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Biomarkers of phthalates and alternative plasticizers in the Flemish Environment and Health Study (FLEHS IV): time trends and exposure assessment

Michiel Bastiaensen[1], Celine Gys [1], Ann Colles[2], Govindan Malarvannan[1], Veerle Verheyen[2,3], Gudrun Koppen[2], Eva Govarts[2], Liesbeth Bruckers[4], Bert Morrens[5], Carmen Francken[6], Elly Den Hond[6], Greet Schoeters[2,3], Adrian Covaci[1*]

[1] Toxicological Center, University of Antwerp, Universiteitsplein 1, 2610 Wilrijk, Belgium

[2] VITO Health, Flemish Institute for Technological Research (VITO), Boeretang 200, 2400, Mol, Belgium

[3] Department of Biomedical Sciences, University of Antwerp, Universiteitsplein 1, 2610 Wilrijk, Belgium

[4] BioStat, Data Science Institute, Hasselt University, Martelarenlaan 42, 3500 Hasselt, Belgium

[5] Faculty of Social Sciences, University of Antwerp, Sint-Jacobstraat 2, 2000 Antwerp, Belgium

[6] Provincial Institute of Hygiene, Kronenburgstraat 45, 2000, Antwerp, Belgium

*-Corresponding author: adrian.covaci@uantwerpen.be ; Fax: +32-3-265-2722

Abstract:

Restrictions on the use of legacy phthalate esters (PEs) as plasticizer chemicals in several consumer products has led to the increased use of alternative plasticizers (APs), such as di-(iso-nonyl)-cyclohexane-1,2-dicarboxylate (DINCH) and di-(2-ethylhexyl) terephthalate (DEHTP). In the fourth cycle of the Flemish Environment and Health Study (FLEHS IV, 2016-2020), we monitored exposure to seven PEs (diethyl phthalate (DEP), di-(2-ethylhexyl) phthalate (DEHP), di-isobutyl phthalate (DiBP), di-n-butyl phthalate (DnBP), butylbenzyl phthalate (BBzP, di-isononyl phthalate (DINP), and di-isodecyl phthalate (DIDP))and three APs (DINCH, DEHTP, and di-(2-ethylhexyl) adipate (DEHA)) by measuring multiple biomarkers in urine of 416 adolescents from Flanders, Belgium (14-15 years old). The reference values show that exposure to PEs is still widespread, although levels of several PE metabolites (e.g., sum of DEHP metabolites, mono-normal-butyl phthalate (MnBP) and mono-benzyl phthalate (MBzP)) have decreased significantly compared to previous human biomonitoring cycles (2003-2018). On the other hand, metabolites of DINCH and DEHTP were detected in practically every participant. Concentrations of AP exposure biomarkers in urine were generally lower than PE metabolites, but calculations of estimated daily intakes (EDIs) showed that exposure to DINCH and DEHTP can be considerable. However, preliminary risk assessment showed that none of the EDI or urinary exposure levels of APs exceeded the available health-based guidance values, while a very low number of participants had levels of MiBP and MnBP exceeding the HBM value. Several significant determinants of exposure could be identified from multiple regression models: the presence of building materials containing PVC, ventilation habits, socio-economic status and season were all associated with PE and AP biomarker levels. Cumulatively, the results of FLEHS IV show that adolescents in Flanders, Belgium, are exposed to a wide range of plasticizer chemicals. Close monitoring over the last decade showed that the exposure levels of restricted PEs have decreased, while newer APs are now frequently detected in humans.

Keywords:

Alternative plasticizers, PEs, human biomonitoring, estimated daily intake, exposure biomarkers, Flanders

1. Introduction

Many polymeric products require additive plasticizer chemicals to obtain their characteristic elasticity and flexibility. As such, phthalate esters (PEs) have been the most prominent plasticizers in consumer goods, personal care products, polyvinyl chloride (PVC) plastics and industrial applications (Wormuth et al. 2006; Koch et al. 2009). Because PEs and other additive chemicals are not chemically bound to the polymers, plasticizers easily get released into the environment (e.g., indoor air, house dust, food) leading to widespread exposure for human populations (Saravanabhavan et al. 2012; Larsson et al. 2017; Giovanoulis et al. 2018; Wang et al. 2019). Humans are primarily exposed to plasticizers by ingestion, inhalation or dermal contact (Wormuth et al. 2006). The use of several phthalate plasticizers – such as di-(2-ethylhexyl) phthalate (DEHP), di-isobutyl phthalate (DiBP), di-n-butyl phthalate (DnBP) and butylbenzyl phthalate (BBzP) - has been restricted in toys, medical devices, personal care products and food contact materials because of their endocrine disrupting properties and reproductive toxicity (Latini et al. 2006; Meeker et al. 2009; Ventrice et al. 2013; Howdeshell et al. 2017). Due to these restrictions, exposure levels of DEHP, DEP, DnBP and BBzP have decreased since 2000 in both Germany and the US (Koch et al. 2017).

However, the demand for plasticizer chemicals remained unchanged which has instigated the use of alternative plasticizers (APs), such as di-(iso-nonyl)-cyclohexane-1,2-dicarboxylate (DINCH), di-(2-ethylhexyl) terephthalate (DEHTP) and di-(2-ethylhexyl) adipate (DEHA). DINCH (marketed as Hexamoll® DINCH) entered the market in 2002 as a substitute for restricted high molecular weight phthalates DEHP and di-iso-nonylphthalate (DINP) (Schütze et al. 2014). DINCH is mainly used in PVC plastics, but its use is also authorized in sensitive applications such as toys, food contact materials and medical devices (Koch et al. 2013b) as current toxicological data suggest that DINCH does not exhibit similar toxic effects as PEs (Bui et al. 2016). DEHTP, a structural isomer of DEHP, and DEHA are also found in consumer goods, building materials, floor and wall coverings, paints and lacquers and toys, but can also be used in food contact materials (Silva et al. 2013b; Schwedler et al. 2020a). Toxicity tests in laboratory animals did not show endocrine disrupting potential or reproductive toxicity similar to PEs (Bui et al. 2016). Mainly DINCH and DEHTP have established themselves as frequently used substitute plasticizers during the last decade. Since 2012, the production of DINCH has been increasing at a rate of 10,000 tons per year, while the production of DEHTP was around 2,000 tons in 2002 and 125,000 tons in 2017 in Europe (Bui et al. 2016; Lessmann et al. 2019).

Human exposure to PEs is commonly estimated by quantifying several biotransformation products in urine. After entering the body, PEs are rapidly metabolized to primary, hydrolytic monoesters. The monoesters of high molecular weight PEs (DEHP, DINP, DIDP) are further oxidized to secondary metabolites (Frederiksen et al. 2007; Koch et al. 2011). Both the monoester and oxidative metabolites can be excreted in urine directly or undergo phase II glucuronidation to facilitate excretion (Koch et al.

