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Human biomonitoring of phthalate exposure in Austrian children and adults and cumulative risk assessment

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ABSTRACT

Phthalates are a class of chemicals widely used as plasticisers in a multitude of common consumer products. Through contact with such products, people are regularly exposed to phthalates, which are suspected to contribute to adverse health effects, particularly in the reproductive system.

In the present study, 14 urinary phthalate metabolites of 10 parent phthalates were analysed by HPLC–MS/MS among the Austrian population aged 6–15 and 18–81 years in order to assess phthalate exposure. In the total study population, ranges of urinary phthalate metabolite concentrations were n.d.–2,105 μg/l (median 25 μg/l) for monoethyl phthalate (MEP), n.d.–88 μg/l (10 μg/l) for mono-*n*-butyl phthalate (MnBP), n.d.–248 μg/l (28 μg/l) for mono-isobutyl phthalate (MiBP), n.d.–57 μg/l (1.8 μg/l) for mono-benzyl phthalate (MBzP), n.d.–20 μg/l (n.d.) for mono-(2-ethylhexyl) phthalate (MEHP), n.d.–80 μg/l (2.6 μg/l) for mono-(2-ethyl-5-hydroxyhexyl) phthalate (5OH-MEHP), n.d.–57 μg/l (1.9 μg/l) for mono-(2-ethyl-5-oxohexyl) phthalate (5oxo-MEHP), n.d.–219 μg/l (11 μg/l) for mono-(5-carboxy-2-ethylpentyl) phthalate (5cx-MEPP), n.d.–188 μg/l (1.6 μg/l) for 3-carboxy-mono-proply phthalate (3cx-MPP), n.d.–5.5 μg/l (n.d.) for mono-cyclohexyl phthalate (MCHP), n.d.–4.5 μg/l (n.d.) for mono-*n*-pentyl phthalate (MnPeP), n.d.–3.4 μg/l (n.d.) for mono-*n*-octyl phthalate (MnOP), n.d.–13 μg/l (n.d.) for mono-isononyl phthalate (MiNP), and n.d.–1.1 μg/l (n.d.) for mono-isodecyl phthalate (MiDP). Generally, children exhibited higher levels of exposure to the majority of investigated phthalates, except to MEP, which was found in higher concentrations in adults and senior citizens at a maximum concentration of 2,105 μg/l. Individual daily intakes were estimated based on urinary creatinine and urinary volume excretion and were then compared to acceptable exposure levels, leading to the identification of exceedances of mainly the Tolerable Daily Intakes (TDI), especially among children. The execution of a cumulative risk assessment based on Hazard Indices showed cause for concern mainly for children, as well as in rare cases for adults.

Although phthalate exposure seems to have decreased in previous years, the wide distribution and existing exceedances of acceptable levels indicate that phthalate exposure should be further monitored in order to identify exposure sources and enable appropriate minimisation measures.

Introduction

Phthalates are the di-esters of 1,2-benzenedicarboxylic acid and a group of man-made environmental chemicals which are produced worldwide in high annual amounts and are primarily used as plasticisers in the production of polyvinyl chloride (PVC), accounting for 87% of the annual global plasticiser production (EAG (Environmental Agency Germany), 2011). Depending on their molecular weight, they are used for divergent applications and can be found in a wide range of consumer products (ECB (European Chemicals Bureau), 2003, 2008; ECHA (European Chemicals Agency), 2009, 2013c; Danish EPA (Danish Environmental Protection Agency), 2011; Hauser and Calafat, 2005; NRC (National Research Council), 2008).

Because phthalates are not chemically bound to the polymer structures of products and articles, they are able to migrate continuously from surfaces into food and environment (Navarro et al.,

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2010; Wormuth et al., 2006), which can lead to human exposure by various routes. Following uptake into the body, phthalates are rapidly absorbed, metabolised by hydrolysis and subsequent oxidation and excreted via urine and faeces. More than 95% of an administrated oral dose of a phthalate is eliminated as the corresponding metabolite(s) through renal excretion within 24 h (Hauser and Calafat, 2005; Koch and Angerer, 2012; Zeman et al., 2013).

Although they are rapidly excreted, particular attention has been paid to phthalates for many years especially because of their endocrine-disrupting effects and toxicity to reproduction (EC (European Commission), 2011; Danish EPA (Danish Environmental Protection Agency), 2013; Kortenkamp et al., 2011). Several phthalates have been identified as endocrine-disrupting chemicals (EDCs) acting as anti-androgens, estrogens, anti-estrogens or inhibitors of steroidogenic enzymes in the body, as well as with thyroid hormones and their related receptors (Fisher, 2004). Anti-androgenic and/or thyroid endocrine disrupting phthalates include DnBP, DiBP, BBzP and DEHP, and additionally, DEP is included in the EU list of potential endocrine disruptors (Danish EPA (Danish Environmental Protection Agency), 2013). Studies in experimental animals as well as in humans have shown phthalates leading to diverse adverse health effects reported elsewhere (ECB (European Chemicals Agency), 2008; ECHA (European Chemicals Agency), 2008, 2013a, 2013b, 2014a, 2014b; Braun et al., 2013; Bornehag and Nanberg, 2010; Hauser and Calafat, 2005; Jaakkola and Knight, 2008; Jurewicz and Hanke, 2011; Kay et al., 2013; Kimber and Dearman, 2010; Latini et al., 2006; Matsumoto et al., 2008; Meeker et al., 2009; Swan, 2008). Some phthalates such as DEHP and DiBP are known to induce peroxisome proliferator-activated receptors (PPAR), which play important roles in the regulation of a variety of biological processes, such as adipocyte proliferation and differentiation, glucose homeostasis, intracellular trafficking of lipids and their metabolism, inflammatory responses, vascular functions and embryonic and fetal development (Lau et al., 2010).

