monitoring samples were brought to the laboratories (the Mailman School of Public Health or the Jagiellonian University), inventoried, and frozen. Once per month, air-monitoring samples were shipped on dry ice to Southwest Research Institute, where they were stored at –12°C. Samples were analyzed in separate batches for each city. The PUF and filter were soxhlet extracted with 6% diethyl ether in hexanes, and the extract was concentrated to 1.0 mL. Gas chromatography–mass spectrometry (MS) analysis for the five phthalates was performed using an Agilent 6890 gas chromatograph with a DB-5.625 column (30 m × 25 mm inner diameter) column and an Agilent 5973 Mass Selective Detector in selected ion monitoring mode (Agilent Technologies, Palo Alto, CA, USA). DEHP, DBP, BBzP, DEP, and di-isobutyl phthalate (DIBP) were quantified by the internal standard method using deuterium-labeled polycyclic aromatic hydrocarbon (PAH) as the internal standard. The relative standard deviation of the initial five-point standard calibration was maintained within 30% for each analyte, except for BBzP (within 31%) and DEHP (within 45%) for some Krakow samples. A continuing calibration standard was processed at the beginning and end of each sequence of 15 extracts. The difference of the relative response factor of the continuing calibration standards differed from the initial calibration average by < 40%, except for BBzP (within 43%) and DEHP (within 61%) for some Krakow samples. Multiple dilutions were usually needed to bring all analytes within the linear calibration range.

Laboratory blank samples were used to assess the level of phthalate contamination inherent to the analytic process of PUF cartridges being used in this study. The laboratory provided values for the phthalate congeners measured in three blank cartridges analyzed along with the New York samples and four blank cartridges analyzed with the Krakow samples. Arithmetic means for the quality assurance/quality control samples were calculated for each congener and then subtracted from the sample values. The blank-subtracted mass value was then divided by the total volume of air drawn for each sample to give the concentration in nanograms per cubic meter. Mean blank levels were considerably lower than the analyte levels, but those of BBzP and DEHP exceeded 10% of the mean sample mass. The relative ranks of the congeners were unchanged before and after adjustment.

Urine sample collection. A spot urine sample was collected from the New York subjects at the conclusion of the personal monitoring and delivered to the laboratory where it was frozen at –70°C. Within 5 months of collection, the samples were sent to the National Center for Environmental Health laboratory at the Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia, where they were processed and analyzed for a variety of biomarkers. The urine samples for New York subjects were matched by identification number to the personal air samples and analyzed where volume was sufficient.

Urine sample analysis. The method for analysis of urine samples was described previously (Blount et al. 2000a). The urine was first treated with glucuronidase enzyme in order to deconjugate the monoester metabolites. They were then extracted twice with Oasis HLB solid-phase extraction cartridges (Waters, Milford, MA, USA) and resuspended in the mobile phase. The samples were analyzed using high-performance liquid chromatography–tandem MS. 4-Methylumbelliferone was used as a quality control measure for the deconjugation step. Urinary creatinine was measured with an ASTRA analyzer (Beckman

Table 1. Concentrations (μg/m^3) of phthalate diesters detected in 100% of 48-hr personal air samples in two populations of pregnant women.

	New York (n = 30)			Krakow (n = 30)		
Phthalate diester	Median	Mean ± SD	Range	Median	Mean ± SD	Range
DBP	0.40	0.58 ± 0.73	0.11–4.1	2.3	2.9 ± 2.5	0.75–15
DEP	2.7	3.0 ± 1.3	1.5–7.1	0.84	1.0 ± 0.67	0.26–2.9
DIBP	0.37	0.42 ± 0.27	0.03–1.3	0.81	1.0 ± 1.4	0.31–8.1
DEHP	0.22	0.22 ± 0.10	0.05–0.41	0.37	0.43 ± 0.24	0.08–1.1
BBzP	0.04	0.10 ± 0.15	0.01–0.63	0.02	0.04 ± 0.04	0.00–0.19

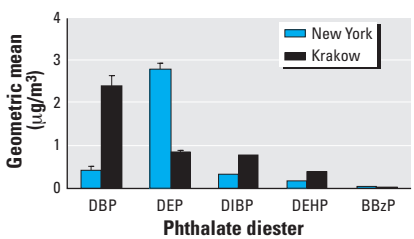

Figure 1. Comparison of geometric means of phthalates in 48-hr personal air samples.