2009). Several *in vivo* studies have shown that DINCH, DEHTP and DEHA are also metabolized to oxidative metabolites and that these metabolites are suitable targets for assessing exposure (Koch et al. 2013b; Lessmann et al. 2016; Nehring et al. 2020). Recent human biomonitoring studies have shown that exposure to APs is widespread and increasing over time, but were limited to the US, Germany, Denmark and Sweden (Silva et al. 2013a; Schütze et al. 2014; Larsson et al. 2017; Lessmann et al. 2017; Lessmann et al. 2019; Silva et al. 2019; Frederiksen et al. 2020).

In this study, we present data on the urinary metabolite levels of seven PEs (DEP, DnBP, DiBP, BBzP, DEHP, DINP and DIDP) and three alternative plasticizers (DINCH, DEHTP and DEHA) in a representative sample of Flemish adolescents. Within the context of the Flemish Environment and Health Study (FLEHS IV), we evaluated current PE exposure levels in comparison to previous cycles and investigated exposure to APs for the first time. Therefore, the objectives of the current study were 1) to determine reference levels of urinary metabolites of multiple PEs and APs in adolescents from Flanders, 2) to study the time trend of PE exposure from FLEHS II to FLEHS IV, 3) to find potential predictors of exposure based on questionnaire data, and 4) to compare the observed levels with available health-based guidance values for preliminary risk assessment.

2. Materials and methods

2.1 Study population

The goal of the Flemish Environment and Health Study (established in 2002) is to investigate the relationship between environmental human exposure and potential health effects for a broad suite of pollutants relevant to public health. In the past, reference values have been determined for organic pollutants (POPs), metals, pesticides, PEs, bisphenol A and other pollutants in different study populations representative for Flanders (Schoeters et al. 2012). One of the objectives of the current program (FLEHS IV, 2016-2020) was to establish reference values for biomarkers of emerging contaminants such as alternative plasticizers, organophosphate flame retardants and new bisphenols. The recruitment for FLEHS IV started in September 2017 and was completed in June 2018. In total, 610 adolescents participated: 182 newborns of FLEHS I (now adolescents) were investigated alongside 428 other adolescents recruited through 20 schools from all five provinces of Flanders (northern part of Belgium) as a representative sample of the Flemish region (Table 1). In this study, we discuss data only from the newly recruited adolescents (reference group). Participating adolescents and their parents had to provide written informed consent, reside in Flanders for at least 5 years and be able to fill in questionnaires in Dutch. Sampling of urine, hair and blood samples was carried out by trained nurses who also determined the body weight (bw) and height of the adolescents at school. As such, urine samples were random spot samples collected during the day (9-16h). Urine samples were collected in clean polyethylene containers, aliquoted into glass vials and kept frozen (-20°C) until analysis.

117 Additionally, questionnaires were used to obtain information on personal habits, behaviour and the
118 living environment (e.g., education, smoking, diet, product use, building materials, etc). The study
119 protocol was approved by the Ethical Committee of the Antwerp University Hospital (Belgian Registry
120 Number: B300201732753). All data were pseudonomised.
121
122 2.2 Measurement of phthalate and alternative plasticizer metabolites in urine
123 Analysis of PE and AP metabolites in urine samples was performed at the Toxicological Center
124 (University of Antwerp). Sample preparation (solid-phase extraction) and instrumental analysis (high
125 performance liquid chromatography coupled to tandem mass spectrometry) were carried out
126 according to a previously published method (Bastiaensen et al. 2020). A description of the protocol is
127 given in the SI.
128 Thirteen PE metabolites and seven AP metabolites were targeted in this study. Included PE metabolites
129 were mono-ethyl phthalate (MEP), mono-(2-ethyl-5-carboxypentyl) phthalate (cx-MEPP), mono-(2-
130 ethyl-5-hydroxyhexyl) phthalate (OH-MEHP), mono-(2-ethyl-5-oxohexyl) phthalate (oxo-MEHP),
131 mono-(2-ethylhexyl) phthalate (MEHP), mono-iso-butyl phthalate (MiBP), mono-normal-butyl
132 phthalate (MnBP), mono-benzyl phthalate (MBzP), mono-hydroxy-isononyl phthlate (OH-MINP),
133 mono(4-methyl-7-carboxyheptyl) phthalate (cx-MINP), mono-carboxy-isodecyl phthalate (cx-MIDP),
134 mono-hydroxy-isodecyl phthalate (OH-MIDP) and mono-oxo-isodecyl phthalate (oxo-MIDP). Included
135 AP metabolites were mono(2-ethylhexyl) adipate (MEHA), mono(2-ethyl-5-hydroxyhexyl) adipate (OH-
136 MEHA), mono(2-ethylhexyl) terephthalate (MEHTP), mono(2-ethyl-5-hydroxyhexyl) terephthalate
137 (OH-MEHTP), cyclohexane-1,2-dicarboxylic mono isononyl ester (MINCH), cyclohexane-1,2-
138 dicarboxylic mono hydroxyisononyl ester (OH-MINCH), and cyclohexane-1,2-dicarboxylic mono (cx-
139 MINCH). Limits of quantification (LOQ) ranged from 0.1 to 0.4 ng/mL depending on the metabolite
140 (Table 2).
141 Internal quality control consisted of different measures such as the repeated analysis of spiked samples
142 (water and urine), control samples (urine) and laboratory blanks (water). In addition, reanalysis of six
143 biobanked FLEHS III samples enabled the valid comparison between FLEHS IV data and data from
144 previous campaigns (measured by different analytical methods) for PE metabolites. The agreement
145 between the two measurements was assessed by Bland-Altman plots (Figure SI-1). Satisfactory results
146 were obtained for all previously measured metabolites. Handling of the stored samples occurred in
147 accordance with the laws of Belgium on biobanking. Samples were registered in Biobank@VITO, Mol,
148 Belgium; ID: BB190064.
149 External quality control was assured through participation to inter-laboratory comparison exercises
150 such as the GERMAN External Quality Assessment Scheme (G-EQUAS) for PE metabolites and Human
151 Biomonitoring for Europe External Quality Assurance Scheme (HBM4EU ICI/EQUAS, 2018-2019) for

