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Phthalate metabolites in obese individuals undergoing weight loss: Urinary levels and estimation of the phthalates daily intake

Alin C. Dirtu [a,*], Tinne Geens [a], Eveline Dirinck [b], Govindan Malarvannan [a], Hugo Neels [a], Luc Van Gaal [b], Philippe G. Jorens [c], Adrian Covaci [a,*]

[a] Toxicological Centre, University of Antwerp, Wilrijk, Antwerp, Belgium
[b] Departments of Endocrinology, Diabetology and Metabolic Disease, University of Antwerp and Antwerp University Hospital, Edegem, Antwerp, Belgium
[c] Department of Clinical Pharmacology, University of Antwerp and Antwerp University Hospital, Edegem, Antwerp, Belgium

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ABSTRACT

Human exposure to chemicals commonly encountered in our environment, like phthalates, is routinely assessed through urinary measurement of their metabolites. A particular attention is given to the specific population groups, such as obese, for which the dietary intake of environmental chemicals is higher. To evaluate the exposure to phthalates, nine phthalate metabolites (PMs) were analyzed in urine collected from obese individuals and a control population. Obese individuals lost weight through either bariatric surgery or a conservative weight loss program with dietary and lifestyle counseling. Urine samples were also collected from the obese individuals after 3, 6 and 12 months of weight loss. Individual daily intakes of the corresponding phthalate diesters were estimated based on the urinary PM concentrations. A high variability was recorded for the levels of each PM in both obese and control urine samples showing the exposure to high levels of PMs in specific subgroups. The most important PM metabolite as percentage contribution to the total PM levels was mono-ethyl phthalate followed by the metabolites of di-butyl phthalate and di 2-ethyl-hexyl phthalate (DEHP). No differences in the PM levels and profiles between obese entering the program and controls were observed. Although paralleled by a significant decrease of their weight, an increase in the urinary PM levels after 3 to 6 months loss was seen. Constant figures for the estimated phthalates daily intake were observed over the studied period, suggesting that besides food consumption, other human exposure sources to phthalates (e.g. air, dust) might be also important. The weight loss treatment method followed by obese individuals influenced the correlations between PM levels, suggesting a change of the intake sources with time. Except for few gender differences recorded between the urinary DEHP metabolites correlations, no other differences were observed for the urinary PM levels as a function of age, body mass index or waist circumference. Linear regression analysis showed almost no significance of the relationship between measured urinary PMs and serum free thyroxine, thyroid-stimulating hormone (TSH) for all obese individuals participating to the study, while for the control samples, several PMs were significantly associated with the serum TSH levels.

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1. Introduction

Phthalates are components of multiple consumer products, including personal care products (cosmetics, perfumes), building materials, textiles, food packaging, paints, adhesives, children's toys, certain medical devices (especially those containing PVC) and pharmaceuticals (ATSDR, 1995, 2001, 2002). Since they are not chemically bound to the end-products, they gradually migrate into the environment resulting in human exposure via multiple pathways, including ingestion, inhalation and dermal contact. After intake and absorption, phthalates are rapidly hydrolyzed to their respective monoesters and, depending on the phthalate, they might undergo further biotransformation to oxidative metabolites. However, all phthalate metabolites (PMs) are glucuronidated before excretion in urine or feces (ATSDR, 1995, 2001, 2002). Due to the widespread presence of phthalates in

Abbreviations: 5Cx-MEPP, mono-(2-ethyl-5-carboxypentyl) phthalate; 5HO-MEHP, mono-(2-ethyl-5-hydroxyhexyl) phthalate; 5Oxo-MEHP, mono-(2-ethyl-5-oxohexyl) phthalate; BBzP, butyl-benzyl phthalate; BMI, body mass index; BW, body weight; DEHP, di-2-ethylhexyl phthalate; DEP, diethyl phthalate; DI, daily intake; D*i*BP, di-*iso*-butyl phthalate; D*i*NP, di-*iso*-nonyl phthalate; DMP, dimethyl phthalate; D*n*BP, di-*n*-butyl phthalate; FT4, free thyroxine; LOD, limit of detection; LOQ, limit of quantification; MBzP, mono-benzyl phthalate; MEHP, mono-(2-ethylhexyl) phthalate; MEP, mono-ethyl phthalate; M*i*BP, mono-*iso*-butyl phthalate; MMP, mono-methyl phthalate; M*n*BP, mono-*n*-butyl phthalate; PM, phthalate metabolite; PPAR, peroxisome proliferator-activated receptor; QA/QC, Quality assurance/Quality control; TDI, tolerable daily intake; TSH, thyroid-stimulating hormone; WC, waist circumference.