Because of the concern regarding phthalates as substances produced and used in high amounts and in a wide range of consumer products, as well as their identified adverse effects on human health, investigations of exposures to populations are of high importance. The present study is one of the first comprehensive investigations of the phthalate exposure of the population in Austria based on data and samples from the Austrian Study of Nutritional Status 2010/2012 (ASNS) performed by the Department of Nutritional Sciences of the University of Vienna. Therefore, phthalate metabolite concentrations were analysed in spontaneous urine samples of a large sample including children and adolescents (6–15 years), adults (18–64 years) and senior citizens (≥65 years) and were used for calculations of daily intakes (DIs) and cumulative risk assessment estimations. The observed findings were compared to Tolerable Daily Intake values (TDI) set out by the European Food Safety Authority (EFSA) (EC (European Commission), 2013; EFSA (European Food Safety Authority), 2005a, 2005b, 2005c, 2005d, 2005e), to the Reference Doses (RfD) set out by the U.S. EPA (United States Environmental Protection Agency) (2007b) and to the References Doses for Anti-Androgenicity (RfD AA) established by Kortenkamp and Faust (2010). Additionally, comparisons with results obtained from several studies, especially from other European countries, were performed in order to identify potential differences and trends in phthalate exposure.

Materials and methods

Study design and study population

The Austrian Study on Nutritional Status (ASNS) performed by the Department of Nutritional Sciences of the University of Vienna comprised a total of 1002 participants including 387 male and female children and adolescents aged 6–15 years, 419 male and female adults aged 18–64 years and 196 male and female senior citizens aged 65–81 years through a quota sampling of a cross-sectional study. The recruitment of children and adolescents occurred in selected Austrian schools in almost all federal states and of adults and senior citizens via companies, municipal offices, clubs and retirement homes. Detailed recruitment and sampling procedures were described in Elmadfa et al. (2012). The fieldwork took place between 2010 and 2012, with data on nutrition, education, employment and health status being collected via questionnaires, and spontaneous urine samples taken were collected before midday.

For the analysis of phthalate exposure, the surveyed data and the urine samples of more than a half of the within ASNS recruited participants were sent to the Environment Agency Austria (EAA) in dependence of the availability of sufficient sample material, including a total of 595 participants comprising 251 children and adolescents aged 6–15 years (142 males and 109 females), 272 adults aged 18–64 years (mean age 39.1 years; 110 males and 162 females), and 72 senior citizens aged 65–81 years (mean age 71.4 years; 34 males and 38 females) being investigated. Due to the recruitment procedure, the group of children and adolescents was further divided into two subgroups according to the level of education: Children I for those aged 6–8 years from the 1st and 2nd levels of education, and Children II for those aged 7–15 years from the 3rd to 8th levels of education. For this reason, small overlaps in age exist between members of the two subgroups. Questionnaires completed by younger children were amended by additional questionnaires given to their respective parents. Study participants originated from almost all Austrian federal states. For investigations of potential regional differences, the study population was grouped according to their residence, with 229 participants living in rural and 284 participants in urban or suburban areas.

The study was approved by the ethics commission of the City of Vienna (EK_10_037_0310).

Chemical analysis

Concentrations of 14 urinary phthalate metabolites (Table 1) were measured by high-performance liquid chromatography tandem-mass spectrometry (HPLC–MS/MS) for simultaneous determination of several metabolites after enzymatic hydrolysis with beta-glucuronidase, an implemented and accredited method developed by the EAA, which was adapted from Koch et al. (2003c) and Preuss et al. (2005), and was extended to the metabolites MCHP, MnPeP, MiNP, MiDP and 3cx-MPP. Validation data for the metabolites also described in Koch et al. (2003c) and Preuss et al. (2005) are comparable. Detailed description of analysis and validation data is published in Hartmann (2014).

The HPLC system used in this study was an Agilent Technologies 1290 Infinity Series (Agilent Technologies, Santa Clara, CA, USA), and the MS detector system was an AB Applied Biosystem MDS SCIEX 4000 QTRAP LC/MS/MS System (AB Sciex Technologies, Framingham, MA, USA) which allowed detection through specific mass transitions in electrospray (ESI) negative mode, and quantification in multiple reaction monitoring (MRM) mode. The analytical column was a Kinetex 2.6μ Phenyl-Hexyl 100A LC Column (Phenomenex, USA).

The limit of quantitation (LOQ) for each substance was determined according to DIN 32645 (see DIN, 2008). Limits of detection (LOD) were set as half of the respective LOQ and were 2.5 μg/l for MEP, 0.53 μg/l for MnBP, 0.59 μg/l for MiBP and MBzP, 0.69 μg/l for MEHP, 0.79 μg/l for 5OH-MEHP, 0.56 μg/l for 5oxo-MEHP, 0.46 μg/l for 5cx-MEPP, 1.6 μg/l for 3cx-MPP, 0.51 μg/l for MCHP, 0.55 μg/l