152 DINCH and PE metabolites. Results were satisfactory for all included target analytes through several
153 rounds (shown in Tables SI-1 and SI-2).
154
155 2.3 Statistical analysis
156 Values below the LOQ were imputed with a random value between 0 and the LOQ drawn from a
157 truncated lognormal distribution which was fitted trough the observed values (above the LOQ). Target
158 metabolite levels were normalized for specific gravity (SG) according to Pearson et al. (2009): $conc_{SG}$ =
159 [conc*(1.024-1)/(SG-1)], where $conc_{SG}$ is the normalized concentration, conc is the uncorrected
160 concentration, 1.024 is a standardized SG value and SG is the specific gravity level of the individual
161 sample. Due to the skewness of the exposure data, normalized concentrations were also transformed
162 by the natural logarithm. Spearman ρ rank correlations were calculated between target analytes. Time
163 trends were assessed for available biomarkers between previous campaigns (FLEHS II 2003-2004,
164 FLEHS III 2008-2009) and the present study (FLEHS IV 2017-2018). The geometric means (GM) in these
165 regression models were adjusted for sex, age and specific gravity.
166 A wide range of information on the lifestyle and habits of the participants was retrieved from
167 questionnaires. Potential exposure determinants were selected based on information from literature
168 and based on product information. Significant determinants of exposure were identified by a stepwise
169 multiple linear regression model per compound using backward selection. Only target analytes with a
170 detection frequency (DF) > 60% were included in statistical analysis. Independent variables were
171 introduced in the multiple model if the p-value was <0.2 in univariate regression model and if the
172 direction of the association was consistent with mechanistic or epidemiological insights. Collinearity
173 among independent variables was also checked by variance inflation factors. Non-significant
174 explanatory variables were removed one by one until only significant variables were retained ($p<0.05$).
175 Secondary variables such as socio-economic status and season were only introduced in the final step
176 as they could be proxies for other determinants. Specific gravity was also added as an independent
177 variable in each model. The R-square of the model reflects the percentage of variation in metabolite
178 levels that could be explained by the remaining independent variables in the final model.
179 Risk assessment was performed in two parts. Firstly, individual urinary metabolite levels were
180 compared with available guidance values (i.e., biomonitoring equivalent or HBM values) (Aylward et
181 al. 2013; Apel et al. 2017). Because guidance values are not available for all chemicals of interest, we
182 also calculated estimated daily intakes (EDIs) based on the urinary metabolite concentrations and
183 compared them with available oral reference doses (tolerable daily intake (TDI) or reference doses
184 (RfD)). These guidance values provide an estimation of the daily exposure for humans that is likely
185 without any adverse effects during a lifetime and can be considered as a tool for risk assessment of
186 human exposure to toxic chemicals. EDIs (in ng/kg bw/day) were calculated based on urinary

concentrations of frequently detected metabolites according to the following equation (Fromme et al. 2014):

$$EDI = \left(\frac{c_{meta} \times V_{urine}}{F_{UE} \times bw}\right) \times \frac{MW_p}{MW_m}$$

where c_{meta} is the specific-gravity normalized metabolite concentration (in ng/mL SG); V_{urine} is the daily excreted volume of urine (estimated at 1200 mL/day for adolescents) (Valentin 2002); F_{UE} is the urinary excretion factor specific to each metabolite (shown in Table SI-3); bw is the body weight of the participant (in kg); and MW_p and MW_m are the molecular weight of the parent compound and its metabolite respectively (in g/mol, Table SI-3).

3. Results and discussion

3.1 Study population

The characteristics of the study population are described in Table 1. Fifty-three percent of the adolescents were girls compared to 47% boys, all aged between 14 and 15 years old. The majority of the participants followed a general education (50.8%). 72% of the participants had a normal weight (BMI between 18.5 and 25 kg/m^2). The proportion of obese adolescents (BMI > 25 kg/m^2) has increased slightly compared to previous FLEHS cycles (Geens et al. 2014; Steunpunt Milieu en Gezondheid 2020). The distribution of the study population characteristics corresponds well those of Flanders in general. Because recruitment was carried out in collaboration with the schools, no samples were collected during summer (Steunpunt Milieu en Gezondheid 2020).

Table 1: Characteristics of the study population (n = 428).

		N	%
Gender	Male	199	46.5
	Female	227	53.5
BMI	Underweight	35	8.2
	Normal weight	308	72.0
	Overweight	85	19.8
School type[a]	General education	215	50.8
	Technical education	130	30.7
	Vocational education	78	18.4
Foreign origin	non-EU	43	10.1
	EU	36	8.4
	Belgium	348	81.5
Season of sampling	Winter	138	32
	Spring	190	44
	Summer	0	0
	Autumn	100	23

N: number of participants in subgroup; BMI: body mass index. [a]Based on the International Standard Classification of Education (ISCED).

210 3.2 Exposure levels of phthalate and alternative plasticizer metabolites in urine

