

In Utero Exposure to Di-(2-ethylhexyl)phthalate and Duration of Human Pregnancy

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Di-(2-ethylhexyl)phthalate (DEHP), the most commonly used plasticizer in flexible polyvinylchloride formulations, is a ubiquitous environmental contaminant. To date, no information exists on the potential health hazards from exposure to DEHP and/or its main metabolite, mono-(2-ethylhexyl)phthalate (MEHP), in high-risk conditions, such as pregnancy and during the neonatal period. The aim of this study was to evaluate prenatal exposure to DEHP and/or MEHP and its possible biologic effects. We measured serum DEHP and MEHP concentrations in the cord blood of 84 consecutive newborns by high-performance liquid chromatography. Relationships between DEHP/MEHP and infant characteristics were tested using Fisher's exact test, unpaired *t*-tests, and univariate linear regression analyses, and significant differences on univariate analysis were evaluated using multiple logistic regression analysis. We found detectable cord blood DEHP and/or MEHP concentrations in 88.1% of the samples. Either DEHP or MEHP was present in 65 of 84 (77.4%) of the examined samples. Mean concentrations of DEHP and MEHP were 1.19 ± 1.15 $\mu\text{g/mL}$ [95% confidence interval (CI), 0.93–1.44, range = 0–4.71] and 0.52 ± 0.61 $\mu\text{g/mL}$ (95% CI, 0.39–0.66, range = 0–2.94), respectively. MEHP-positive newborns showed a significantly lower gestational age compared with MEHP-negative infants ($p = 0.033$). Logistic regression analysis results indicated a positive correlation between absence of MEHP in cord blood and gestational age at delivery (odds ratio = 1.50, 95% CI, 1.013–2.21; $p = 0.043$). These findings confirm that human exposure to DEHP can begin *in utero* and suggest that phthalate exposure is significantly associated with a shorter pregnancy duration. **Key words:** di-(2-ethylhexyl)phthalate, environmental hazards, gestational age, mono-(2-ethylhexyl)phthalate, prenatal exposure. *Environ Health Perspect* 111:1783–1785 (2003). doi:10.1289/ehp.6202 available via <http://dx.doi.org/> [Online 18 August 2003]

Phthalate esters are used widely as plasticizers for polyvinylchloride (PVC) formulations in several applications, including medical devices, toys, food wraps, and building products, to impart flexibility to an otherwise rigid PVC. Di-(2-ethylhexyl)phthalate (DEHP) is the most commonly used plasticizer. Because DEHP does not bind with the plastic, it leaches with time and use from vinyl products, thus becoming a ubiquitous environmental contaminant (Bauer and Herrmann 1997; Bradbury 1996; Giam et al. 1978; Griffiths et al. 1985; Mayer et al. 1972; Mes et al. 1974; Øie et al. 1997; Sharman et al. 1994). In particular, leaching of DEHP from PVC medical devices and deposits in tissue have been well documented (Latini 2000; Tickner et al. 2001). Because the DEHP action depends on dose, time, and age (Latini 2000) and because DEHP effects are influenced by the stage of development at exposure among animals (Akingbemi et al. 2001), the DEHP-related exposure risk is potentially higher for the developing fetus and newborn, particularly preterm. Recently, our preliminary findings indicated that the exposure to these environmental contaminants begins during intrauterine life, that these chemicals are able to cross the placental barrier, and that

fetal exposure is closely related to maternal exposure (Latini et al. 2003). The aim of this study was to measure concentrations of DEHP and/or its main metabolite, mono-(2-ethylhexyl)phthalate (MEHP), in a larger population of human neonates and to evaluate possible biologic effects from prenatal exposure to DEHP and/or MEHP.

Patients and Methods

Subjects. Cord blood samples were collected from 84 consecutive newborns (82 singletons, two twins), born at the general-practice Brindisi Hospital, with the following characteristics: 39 male, 45 female; maternal age at delivery, 29.5 ± 5.1 years (range = 18–42); vaginal delivery, $n = 65$ (77.4%); gestational age, 38.4 ± 2.2 weeks (range = 27–42); birth weight, $3,220 \pm 680$ g, (range = 1,150–4,350); 1-min Apgar score, 7.9 ± 0.9 ; 5-min Apgar score, 8.8 ± 0.5 . Eleven of 84 infants were preterm; only three had very low birth weight. Moreover, four infants who were small for gestational age (SGA) were present in our population. None of the examined infants was born after *in vitro* fertilization pregnancy. The study was approved by the ethics committee of the Brindisi Hospital (Brindisi, Italy), and written informed consent from the parents

was obtained. Blood specimens were immediately centrifuged ($3,500 \times g$, 7 min), and serum was stored at -20°C until assay. To avoid any contamination from plasticizers in lab equipment, the serum sample collection, preservation, and treatment were performed only with glass devices. The concentrations of DEHP and MEHP were determined by high-performance liquid chromatography, at the Department of Chemistry of the University of L'Aquila, an institution certified in agreement with the International Organization for Standardization 9001 quality system, as described previously (Paris et al. 2003).

Data analysis. Data are expressed as mean \pm SD. Pairwise differences between groups were assessed using either Fisher's exact test (categorical variables) or unpaired *t*-tests (continuous variables). The relation between presence of phthalates in the cord blood and potential prenatal risk factors was evaluated using univariate analysis (MedCalc for Windows, version 7.0; MedCalc Software, Mariakerke, Belgium). The effects of potential confounders on the presence of DEHP/MEHP in the cord blood were also examined by using multivariable logistic regression models (SPSS release 6.1 statistical package; SPSS Inc., Chicago, IL, USA). Factors with p -values < 0.25 at univariate analysis were included in the multivariable logistic regression models. The p -values were assessed by using pairwise comparisons of each end point with explanatory variables, excluding the others. A two-sided p -value < 0.05 was considered statistically significant, and the Bonferroni-corrected significance levels were used for multiple *t*-tests.

Results

DEHP, MEHP, or both were present in 74 of 84 (88.1%) of the examined cord serum samples. DEHP and MEHP were each present in 65 of 84 (77.4%) of the examined samples. Mean concentrations of DEHP and MEHP were 1.19 ± 1.15 $\mu\text{g/mL}$ [95% confidence interval (CI), 0.93–1.44, range = 0–4.71] and

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