* Corresponding authors at: Toxicological Center, University of Antwerp, Universiteitsplein 1, 2610 Wilrijk, Belgium. Tel.: +32 3 265 2498; fax: +32 3 265 2722.
E-mail addresses: alin.dirtu@gmail.com (A.C. Dirtu), adrian.covaci@ua.ac.be (A. Covaci).

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various environments, their direct monitoring is problematic since multiple contamination pathways might influence or even alter their chemical measurement. The monitoring of PMs in urine is more convenient given the relatively short half-life of phthalates in humans (6–24 h) and since it avoids external contamination with the parent compounds (Koch et al., 2007).

Several studies already documented the human exposure to phthalates through PM urinary measurement (Boas et al., 2010; Frederiksen et al., 2011; Hines et al., 2009; Koch et al., 2011). Other studies also showed various associations between human exposure levels to PMs and health outcomes (Meeker et al., 2009), including signs of decreased androgenic action, such as hypospadias, decreased anogenital distance and altered endogenous reproductive hormone levels in infant boys (Main et al., 2006; Ormond et al., 2009), associations with decreased semen quality (Hauser et al., 2006). Due to the effect on insulin resistance (Lind et al., 2012a, 2012b; Stahlhut et al., 2007), they were suggested to be related to diabetes prevalence (James-Todd et al., 2012; Lind et al., 2012a, 2012b). Additionally, several phthalates were classified as potential carcinogens, as well as endocrine disruptors in humans (ECHA, 2008a, 2008b; Oomen et al., 2008) and restrictions on the phthalates applicability were issued worldwide. At the European level, we mention the directives from the European Commission restricting the use of di-*n*-butyl phthalate (D*n*BP), butylbenzyl phthalate (BBzP), di-(2-ethylhexyl) phthalate (DEHP) and di-*iso*-nonyl phthalate (D*i*NP) in several consumer products, such as toys and childcare for small children (Decision 2005/84/EC), cosmetics, paints and glues (Decision 2004/93/EC) and food contact materials (Decision 2007/19/EC).

There are several reports suggesting the widespread and substantial contamination of the indoor environment with phthalates, e.g. air and dust (Bergh et al., 2010; Nagorka et al., 2005; Rudel and Perovich, 2009). Food is of special concern for human exposure, while indoor air or dust contamination may play an important role depending on the time spent indoors and on the quality of the indoor environment. In the case of dietary intake, people with increased food intake, such as obese individuals, may need special attention. Since PMs are peroxisome proliferator-activated receptors (PPAR) agonists, they are capable of influencing glucose homeostasis and adipogenesis (Staels, 2007). Therefore, it is not surprising that recent literature has shown an increasing interest over the intake, dynamics and possible effects of several contaminants, including PMs, possibly linked to obesity.

In the light of the above, we aimed to: 1) compare the PM urinary levels in an obese and control population sampled in Belgium; 2) evaluate the dynamics of urinary PM levels in obese individuals during one year of weight loss; 3) estimate the PM daily intake (DI_{PMs}) and evidence intake differences during weight loss based on normal intake scenarios and excretion fractions reported for PMs in humans; 4) link PM urinary levels to anthropometric data; and 5) evaluate variations in the exposure sources depending on the treatment method used for weight loss in the obese individuals.