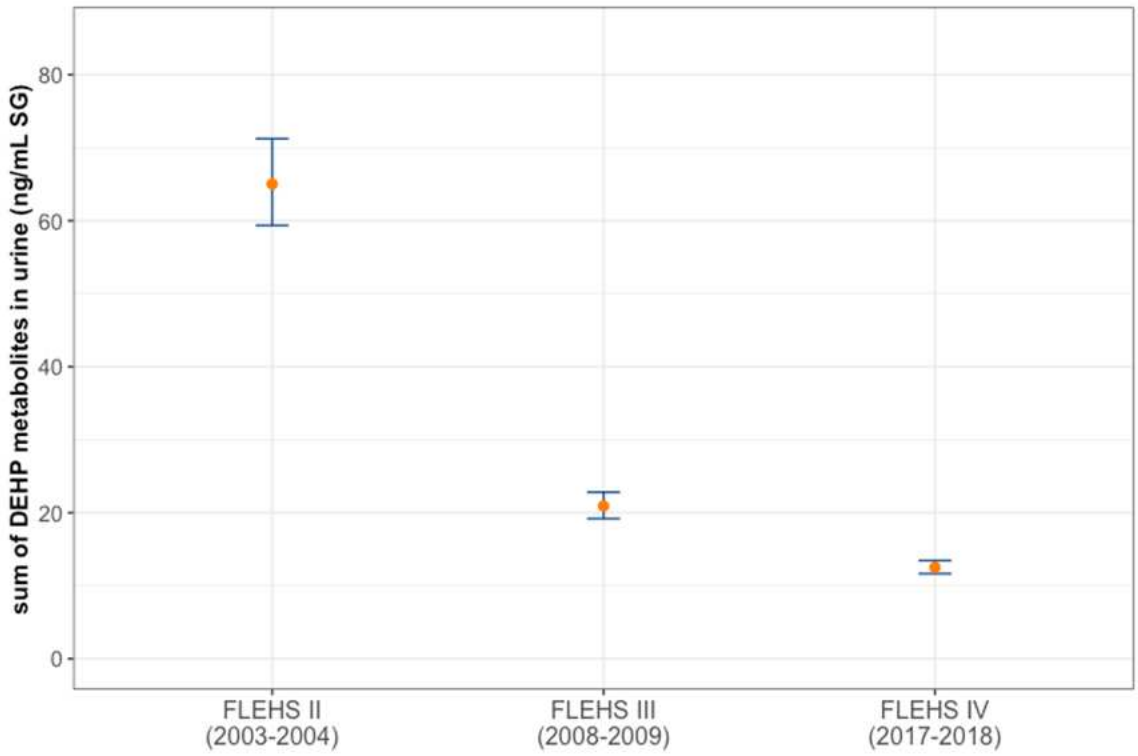
211 A total of 20 metabolites were measured, which represent the exposure to 7 PEs (DEP, DnBP, DiBP,
212 BBzP, DEHP, DINP and DIDP) and 3 APs (DINCH, DEHTP and DEHA). The distribution of the investigated
213 biomarkers in urine samples of Flemish adolescents is shown in Table 2. The majority of the
214 metabolites were quantifiable in >80% of the participants. Only OH-MEHA, MEHA, MEHTP and MINCH
215 were found in low detection frequencies (<20%) and therefore excluded from further statistical
216 analyses. MEP was the PE metabolite with the highest geometric mean concentration (32.8 ng/mL)
217 followed by MiBP, MnBP and cx-MEPP. Levels of AP metabolites had lower geometric mean
218 concentrations ranging from 0.51 ng/mL for OH-MEHTP to 1.15 ng/mL for OH-MINCH. However, the
219 high detection frequencies of these compounds indicate their suitability as biomarkers of exposure to
220 APs. Furthermore, direct comparisons of PE and AP metabolite concentrations are not appropriate also
221 because of differences in fractions of urinary excretion (F_{UE}; Table SI-1). Levels of OH-MINCH, cx-MINCH
222 and OH-MEHTP are in line with other study populations of approximately the same age category from
223 the US and Europe (Table 3) (Frederiksen et al. 2011; Correia-Sá et al. 2017; Lessmann et al. 2017; CDC
224 2019; Schwedler et al. 2019; Schwedler et al. 2020a), with one exception for OH-MEHTP (higher in the
225 US, Silva et al. (2019)) and OH-MINCH (higher in Australia, Ramos et al. (2016)). It should be noted that
226 OH-MEHTP is not the major specific biomarker for DEHTP exposure. Results from the German
227 Environmental Survey (GerES V) and the U.S. National Health and Nutrition Examination Survey
228 (NHANES) have shown that concentrations of the carboxypentyl metabolite (mono-(2-ethyl-5-
229 caboxylpentyl) benzene-1,4-dicarboxylate (5cx-MEPTP)) are generally higher than OH-MEHTP (Silva et
230 al. 2019; Schwedler et al. 2020a). This is likely also the case for exposure to DEHA (OH-MEHA vs mono-
231 5-carboxy-2-ethylpentyl adipate (5cx-MEPA)) (Nehring et al. 2020), but this has not yet been confirmed
232 in the general population.

233 Strong correlations (Spearman $\rho > 0.7$) were observed between oxidative metabolites originating from
234 the same parent compound (Figure SI-2), such as OH-MEHP and oxo-MEHP (ρ=0.97), OH-MINP and cx-
235 MINP (ρ=0.67), OH-MIDP and oxo-MIDP (ρ=0.71), and OH-MINCH and cx-MINCH (ρ=0.87), which has
236 been reported by several studies (Dewalque et al. 2014b; Giovanoulis et al. 2016). Weak to moderate
237 correlations were found between all frequently detected metabolites, which suggests that their
238 corresponding parent compounds are sometimes applied within the same consumer products.

239 Concentrations of PE metabolites measured in this study were generally consistent with studies of
240 adolescents from the US, Canada and Germany (CDC 2019; Health Canada 2019; Schwedler et al.
241 2020b). The highest levels were found for MEP, whereas concentrations of DIDP metabolites were
242 consistently the lowest (Table 3). However, some clear differences were observed with higher
243 concentrations of MnBP, MiBP, MBzP, DEHP and DINP metabolites in studies of younger children from
244 Sweden, Poland, Portugal and the US (Larsson et al. 2014; Correia-Sá et al. 2018; Garí et al. 2019;

245 Hammel et al. 2019). Age is an important predictor of PE exposure, because of higher exposure relative
246 to body size in younger individuals. Exposure sources also differ significantly between children and
247 adults due to changing behavior (related to food, hand-to-mouth contact with toys for children or use
248 of personal care products for adolescents) (Frederiksen et al. 2007; Wittassek et al. 2011).
249 Furthermore, the exposure profile might also change as a result of differences in metabolism: oxidative
250 metabolism seems to be favored in young children compared to adults (Koch et al. 2009). Decreasing
251 concentrations with age have also recently been reported for DINCH and DEHTP (Schwedler et al. 2019;
252 Silva et al. 2019). Variation in PE metabolite levels between different countries has been described in
253 detail elsewhere and is attributable to differences in sources, in products available on the market and
254 in regulations (Den Hond et al. 2015; Wang et al. 2019).
255 Although the use of several PEs (DEHP, DnBP, DiBP, BBzP, DINP, DIDP) is strictly regulated within the
256 European Union (e.g., in toys, childcare articles, food contact materials, personal care products and
257 medical devices) (ECHA 2019), exposure to these endocrine disrupting chemicals is still ubiquitous in
258 participants of this and other studies. However, it is clear that efforts to reduce human exposure
259 through stringent regulations are reflected in the results of this study. As shown in Figure 1, the
260 adjusted geometric mean concentration of the sum of OH-MEHP, oxo-MEHP, and MEHP decreased
261 significantly from 65.02 ng/mL SG in FLEHS II (2008-2009) to 20.92 ng/mL SG in FLEHS III (2013,
262 $p<0.001$) and further to 12.52 ng/mL SG in FLEHS IV (2017-2018, $p<0.001$). In fact, levels of all PE
263 metabolites that were measured in adolescents during previous cycles decreased but not always
264 significantly (MEP, MnBP, MiBP, MBzP; Figures SI-3). A similar significant decrease in exposure over
265 time was reported for the urinary excretion of DEP, DiBP, DnBP, BBzP and DEHP metabolites in German
266 (1988 - 2015) and Danish (2009-2017) adolescents (Koch et al. 2017; Frederiksen et al. 2020) and in
267 the general population of the U.S. between 1999 and 2016 (CDC 2019). The Danish study also observed
268 a decrease in DINP metabolite levels, while the excretion of these compounds remained stable in
269 German and US population. No such data exist for Flanders since metabolites of DINP, DIDP, DINCH,
270 DEHTP and DEHA were measured only for the first time in this study.
271 As the European Union will further restrict the use of DEHP, DnBP, DiNP and BBzP in 2020 (EU
272 Commission 2018), background exposure levels are expected to continue to decrease the coming
273 years. However, this process will likely be accompanied by a concurrent increase in exposure to
274 alternative plasticizers such as DINCH and DEHTP. Metabolite levels of these substitute chemicals have
275 significantly increased during the last decade in the U.S., Denmark and Germany with detection
276 frequencies of DEHTP metabolites going from close to 0% in 2009 to 100% in 2017 (Silva et al. 2013a;
277 Schütze et al. 2014; Lessmann et al. 2019; Frederiksen et al. 2020). The results of this study (i.e.,
278 decreasing exposure to classical PEs, frequent detection of APs) suggest that the substitution process

