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Internal phthalate exposure over the last two decades – A retrospective human biomonitoring study

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Abstract

In a retrospective human biomonitoring study we analyzed 24 h urine samples taken from the German Environmental Specimen Bank for Human Tissues (ESBHum), which were collected from 634 subjects (predominantly students, age range 20–29 years, 326 females, 308 males) in 9 years between 1988 and 2003 (each $n \geqslant 60$), for the concentrations of primary and/or secondary metabolites of di-*n*-butyl phthalate (DnBP), di-iso-butyl phthalate (DiBP), butylbenzyl phthalate (BBzP), di(2-ethylhexyl) phthalate (DEHP) and di-iso-nonyl phthalate (DiNP). Based on the urinary metabolite excretion we estimated daily intakes of the parent phthalates and investigated the chronological course of the phthalate exposure. In over 98% of the urine samples metabolites of all five phthalates were detectable indicating a ubiquitous exposure of the German population to all five phthalates throughout the last 20 years. The median daily intakes in the subsets between 1988 and 1993 were quite constant for DnBP (approx. 7 μg/kg bw/d) and DEHP (approx. 4 μg/kg bw/d). However, from 1996 the median levels of both phthalates decreased continuously until 2003 (DnBP 1.9 μg/kg bw/d; DEHP 2.4 μg/kg bw/d). By contrast, the daily intake values for DiBP were slightly increasing over the whole time frame investigated (median 1988: 1.1 μg/kg bw/d; median 2003: 1.4 μg/kg bw/d), approximating the levels for DnBP and DEHP. For BBzP we observed slightly decreasing values, even though the medians as of 1998 levelled off at around 0.2 μg/kg bw/d. Regarding daily DiNP exposure we found continuously increasing values, with the lowest median being 0.20 μg/kg bw/d for the subset of 1988 and the highest median for 2003 being twice as high. The trends observed in phthalate exposure may be associated with a change in production and usage pattern. Female subjects exhibited significantly higher daily intakes for the dibutyl phthalates (DnBP $p = 0.013$; DiBP $p = 0.004$). Compared to data from US National Health and Nutrition Examination Surveys (NHANES) exposure levels of the dibutyl phthalates were generally higher in our German study population, while levels of BBzP were somewhat lower. Overall, for a considerable 14% of the subjects we observed daily DnBP intakes above the tolerable daily intake (TDI) value deduced by the European Food Safety Authority (EFSA) (10 μg/kg bw/d). However, the frequency of exceedance decreased during the years and was beneath 2% in the 2003 subset. Even though transgressions of the exposure limit values of the EFSA and the US

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Environmental Protection Agency (US EPA) occurred only in a relatively small share of the subjects, one has to take into account the cumulative exposure to all phthalates investigated and possible dose-additive endocrine effects of these phthalates.

Keywords: Phthalates; Di-*n*-butyl phthalate; Di-iso-butyl phthalate; Butylbenzyl phthalate; Di(2-ethylhexyl) phthalate; Di-iso-nonyl phthalate; Biomonitoring; Daily intake

Introduction

Phthalate diesters have been used commercially in a large variety of industrial and consumer applications for about one century now. Linked to the development of polyvinyl chloride (PVC) in the late 1920s the large scale production and application of the phthalates has begun (Lorz et al., 2002). Currently over 1 million tons of phthalates are produced annually in Western Europe alone (AgPU, 2006; Cadogan, 2006).

The major field of application for phthalates is the usage as general-purpose plasticizers in polymers, primarily in PVC. Typical products containing phthalates are floorings, roofings, wall coverings, cables, sealants, coatings, paints, clothing, packaging materials, toys, lacquers and adhesives (ECB, 2003, 2004a, b, 2006; Lorz et al., 2002). DEHP is still the major plasticizer for PVC-containing medical devices like bags for blood or parenteral nutrition, tubings and catheters (FDA, 2001; Green et al., 2005; Health Canada, 2002). DnBP is used in the pharmaceutical field as a constituent of gastric juice resistant coating of capsules (FDA, 2006; Hauser et al., 2004; Koch et al., 2004c).

Some phthalates have been shown to produce adverse effects on reproduction and development in rodents, e.g., di-*n*-butyl phthalate (DnBP) (Barlow and Foster, 2003; Foster et al., 2000; Lee et al., 2004; Mylchreest et al., 2000), di-iso-butyl phthalate (DiBP) (Borch et al., 2006; Saillenfait et al., 2006), butylbenzyl phthalate (BBzP) (Nagao et al., 2000; Tyl et al., 2004), di(2-ethylhexyl) phthalate (DEHP) (Gray et al., 2000; Parks et al., 2000; Wolfe and Layton, 2003) and di-iso-nonyl phthalate (DiNP) (Borch et al., 2004; Gray et al., 2000). The reproductive abnormalities in offspring range from diminished birth weight and reduced survival rate to malformations of the external genitalia, undescended testicles (cryptorchidism), retention of nipples/areolae or reduced anogenital distance in male rodents. Moreover, an impaired spermatogenesis and a general reduction of male fertility have been observed. Most of these effects are probably caused by a modulation of testicular testosterone levels (Akingbemi et al., 2001; Parks et al., 2000; Sharpe and Irvine, 2004). Phthalates are suspected of acting as endocrine disrupters also in humans, effecting male reproductive tract development (Akingbemi et al., 2004; Fisher, 2004; Hoppin, 2003; Liu et al., 2005; Sharpe and Irvine, 2004; Shelby, 2002; Swan et al., 2005; Wilson et al., 2004).

Because of their large and widespread use phthalates are taken up by the general population from various sources (Clark et al., 2003; Doull et al., 1999; Meek and Chan, 1994; Wormuth et al., 2006). Since exposure to phthalates may be harmful to human health several authorities such as the European Food Safety Authority (EFSA) or the US Environmental Protection Agency (US EPA) have deduced exposure limit values for some phthalates (EFSA, 2005a–d; EPA, 1990, 1991, 1993). For purposes of health prevention, it is necessary to determine the human phthalate doses taken up by humans and if necessary to reduce exposure. An assessment of the internal phthalate exposure is generally possible by measuring the amount of specific metabolites excreted via urine (Blount et al., 2000; CDC, 2005; Koch et al., 2003c). With the knowledge of human metabolism and elimination properties of the metabolites measured as a precondition (Anderson et al., 2001; Koch and Angerer, 2007; Koch et al., 2004a, 2005; Schmid and Schlatter, 1985), daily phthalate intakes are deducible from urinary metabolite levels (David, 2000; Kohn et al., 2000; Koch et al., 2003a, 2007a; Wittassek et al., 2007).

In a retrospective biomonitoring study we determined metabolites of five of the most important phthalates (DnBP, DiBP, BBzP, DEHP, DiNP) in urine samples of the German Environmental Specimen Bank for Human Tissues (ESBHum), which have been collected during the last 20 years. Additionally, we deduced daily intakes from these urinary concentrations. The purpose of this study was to elucidate the internal exposure to phthalates during the last two decades.

Materials and methods

Subjects and urine specimens

We analyzed 24 h urine samples of 634 volunteers, predominantly students (age range 20–29 years, 326 females, 308 males), collected between 1988 and 2003 at the University of Münster (Germany). The sampling years, the sample size per sampling year, the age and sex distribution of the study population are given in Table 1. The urine samples were collected by the ESBHum which