Coulter, Palo Alto, CA, USA) based on the Jaffe rate reaction. Creatinine (reported in micrograms per deciliter) was used to adjust for variability in urine dilution. Creatinine excretion changes during pregnancy may have an effect on the validity of creatinine adjustment in the data analysis. However, in this data set, the results were essentially the same whether the data were analyzed with or without creatinine adjustment. Measures were taken to eliminate phthalate contamination from the laboratory environment, including substitution of certain materials that were shown to contain phthalates. Method blanks were used to monitor contamination. If a blank had > 5 ppb of any phthalate analyte, all the analytical results for that day were rejected until the source of contamination was identified.

Urine quantity was adequate to measure phthalate metabolite levels in 25 of 30 New York subjects for whom there were corresponding personal air samples. Eight monoester metabolites were quantified, including monoethylhexyl phthalate (mEHP), monobenzyl phthalate (mBzP), monobutyl phthalate (mBP), monoethyl phthalate (mEP), monocyclohexyl phthalate (mCHP), mono-*n*-octyl phthalate (mOP), mono-isononyl phthalate (mINP), and monomethyl phthalate (mMP). Where the values were below the limit of detection, they were set to one-half the limit of detection for that congener.

Statistical analyses. We used SPSS for Windows 11.1 (SPSS Inc., Chicago, IL, USA) for the calculation of descriptive statistics and Spearman's rank correlation coefficients. Statistical significance is set at a p-value < 0.05. The exposure and urine data are both nonnormally distributed and right-skewed. They were analyzed using nonparametric methods such as Spearman's rank. Geometric means are used to visually compare the five most prevalent phthalates in the personal air of the women in New York and Krakow using bar graphs generated by Excel (version 9.0; Microsoft, Redmond, WA, USA). Blank adjustments for the personal air data and creatinine adjustments for the urinary metabolite data were done in SPSS.

Results

The New York sample is 70% Dominican or Dominican American and 30% African American. The Krakow women are 100% ethnically Polish. The New York study population can be characterized as low income, whereas the Krakow population is middle income by country-specific standards. The mean age of the New York women is 22 years (range, 18–31 years), and the Krakow mean age is 27 (range, 18–34 years).

The five congeners listed in Table 1 were detected in 100% of the air samples analyzed. Figure 1 shows the relative distributions of the five congeners detected in air in New York and Krakow. DEP and DBP are the two most prevalent phthalates in both New York and Krakow, although their relative proportions are reversed. DIBP and DEP are present in approximately equal amounts in Krakow.

Descriptive statistics for the four phthalates detected in 100% of urine samples are summarized in Table 2. As in the personal air samples, mEP is present in the highest concentration, followed by mBP. Results for four of the congeners analyzed (mCHP, mOP, mINP, and mMP) are not reported because they were largely nondetected values. Concentrations of the three monoesters in urine are all < 1 μg/g creatinine.

The correlations between personal air and urinary metabolite measurements for the New York women are shown in Table 3. A significant correlation between personal air and urinary measures were seen for BBzP (r = 0.65, p < 0.01), DBP (r = 0.58, p < 0.01), and DEP (p = 0.42, p < 0.05). DEHP, a larger molecule, is not significantly correlated with the internal dosimeter.

Discussion

These are the first data to demonstrate that pregnant women in New York and Krakow are exposed to a range of phthalates in their personal environments. Four phthalates were detected in 100% of the samples in New York and Krakow. DEP and DBP are present in the highest concentrations in both the air and urine. DIBP is the next highest congener in both cities.

Inhalation appears to be a significant route of exposure, given the high correlations between air and urine measures for DEP, DBP, and BBzP. This counters the general belief that ingestion of contaminated food products is the most significant exposure pathway (CERHR 2000a, 2000b, 2000c) and suggests that inhalation and possibly dermal absorption may also be determining a woman's exposure. The lack of a correlation between air and urine for DEHP and BBzP may correspond to pharmacokinetic differences between the shorter and longer chain congeners.