279 is also ongoing in Belgium. Future studies should therefore not only focus on legacy PEs, but also on
280 the APs that are replacing them.
281



282
283 **Figure 1: Time trend of the sum of DEHP metabolites (OH-MEHP, oxo-MEHP and MEHP) in the urine**
284 **of Flemish adolescents.** Adjusted for sex, age and specific gravity. $N_{FLEHS\ II}$ = 209; $N_{FLEHS\ III}$ = 207; $N_{FLEHS\ IV}$
285 = 416. P-value trend: <0.001.
286

287 **Table 2: Concentrations of PE and AP metabolites in the urine of Flemish adolescents (n = 416, in ng/mL).**

Parent compound	Metabolite	LOQ	% > LOQ	GM	(95% CI)	P5	P25	P50	P75	P95
DEP	MEP	0.5	100	32.8	(28.7; 37.6)	5.0	14.0	24.7	69.6	429.1
DiBP	MiBP	0.5	100	22.0	(19.9; 24.3)	3.9	12.7	21.0	39.1	124.2
DnBP	MnBP	0.5	100	17.0	(15.7; 18.5)	3.5	10.4	17.3	29.9	64.6
BBzP	MBzP	0.2	98	2.6	(2.2; 2.9)	0.4	1.2	2.3	5.5	34.7
DEHP	5-cx-MEPP	0.5	100	14.0	(13.2; 14.8)	5.5	10.2	14.5	19.6	31.9
	5-OH-MEHP	0.2	100	5.7	(5.2; 6.3)	1.3	3.4	6.0	10.1	23.1
	5-oxo-MEHP	0.2	100	3.6	(3.3; 4.0)	0.8	2.2	3.8	6.3	15.5
	MEHP	0.5	83	1.1	(1.0; 1.2)	n.d.	0.7	1.1	2.0	5.5
DINP	OH-MINP	0.2	100	3.88	(3.57; 4.22)	0.92	2.37	3.85	6.11	15.33
	cx-MINP	0.2	99	1.71	(1.57; 1.86)	0.41	1.04	1.66	2.64	7.23
DIDP	OH-MIDP	0.2	95	0.63	(0.57; 0.70)	n.d.	0.38	0.63	1.15	2.84
	cx-MIDP	0.2	100	1.19	(1.15; 1.23)	0.90	0.99	1.10	1.29	1.97
	oxo-MIDP	0.2	77	0.36	(0.33; 0.40)	n.d.	0.22	0.37	0.65	1.69
DEHA	OH-MEHA	0.2	20	n.a.					n.d.	0.33
	MEHA	0.2	4	n.a.						n.d.
DEHTP	OH-MEHTP	0.2	87	0.51	(0.45; 0.57)	n.d.	0.28	0.52	0.92	3.69
	MEHTP	0.2	1	n.a.						
DINCH	OH-MINCH	0.2	95	1.15	(1.03; 1.29)	n.d.	0.59	1.06	2.14	6.94
	cx-MINCH	0.2	98	0.98	(0.91; 1.05)	0.27	0.61	0.98	1.61	3.42
	MINCH	0.2	6	n.a.					n.d.	0.25

288 LOQ: limit of quantification; GM: geometric mean; 95% CI: 95% confidence interval P5-P95: percentiles; n.d.: not detected; n.a.: not available

289

290 **Table 3: Geometric mean concentrations (in ng/mL) found in the urine of adolescents and children from different studies.**

					DEP	DiBP	DnBP	BBzP	DEHP				DINP		DIDP			DEHTP	DINCH	
Reference	n	Country	Sampling years	Age (y)	MEP	MiBP	MnBP	MBzP	cx-MEPP	OH-MEHP	oxo-MEHP	MEHP	OH-MINP	cx-MINP	OH-MIDP	cx-MIDP	oxo-MIDP	OH-MEHTP	OH-MINCH	cx-MINCH
This study	416	Belgium	2017-2018	14-15	32.8	22.0	17.0	2.6	14.0	5.7	3.6	1.1	3.9	1.7	0.6	1.2	0.4	0.5	1.2	1.0
CDC (2019); Silva et al. (2019)	403	USA	2015-2016	12-19	35.6	10.4	11.6	6.1	7.3	5.8	3.8	1.2		10.3		2.2		8.1	0.8	0.7
Health Canada (2019)	534	Canada	2016-2017	12-19	25.0	13.0	16.0	5.3	6.9	5.9	4.0	1.1	0.8	1.2	0.3	0.8	0.4		<LOQ	<LOQ
Dewalque et al. (2014b)	261	Belgium	2013	12-85	37.6	26.2	31.3	5.5		8.6	5.8	2.7								
Schwedler et al. (2019); Schwedler et al. (2020a); Schwedler et al. (2020b)	2228	Germany	2015-2017	3-17	25.8	26.1	20.9	3.1	11.9	11.0	7.6	1.4	6.9	5.9	1.5	0.9	0.6	0.6	2.3	1.1
Giovanoulis et al. (2016)	61	Norway	2013-2014	adults	24.4	13.3	11.7	3.3		4.9	4.6	<LOQ							0.3	0.2
Frederiksen et al. (2020) (*)	100	Denmark	2017	18-30	23.9	23.1	20.9	2.5	7.5	5.6	3.8	1.1	2.9	4.1	0.4	0.4	0.9	0.7	1.6	0.7
Larsson et al. (2014)	98	Sweden	2013	6-11	28.8		76.9	19.9	21.5	24.6	15.7	2.7	9.7	21.7						
Garí et al. (2019)	250	Poland	2014-2015	7	42.0	76.2	55.0	5.5	31.4	27.1	19.9	2.7	9.5	7.6	1.8	0.9	0.9			
Correia-Sá et al. (2017); Lessmann et al. (2017); Correia-Sá et al. (2018)	112	Portugal	2014-2015	4-11	58.3	16.8	12.8	2.3	16.1	10.9	7.6	1.9	5.6	7.4	1.3	1.2	0.7	0.45*	2.14*	1.08*
Ding et al. (2019)	478	China	2017	16-20	29.7		42.5		13.2	4.7	6.3	3.4								
Hammel et al. (2019) (*)	180	USA	2014-2016	3-6	39.0	19.0	20.0	17.0	31.0	20.0	13.0	1.9		21.0		4.3				
Ramos et al. (2016)	2400	Australia	2012-2013	0-60+	127.0	20.6	24.4	5.2	41.6	25.6	15.6	5.7		38.9		2.8			3.9	

