International Journal of Hygiene and Environmental Health xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

International Journal of Hygiene and Environmental Health

journal homepage: www.elsevier.com/locate/ijheh

Austrian reference values for phthalate metabolite exposure in children/adolescents and adults

Christina Hartmann[a,b,*], Maria Uhl[a], Stefan Weiss[a], Sigrid Scharf[a], Jürgen König[b]

[a] Environment Agency Austria, Vienna, Austria
[b] Department of Nutritional Sciences, University of Vienna, Vienna, Austria

ARTICLE INFO

Keywords:
Human biomonitoring
Reference values
Phthalate metabolites
Urine
Austria

ABSTRACT

Reference values (RV_{95}) are statistically derived values comprising the rounded 95th percentiles within the 95% confidence interval and indicate the upper margin of background exposure to chemical substances in a population at a given time period. Based on representative national human biomonitoring data on several urinary phthalate metabolites in children, adolescents and adults from 2010 to 2011, RV_{95} were derived for the Austrian population based on a IUPAC guideline and the recommendation of the German Human Biomonitoring Commission. The RV_{95} (rounded values) for phthalate metabolites in children and adolescents aged 6–15 years are 110 µg/l (confidence interval of 95th population percentile: 83.7–163) for mono-ethyl phthalate (MEP), 45 µg/l (40.9–60.6) for mono-*n*-butyl phthalate (MnBP), 130 µg/l (126–161) for mono-isobutyl phthalate (MiBP), 25 µg/l (17.8–33.6) for mono-benzyl phthalate (MBzP), 100 µg/l (94.0–126) for the sum of the di(2-ethylhexyl) phthalate (DEHP) metabolites including mono(2-ethylhexyl) phthalate (MEHP), mono(2-ethyl-5-hydroxyhexyl) phthalate (5OH-MEHP), mono(2-ethyl-5-oxohexyl) phthalate (5oxo-MEHP) and mono(2-ethyl-5-carboxypentyl) phthalate (5cx-MEPP), and 1.5 µg/l (0.64–1.6) for mono-cyclohexyl phthalate (MCHP). In adults aged 18–81 years, RV_{95} are 440 µg/l (353–636) for MEP, 40 µg/l (33.1–52.1) for MnBP, 110 µg/l (87.3–118) for MiBP, 10 µg/l (7.2–11.8) for MBzP, 50 µg/l (44.6–68.3) for the sum of MEHP, 5OH-MEHP, 5oxo-MEHP and 5cx-MEPP, and 1.5 µg/l (0.95–1.8) for MCHP. For almost all investigated metabolites, children and adolescents exhibit higher RV_{95} than adults, with the exceptions being MEP and MCHP. Compared to available RV_{95} for Germany and Canada, Austrian values are lower for all investigated population groups.

1. Introduction

Phthalates are a group of man-made environmental chemicals used as plasticizers mainly in the products of polyvinyl chloride (PVC) (German Environment Agency, 2011). They are produced globally in large quantities and can be present in a wide range of common consumer products such as building materials, toys, food packaging materials, cosmetics, pharmaceuticals, medical devices and clothing (Hauser and Calafat, 2005; Heudorf et al., 2007). Phthalates are not chemically bound to the polymer of the products, which can lead to a migration from surfaces into food and the environment (Navarro et al., 2010), as well as further to human exposure via different routes including oral exposure (e.g. via consumption of food, pharmaceuticals, toys placed into mouth), dermal exposure (via skin contact with e.g. cosmetics, clothing), exposure via inhalation (e.g. via contaminated house dust, indoor air) and intravenous exposure (e.g. via medical devices) (Schettler, 2006). Once in the organism, phthalates are rapidly absorbed and metabolised by hydrolysis and subsequent oxidation. Their metabolites are eliminated primarily via urine. Although elimination is rapid and more than 95% of an uptaken oral dose is excreted as metabolites within 24 h (Koch and Angerer, 2012; Hauser and Calafat, 2005), evidence of negative health impacts exists for several phthalates (ECHA, 2016). Four phthalates including di(2-ethylhexyl) phthalate (DEHP), di-isobutyl phthalate (DiBP), di-*n*-butyl phthalate (DnBP) and butyl benzyl phthalate (BBzP) have also been identified as endocrine disruptors, which has been confirmed by the ECHA member states committee (ECHA, 2014c, 2018). Additionally, some phthalates comprising DEHP and DiBP can induce peroxisome proliferator-activated receptors (PPAR) which play an important role in biological process regulation (Boberg et al., 2008; Feige et al., 2010). Several experimental animal studies and evidence from human epidemiological studies have demonstrated adverse effects on reproduction, development and the immune system, for example the decrease in anogenital distance and certain malformations in male reproductive organs, the increase of asthma and allergies in school children, and the occurrence of insulin resistance (reported e.g. in Braun et al., 2013; ECB, 2008;