2. Materials and methods

2.1. Sample collection

The ENDORUP trial, conducted at the weight management clinic of the Department of Endocrinology, Diabetology and Metabolism of the Antwerp University Hospital, was a prospective study designed to investigate the hypothesis of endocrine disruption by POPs in obesity (registered at clinicaltrials.gov number NCT01778868). A cohort of 152 adult overweight and obese individuals was prospectively selected from patients visiting the weight management clinic between November 2009 and February 2012. A control group of 43 adult lean men and women, matched by age and sex, was recruited from hospital staff and volunteers during the same period. Anthropometric measures were taken in the morning with patients in a fasting state and undressed. Height was measured to the nearest 0.5 cm and body weight (BW) was measured with a digital scale (with a precision of 0.2 kg). Waist circumference (WC) was measured at the mid-level between the lower rib margin and the iliac crest. The subject characteristics are described in Table 1. Urine samples were taken before weight loss (*0M*, N = 152) and after three (*3M*, N = 95), six (*6M*, N = 53) and twelve months (*12M*, N = 39). The day prior to the in hospital investigations, 24-hour urine was collected at home in phthalate free containers. Urinary creatinine concentration was measured using an enzymatic method. Phthalate metabolite concentrations were adjusted for urinary dilution by creatinine levels. The study was approved by the Ethical Committee of the Antwerp University Hospital and all participants provided their written informed consent.

2.2. Target analytes

Nine phthalate metabolites were targeted for analysis in this study, namely: mono-methyl phthalate (MMP), mono-ethyl phthalate (MEP), mono-(2-ethyl-5-carboxypentyl) phthalate (5Cx-MEPP), mono-(2-ethyl-5-hydroxyhexyl) phthalate (5HO-MEHP), mono-(2-ethyl-5-oxohexyl) phthalate (5Oxo-MEHP), mono-(2-ethylhexyl) phthalate (MEHP), mono-*iso*-butyl phthalate (M*i*BP), mono-*normal*-butyl phthalate (M*n*BP) and mono-benzyl phthalate (MBzP). A complete list including detailed and abbreviated nomenclature used in this manuscript for all targeted analytes together with additional information concerning their analysis (e.g. internal standards (ISs) used for their quantification, ions used for the analytes quantification/qualification, instrumental technique) is given in Table SI.1. All individual standards of PMs together with their corresponding labeled ISs were obtained from Cambridge Isotope Laboratories, Inc. (Andover, MA, USA).

2.3. Sample preparation and analysis

Sample preparation protocol for analysis of the PMs was applied on 1 mL of urine fortified with 25 ng of each of the ^{13}C-labeled PMs (see Table SI.1 for additional details). To ensure complete deconjugation of PMs, 35 μL of β-glucuronidase/arylsulphatase (from Helix Pomatia, corresponding to ≈1 IUI enzyme per mL of urine) (Merck, Darmstadt, Germany) and 250 μL of phosphate buffer solution (pH = 6) were added to the urine and the mixture was kept at 37 °C for 90 min. The samples were further diluted with 1 mL of MilliQ water and extracted using Oasis MAX (30 mg/3 mL, Waters, Milford, MA, USA). Afterwards, the sorbent bed was washed with MeOH containing 5% NH_4OH, followed with MilliQ water and dried under vacuum. Elution of PMs was performed using 5 mL of MeOH containing 2% formic acid. The eluate was evaporated to dryness, reconstituted in 100 μL acetonitrile, the extract was filtrated using centrifugal filters of 0.45 μm pore size (VWR International), and injected into a LC(ESI)-MS/MS system (liquid chromatograph 1200 Series coupled to a 6410 Triple Quad mass spectrometer, Agilent, USA). Additional instrumental conditions employed for the analysis of PMs are given in Table SI.2. All solvents used in analyses (MeOH, acetonitrile) were of gradient grade for liquid chromatography and they were obtained from Merck (Darmstadt, Germany). Formic acid (98–100%) was from Merck and NH_4OH (aqueous solution of 28–30%) was acquired from Sigma-Aldrich. All glassware was soaked for 12 h in an alkali solution (diluted RBS T 105, pH 11–12) and after washing, glassware was rinsed with water and dried overnight at 400 °C. Prior to use, glassware was rinsed with acetonitrile.

2.4. Quality assurance/Quality control (QA/QC)

For implementation and to ensure reliability of the data obtained for the PMs targeted in our study, several validation parameters (calibration linearity, accuracy, precision, and method limits of detection

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