291 (*) median concentrations

3.3 Potential predictors of exposure

Several characteristics of the indoor environment were found to be significant predictors of exposure to PEs and APs in multiple regression analysis (Table 4). MBzP levels were on average 2.57 times higher in participants with PVC floors in their living or bedroom, which was not surprising because BBzP and other PEs are the major plasticizers in PVC polymers found in building materials, floor and wall coverings, etc (Wormuth et al. 2006). Similar findings have been reported by Carlstedt et al. (2013) and Larsson et al. (2014) for MBzP in Swedish children's urine. Adolescents living in homes with double glass windows also had significantly higher levels of DINP metabolites, possibly due to the presence of DINP in the PVC framework of the windows. Fully or partly insulated walls also were also associated with higher levels of OH-MEHTP (1.6 to 2 times higher compared to no insulation), which confirms that certain building materials could be sources of PE and AP exposure. Interestingly, we found that adolescents living in recently built homes (> 2006) had lower levels of MnBP (-26%, p=0.006) and MiBP (-26%, p=0.051). The building year of the home was also a significant predictor in the opposite direction for DINCH, with higher levels for more recently built homes. Since 2020, DiBP and DnBP cannot be used individually or in any combination with DEHP or BBzP in a concentration equal or greater than 0.1% by weight of the plasticized material (EU Commission 2018). These associations seem to indicate that PEs are also being substituted by alternative plasticizers in building materials and other consumer products present in the indoor environment. Concerning ventilation habits, we found that the use of a mechanical ventilation system was associated with 28% lower levels of DINCH, but ventilation through air draft resulted in higher levels of DINP and DIDP metabolites (+27% and +15%, respectively, Table 4). The effect of ventilation on indoor air or dust levels of PEs and APs is not well understood, but diluting or removing indoor pollutants through ventilation is recognized as an important component of a 'healthy' building (Dimitroulopoulou 2012). Poor ventilation could in turn lead to higher exposure for humans as a result of increased concentrations of plasticizers in dust or air (Huo et al. 2016).

Ingestion of contaminated food and the use of personal care products are two other major sources of PE exposure (Wittassek et al. 2011; Giovanoulis et al. 2018). Diet is the most significant pathway for exposure to DEHP, DINP and DIDP, whereas DEP, DiBP, DnBP and BBzP are primarily linked to non-food exposure (Koch et al. 2013a). However, as shown by the results of this and other studies, the relationship between low and high molecular weight PEs and non-food sources is not always black and white (Sakhi et al. 2017; Husøy et al. 2019). While we found no direct associations with variables of food intake, MBzP levels were 4.18 times higher when samples were collected on days with high average UV radiation (> 2000 J/m^2). This increase was likely due to the application of sunscreen containing BBzP (Wormuth et al. 2006), although we did not find a direct association with the number of personal care products used by our study participants, nor did we find the same association for

327 other PEs. Surprisingly, OH-MEHTP concentrations were also 3.08 times higher when samples were
328 collected on days with high average UV radiation. We are however not aware of any personal care
329 products containing DEHTP, which is mainly used as an alternative to DEHP in products such as flooring,
330 food packaging, toys and medical devices (Schwedler et al. 2020a). So, this might be a chance finding
331 or a proxy for another underlying predictor (e.g., heat/UV radiation impact on release from products).
332 Various studies have reported elevated exposure to low molecular weight PE (DEP, DnBP, DiBP) when
333 personal care products (PCPs, such as sunscreen, body lotion, make-up, shampoo) were used, but
334 results were not always consistent (Buckley et al. 2012; Cantonwine et al. 2014; Larsson et al. 2014;
335 Gao et al. 2017; Sakhi et al. 2017). Other studies have also found that the more frequent use of PCPs
336 was associated with increased urinary MEP levels, particularly in women (Romero-Franco et al. 2011;
337 Philippat et al. 2015; Giovanoulis et al. 2016). The geometric mean concentrations of MEP in girls of
338 our study population were 87% higher than boys of the same age (14-15 years old), which was possibly
339 due to the use of cosmetics. None of the levels of other PEs or APs were significantly different between
340 boys and girls. Regarding the lack of association with variables on food intake, it is possible that the
341 employed questionnaire was not detailed enough to distinguish between products that contain PEs
342 and APs and those that do not, or that the behavioral differences and lifestyle habits were highly similar
343 among participants.
344 The concentrations of certain PE metabolites were significantly higher in families with lower monthly
345 income (MEP, MiBP, MnBP) and in those adolescents living in rented homes (MEP, MnBP, MBzP).
346 Furthermore, we found that adolescents or their parents who were born outside the European Union
347 had higher exposure to DINP (+31%). The negative association between socio-economic status (not
348 only income, but also education level) and PE metabolite levels is consistent with results from previous
349 studies (Belova et al. 2013; Tyrrell et al. 2013; Geens et al. 2014; Den Hond et al. 2015; Garí et al. 2019).
350 Some reports also found higher levels of MBzP, MnBP and MiBP in children from urban areas (Larsson
351 et al. 2014; Garí et al. 2019), while for other studies, place of residency was not a significant predictor
352 (Den Hond et al. 2015). In our study, adolescents living in urban areas had higher levels of MnBP (+28%)
353 but not of other PEs or APs. The underlying factors (e.g., food consumption, use of consumer products
354 and personal care products) that impact these associations did not remain significant in the multiple
355 regression models but are probably related to differences in behaviour or habits of the participants
356 and their families (e.g., buying cheaper consumer products, more processed foods, etc).
357 Finally, our results showed that PE metabolite concentrations varied by the season of sampling.
358 Significantly higher levels of MiBP, MnBP and DEHP were found in spring (Table 4). Similar results were
359 reported for Flemish adolescents in FLEHS III (Geens et al. 2014). One study from China found the
360 highest levels of low molecular weight PE metabolites in summer (Gao et al. 2017), however this could
361 not be confirmed here (no recruitment during summer because of school holidays) or in other studies