* Corresponding author at: Environment Agency Austria, Spittelauer Lände 5, A-1090, Vienna, Austria.
E-mail address: christina.hartmann@umweltbundesamt.at (C. Hartmann).

https://doi.org/10.1016/j.ijheh.2018.06.001
Received 29 January 2018; Received in revised form 6 June 2018; Accepted 6 June 2018

ECHA, 2008, 2013a,b, 2014a,b; Jaakkola and Knight, 2008; Latini et al., 2006; Swan, 2008).

For the evaluation of potential associations between phthalate exposure and health alterations or changes in biological endpoints, human biomonitoring (HBM) is used as an important tool for exposure assessment (Angerer et al., 2007, 2011). For the interpretation of data derived from HBM studies, the derivation of reference values as well as the comparison of exposure levels with specific human biomonitoring values is essential for the identification of potential risks to human health as a result of exposure to chemicals.

Reference values (RV_{95}) are used to describe the internal exposure to a chemical substance from different exposure routes within a defined population at a defined time (German HBM Commission, 2009, 2014). They are statistically derived and defined as the rounded 95th percentile within the 95% confidence interval of a substance concentration in a human biological material of a reference population (German HBM Commission, 1996, 2014) according to an IUPAC guideline (Poulsen et al., 1997) and the German HBM Commission. Data used for RV_{95} derivation is generally based on population HBM studies, whereby derivation is intended to be performed based on studies which are representative of the general population. Nevertheless, RV_{95} can also be defined for special population groups, especially for substances for which exposure clearly differs between groups, e.g. regarding sex or age (Ewers et al., 1999). In Europe, RV_{95} have been derived for several substances and various populations of e.g. Germany (German Environment Agency, 2015), Italy (Bocca et al., 2010; Forte et al., 2011), Czech Republic (Batáriová et al., 2006; Černá et al., 2007, 2012), France (Fréry et al., 2012), Belgium (Schoeters et al., 2012a, 2012b), the United Kingdom (Bevan et al., 2013) and several other European countries (Den Hond et al., 2015). Additionally, some RV_{95} for non-European countries such as Canada (Khoury et al., 2018), Brazil (Kira et al., 2016; Kuno et al., 2013) and the Democratic Republic of the Congo (Tuakuila et al., 2015) are available.

For the identification of potential risks to human health by exposure to substances, human biomonitoring (HBM) values are derived by the German Human Biomonitoring Commission of the German Federal Environment Agency based on the results of epidemiological and toxicological studies. These values reflect toxicologically derived, health-related exposure limits (Ewers et al., 1999). Two different values exist according to current scientific knowledge and the commission's judgement: HBM-I and HBM-II. Whereas HBM-I values (control or alert values) represent the concentration of a chemical substance in a human biological material such as urine or blood at and below which no risk of adverse effects on health in individuals of the general population exists, HBM-II values (intervention or action values) represent the concentration of a chemical substance in human biological material at and above which an increased risk of adverse human health effects is presented (Apel et al., 2017; Ewers et al., 1999; German HBM Commission, 1996, 2014). For HBM value derivation, different methods exist and are reported elsewhere (see e.g. Angerer et al., 2011; Apel et al., 2017; German HBM Commission, 2007a, 2014).