For the sake of comparing phthalate exposure levels in pregnant women with those in the general population, the New York sample values are compared with phthalate monoester concentrations generated as part of the 1999–2000 sampling of the National Health and Nutrition Examination Survey (NHANES) conducted by the CDC (2003). The purpose of these qualitative comparisons is to identify possible differences in phthalate exposure between pregnant women and the general population. The NHANES sample includes 2,541 nonpregnant women, pregnant women, men, and people of different age and racial/ethnic groups. These comparisons do not control for potential confounders such as geographic location, diurnal variation in metabolite levels, or season of sample collection. Another comparison is made of mBP levels in the New York women to levels in all females (≥ 6 years of age) in the NHANES sample.

Based on a crude comparison, the New York women are receiving exposures to DBP above the background levels for the United States. mBP levels in urine reported here are elevated 30–70% across percentiles compared with those seen in urine samples collected from the general population (CDC 2003). The median creatinine-adjusted level in the New York women is 2-fold higher than in the NHANES sample (42.6 vs. 21.9 μg/g creatinine) (CDC 2003). Compared with all females in the NHANES sample (n = 1,326) who were ≥ 6 years of age, the median mBP concentration in the New York women is 1.5-fold higher (42.6 vs. 28.6 μg/g creatinine). Levels of the other three urinary metabolites (mEP, mEHP, and mBzP) are similar between the New York and NHANES subjects.

These data do not allow for conclusions on potential sources of phthalates in these women's environments, because the samples were analyzed *a posteriori* and individual-level information on cosmetic use and other lifestyle

Table 2. Creatinine-adjusted phthalate monoester concentrations (μg/g creatinine) detected in 100% of urine samples in New York subjects (n = 25).

Monoester metabolite	Median	Mean ± SD	Range
mEP	236	$690 \pm 1.43 \times 10^3$	$26.7–5.52 \times 10^3$
mBP	42.6	54.4 ± 24.5	21.3–105
mBzP	12.1	26.0 ± 28.2	5.60–120
mEHP	4.60	40.5 ± 98.4	1.80–449

Table 3. Spearman's rank correlation coefficients between personal air diester concentrations and urinary monoester metabolites in a 48-hr period in the third trimester of pregnancy in New York (n = 25).

	DEHP	BBzP	DBP	DEP
mEHP	0.37	—	—	—
mBzP	—	0.65**	—	—
mBP	—	—	0.58*	—
mEP	—	—	—	0.42*

*p < 0.05; **p < 0.001.

factors was not collected. Correlations with demographic and proxy exposure variables were examined, but no clear trends emerged, largely because of small cell sizes across categories. To test the hypothesis that cosmetic use is driving these exposure levels, survey instruments are being incorporated into existing epidemiologic studies to gather detailed information on cosmetic use, timing of use in relation to sample collection, and even brand name and dose information on the cosmetics used.

There are limitations to the extrapolation of the findings to estimates of exposure levels at the population level. The sample size is small, making it difficult to draw statistical inferences. Estimates are influenced by a few extreme values. The comparisons between exposure levels in New York and Krakow should be viewed as crude and unadjusted for potential confounders including differences in the timing of the urine samples, major seasonal differences in sampling between the two cities, and differences in ventilation of the women's apartments.

The New York sample is composed of Dominican and African-American women generally with low income and low educational status. Therefore, conclusions cannot be drawn on metabolite levels among all women. By limiting the population to two racial/ethnic groups, the ability to study genetic polymorphisms specific to these populations and their relation to phthalate metabolism and endocrine disruption is increased. Polymorphisms such as the 5-α reductase deficiency in Dominican women may be of particular interest to understanding effects of *in utero* phthalate exposure on the male fetus (Cai et al. 1996; Katz et al. 1995). If racially determined genetic factors prove to be important, the ability to generalize these findings to women of other races is lost.

The estimates of urinary metabolite levels are also crude and unadjusted for factors such as enzymatic differences and diurnal variation in phthalate metabolism. Comparisons with other study populations are also not adjusted for the degree to which phthalate metabolism changes during pregnancy and other potential confounders such as geographic location, occupation, age differences, cosmetic use, and dietary patterns.

Nonetheless, the evidence indicates that pregnant women in New York and Krakow are experiencing a range of exposure levels to phthalates with some extreme values that may be associated with a biologic response. The New York women appear to be exposed at levels above background levels in the United States, which may have implications for their pregnancy and/or the fetus. These results require further investigation. A molecular epidemiologic study is being carried out to more thoroughly characterize exposures in these two cohorts and to incorporate placental markers of *in utero* endocrine disruption that may be related to placental function and pregnancy outcomes.

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