362 (Peck et al. 2010). Interestingly, we also found that mild outdoor temperatures (6-14°C on average on
363 the sampling day and six days prior) were consistently associated with higher levels of MBzP (+49%),
364 DINP (+42%), DIDP (+27%) and OH-MEHTP (+28%) compared to colder (< 6°C) and warmer days
365 (>14°C). Various reasons might explain the observed predictors such as differences in time spent
366 indoor or outdoor, changes in food consumption or more frequent use of certain consumer products
367 in specific seasons. The overall proportion of variance in urinary metabolite concentrations explained
368 by the multiple regression models was relatively low ($0.091 < R^2 < 0.248$), which suggests that major
369 predictors of PE and AP exposure could not be identified and that questionnaires should be refined for
370 future use. Identification of specific determinants of exposure was also hindered by the employed
371 sampling strategy (random spot samples, see also Bastiaensen et al. (2020)), overall lower variation in
372 this study population (confidence intervals were smaller in FLEHS IV, see Figure 1) and the fact that
373 exposure originates from multiple heterogenous sources.
374
375 **Table 4: Multiple linear regression models of PE and AP metabolites, normalised for specific gravity.**
376 **Multiplicative changes in biomarker levels are expressed as ß-values with 95% confidence intervals**
377 **(95%CI).**

MEP	**n**	**R^2 = 0.119**	**ß (95%CI)**			**p-value**
Sex	163	boys	ref			
	180	girls	1.87	1.42	2.46	
Income of the household	85	€ 0-1250	ref			**0.004**
	73	€ 1251- 1600	1.48	0.99	2.22	0.057
	68	€ 1601- 2000	0.74	0.48	1.13	0.16
	117	> €2000	0.78	0.53	1.15	0.212
Owner of the home	66	rented	ref			
	277	owned	0.66	0.46	0.96	**0.031**
MiBP	**n**	**R^2 = 0.145**	**ß (95%CI)**			**p-value**
Building type	300	house	ref			
	20	apartment	1.69	1.14	2.49	**0.009**
Building year of the home	100	< 1960	ref			
	63	1960-1980	1.26	0.98	1.64	0.076
	70	1981-2000	0.96	0.75	1.23	0.742
	43	2001-2006	1.01	0.75	1.35	0.961
	44	> 2006	0.74	0.54	1	0.051
Income of the household	67	€ 0-1250	ref			
	70	€ 1251- 1600	0.88	0.67	1.16	0.376
	68	€ 1601- 2000	0.62	0.47	0.82	**0.001**
	115	> €2000	0.68	0.53	0.88	**0.003**
Season	98	winter	ref			
	150	spring	1.33	1.07	1.65	**0.009**
	72	autumn	1.18	0.92	1.52	0.197
MnBP	**n**	**R^2 = 0.189**	**ß (95%CI)**			**p-value**
Building year of the home	112	< 1960	ref			
	70	1960-1980	1.13	0.93	1.36	0.215
	79	1981-2000	0.94	0.78	1.12	0.48
	51	2001-2006	0.87	0.71	1.07	0.194
	48	> 2006	0.74	0.6	0.92	**0.006**
Consumption of locally grown foods during the last year (relative to total consumption)	113	0%	ref			
	78	0-5%	0.9	0.75	1.08	0.249
	66	5-15%	1.02	0.84	1.23	0.846

	57	15-30%	0.79	0.65	0.96	**0.019**
	46	>30%	1.14	0.92	1.41	0.223
Degree of urbanisation	43	cities	ref			
	265	towns ans suburbs	0.94	0.77	1.16	0.571
	52	rural areas	0.72	0.56	0.93	**0.011**
Season	112	winter	ref			
	163	spring	1.37	1.17	1.6	**<0.001**
	85	autumn	1.22	1.02	1.45	**0.029**
Owner of the home	56	rented	ref			
	304	owned	0.75	0.63	0.9	**0.002**
MBzP	**n**	**R^2 = 0.248**		**ß (95%CI)**		**p-value**
Vinyl or PVC used in floors of living or bedroom	230	no	ref			
	31	yes	2.57	1.7	3.88	**<0.001**
Average daily temperature on sampling day and six days prior	86	<6 °C	ref			
	101	6-14 °C	1.49	1.05	2.12	**0.027**
	74	>14 °C	0.47	0.19	1.18	0.108
Average UV radiation on sampling day and 2 days prior	101	<300 J/m²	ref			
	79	300-2000 J/m²	1.22	0.86	1.75	0.266
	81	>2000 J/m²	4.18	1.8	9.73	**0.001**
Consumption of alcohol	167	never	ref			
	55	< monthly	0.52	0.37	0.73	**<0.001**
	39	monthly or more	0.96	0.65	1.41	0.82
Owner of the home	50	rented	ref			
	211	owned	0.62	0.44	0.88	0.008
DEHP (OH + oxo-MEHP)	**n**	**R^2 = 0.130**		**ß (95%CI)**		**p-value**
Insulation of outer walls	56	nowhere	ref			
	55	partly	1.41	1.08	1.83	**0.011**
	192	everywhere	1.02	0.82	1.26	0.886
Income of the household	65	€ 0-1250	ref			
	67	€ 1251- 1600	1.01	0.79	1.29	0.941
	62	€ 1601- 2000	0.9	0.7	1.15	0.391
	109	> €2000	0.76	0.61	0.95	**0.014**
Season	93	winter	ref			
	141	spring	1.3	1.07	1.58	**0.007**
	69	autumn	1.07	0.86	1.34	0.53
DINP (OH + cx-MINP)	**n**	**R^2 = 0.124**		**ß (95%CI)**		**p-value**
Presence of double glass	46	nowhere or partly	ref			
	332	yes everywhere	1.29	1.02	1.62	**0.033**
Sometimes ventilation through air draft	276	no	ref			
	102	yes	1.27	1.08	1.51	**0.005**
Descent based on place of birth	305	Belgian	ref			
	33	EU	1.26	0.97	1.64	0.079
	40	non-EU	1.30	1.02	1.66	**0.037**
Average daily temperature on sampling day and six days prior	128	<6 °C	ref			
	171	6-14 °C	1.44	1.22	1.70	**<0.001**
	79	>14 °C	1.27	1.03	1.57	**0.023**
DIDP (OH + oxo + cx-MIDP)	**n**	**R^2 = 0.108**		**ß (95%CI)**		**p-value**
Sometimes ventilation through air draft	283	no	ref			
	104	yes	1.15	1.02	1.3	**0.023**
Average daily temperature on sampling day and six days prior	132	<6 °C	ref			
	175	6-14 °C	1.27	1.12	1.43	**<0.001**
	80	>14 °C	1.11	0.96	1.29	0.176
DINCH (OH + cx-MINCH))	**n**	**R^2 = 0.091**		**ß (95%CI)**		**p-value**
Building year of the home	108	< 1960	ref			
	62	1960-1980	1.42	1.09	1.84	**0.01**
	68	1981-2000	1.38	1.07	1.78	**0.013**
	41	2001-2006	1.1	0.81	1.48	0.548
	40	> 2006	1.56	1.1	2.2	**0.012**
Mechanical ventilation system	260	no	ref			
	59	yes	0.72	0.54	0.94	**0.018**
Average sunshine radiation on sampling day and 6 days prior	94	<3500 Wh/m²	ref			
	104	3500-15000 Wh/m²	1.47	1.16	1.86	**0.001**