For phthalates, the German HBM Commission has derived HBM values for di(2-ethylhexyl) phthalate (DEHP) based on the tolerable daily intake and the two urinary DEHP metabolites mono(2-ethyl-5-oxohexyl) phthalate (5oxo-MEHP) and mono(2-ethyl-5-hydroxyhexyl) phthalate (5OH-MEHP), which account for 40% of metabolites excreted via urine after oral DEHP administration. HBM-I values for DEHP were set at 500 µg/l for 6-13-year-old children, at 300 µg/l for females of childbearing age and at 750 µg/l for males > 14 years of age and the remaining population. HBM-II values have not been derived (German HBM Commission, 2007b).

Based on a representative HBM study investigating the Austrian general population consisting of children, adolescents and adults (published in Hartmann et al., 2015) we have derived, for the first time, Austrian RV_{95} for several phthalate metabolites and evaluated these values based on available RV_{95} values for phthalate metabolites from Germany and Canada.

2. Materials and methods

2.1. Data used for the derivation of reference values

For the derivation of reference values (RV_{95}) of phthalate metabolite exposure in the Austrian population, data were obtained from a study conducted between 2010 and 2014. Details on the study and its results are published in Hartmann (2014) and Hartmann et al. (2015). In short, samples used for the investigation of urinary phthalate metabolite concentrations were provided by the "Austrian Study on Nutritional Status 2010–2012" (ASNS) comprising a representative sample including male and female children and adolescents of 1st to 8th education level aged 6–15 years and adults aged 18–81 years through a quota sampling of a cross-sectional study (sampling period 2010–2011). The urine samples were spot samples taken in the morning. Overall, 595 participants of the Austrian general population were included in this study. Urinary concentrations of a total of 14 phthalate metabolites of 10 parent phthalates were analysed by high-performance liquid chromatography tandem-mass spectrometry (HPLC–MS/MS) after enzymatic hydrolysis with a beta-glucuronidase, an accredited analytical method which has been proven successfully by inter-laboratory comparison tests within European COPHES/DEMOCOPHES projects (Consortium to Perform Human Biomonitoring on an European Scale / Demonstration of a Study to Coordinate and Perform Human Biomonitoring on an European Scale). The investigated phthalate metabolites include mono-ethyl phthalate (MEP), mono(2-ethylhexyl) phthalate (MEHP), mono(2-ethyl-5-hydroxyhexyl) phthalate (5OH-MEHP), mono(2-ethyl-5-oxohexyl) phthalate (5oxo-MEHP), mono(5-carboxy-2-ethylpentyl) phthalate (5cx-MEPP), mono-*n*-butyl phthalate (MnBP), mono-isobutyl phthalate (MiBP), mono-benzyl phthalate (MBzP), mono-cyclohexyl phthalate (MCHP), mono-*n*-ocytl phthalate (MnOP), mono-isononyl phthalate (MiNP), mono-isodecyl phthalate (MiDP) and 3-carboxyl-mono-propyl phthalate (3cx-MPP) (Hartmann et al., 2015). RV_{95} were derived for all investigated phthalate metabolites except for 3cx-MPP, which could be the metabolite of three different parent compounds including Di-*n*-octyl phthalate (DnOP), Di-isononyl phthalate (DiNP) and DnBP.

Based on the recommendations of the World Health Organization (WHO) and the German HBM Commission (German Environment Agency, 2005; WHO, 1996), urine samples with creatinine concentrations outside the range of 0.3 and 3.0 g creatinine/l were excluded from the derivation to ensure that extremely diluted or highly concentrated urine samples were not taken into account. Thus, 541 out of 595 participants investigated in Hartmann et al. (2015) were included in the derivation, which was finally based on the urine samples of 230 children and adolescents aged 6–15 years (128 males and 102 females), and of 311 adults aged 18–81 years (133 males and 178 females). Descriptive data for the phthalate metabolites are given in the supplemental material.

2.2. Derivation of reference values

RV_{95} for phthalate metabolites for the Austrian population were derived according to the International Union of Pure and Applied Chemistry (IUPAC) guideline published by Poulsen et al. (1997) and the recommendations of the German HBM Commission (German HBM Commission, 1996, 2009, 2014), calculating 95th percentiles and the corresponding 95% confidence intervals. RV_{95} are expressed as the rounded 95th percentiles.

3. Results and discussion

RV_{95} (rounded values) for urinary phthalate metabolites derived for the Austrian population are listed in Table 1. For Austrian children and