	121	>15000 Wh/m²	1.05	0.83	1.31	0.695
OH-MEHTP	**n**	**R^2 = 0.146**		**ß (95%CI)**		**p-value**
Insulation of walls	27	nowhere	ref			
	38	partly	2.07	1.25	3.44	**0.005**
	116	everywhere	1.60	1.04	2.48	**0.033**
Time of urine collection	49	< 10h	ref			
	84	10-12h	1.51	1.04	2.19	**0.03**
	48	> 12h	1.01	0.66	1.54	0.976
Average daily temperature on sampling day and six days prior	49	<6 °C	ref			
	85	6-14 °C	1.28	0.87	1.89	0.216
	47	>14 °C	0.30	0.11	0.80	**0.017**
Average UV radiation on sampling day and 6 days prior	81	<300 J/m²	ref			
	47	300-2000 J/m²	0.72	0.49	1.06	0.096
	53	>2000 J/m²	3.08	1.26	7.52	**0.014**

3.4 Reverse dosimetry and comparison with guidance values

Risk assessment was carried out by 1) by direct comparison of urinary metabolite levels with available HBM- or BE values and 2) calculating estimated daily intakes (EDI) for the parent compounds based on the urinary metabolite concentrations and comparing them with available reference doses (TDI or RfD). Results of EDI calculation and comparison with guidance values are shown in Table 5.

Guidance values such as the biomonitoring equivalent (BE) or human biomonitoring guidance values (HBM-GV) define the concentration of a chemical or its metabolites in a biological matrix that is consistent with existing noncancer health-based exposure guidances values such as the reference doses (RfD) determined by the U.S. Environmental Protection Agency or tolerable daily intakes (TDI) calculated by the European Food Safety Authority (Aylward et al. 2013; Apel et al. 2017). They allow for a direct comparison of the measured biomonitoring concentration and are intended as screening tools to assess which biomarkers are near or above risk assessment values.

Health-based guidance values were available for DEP, DiBP, DnBP, BBzP, DEHP, DINP and DINCH (Aylward et al. 2013; Apel et al. 2017). None of the adolescents exceeded the biomonitoring equivalent (BE) values for MEP (18000 ng/mL), DiBP (2700 ng/mL), DnBP (200 ng/mL), BBzP (3800 ng/mL), DEHP (400 ng/mL) and DINP (390 ng/mL), and the HBM-I values for BBzP (3000 ng/mL), DEHP (500 ng/mL) and DINCH (3000 ng/mL). However, in accordance with the EDI – TDI comparison, a small percentage of participants had concentrations in urine above the HBM-GV value (1.9% for MiBP and 0.5% for MnBP) where adverse health effects cannot longer be excluded.

DEHP was the compound with the highest median EDI (1203 ng/kg bw/day) followed by DEP, DiBP, DEHTP, DINP, DnBP, DINCH, DIDP and BBzP. This finding highlights the importance of considering the fraction of urinary excretion (F_{ue}) of the measured biomarkers in exposure assessment (Table SI-1). The order of compounds based on daily exposure doses (EDI) differs from the order solely ranked based on the raw median concentrations in urine (Table 2; DEP > DiBP > DnBP > DEHP > DINP > BBzP > DIDP > DINCH > DEHTP). The median EDIs of PEs in Flemish adolescents (2016-2020) were lower compared to Belgian adults and Danish adolescents (6-21 years old) (Frederiksen et al. 2011; Dewalque et al.

405 2014a), but higher compared to Norwegian adults (Giovanoulis et al. 2016). The median EDI of DINCH
406 was comparable to those reported for Portuguese adolescents (12-17 years old), whereas the EDI of
407 DEHTP was higher in the current study (Correia-Sá et al. 2017; Lessmann et al. 2017). The EDIs of all
408 measured compounds for Flemish adolescents (2016-2020) were lower than the reference doses (RfD)
409 determined by the U.S. Environmental Protection Agency (Table 5). Similar results were obtained when
410 values were compared with available tolerable daily intakes (TDI) calculated by the European Food
411 Safety Authority. Only a small percentage of participants (6% which corresponds to 24 adolescents)
412 exceeded the limit for DiBP ($1.0x10^4$ ng/kg bw/day).
413 Overall, these results indicate a low risk potential of PE and AP exposure for Flemish adolescents based
414 on current knowledge and based on risk assessment of single compounds neglecting potential
415 cumulative effects of PEs. Continued monitoring is recommended given the known, sometimes
416 cumulative, toxic effects of PEs and other environmental chemicals on human health (Howdeshell et
417 al. 2017).
418

419 **4. Conclusions**

420 The results of FLEHS IV show that adolescents in Flanders, Belgium, are simultaneously exposed to
421 various PEs and APs, indicating the widespread use of these chemicals present in our daily lives. We
422 also found significant associations with determinants identified from questionnaire data such as the
423 presence of building materials containing PVC, ventilation habits, socio-economic status and season.
424 Although levels of several PE metabolites (DEHP, MEP, MnBP, MiBP and MBzP) have decreased
425 significantly compared to previous cycles, we have now detected for the first time in Flemish
426 adolescents several substitute chemicals, such as DINCH and DEHTP in almost every sample. However,
427 preliminary risk assessment showed that none of the exposure levels of APs exceeded the available
428 health-based guidance values. A small proportion of participants exceeded the HBM value of MnBP
429 (0.5%) and MiBP (1.9%), which shows that continuous surveillance of exposure to legacy PEs is
430 warranted despite the strict regulations implemented by the European institutions. The exposure data
431 presented in this work are representative for Flanders, Belgium and will not only serve as future
432 reference, but will also contribute to the aligned studies of the European project HBM4EU in order to
433 promote the protection of European citizens against environmental health risks.

434 **Table 5: Estimated daily intakes (EDI in ng/kg bw/day) of PEs and APs, calculated based on urinary metabolite concentrations (*n* = 407).**

	DEP	DiBP	DnBP	BBzP	DEHP	DINP	DIDP	DEHTP	DINCH
	based on MEP	based on MiBP	based on MnBP	based on MBzP	based on 4 metabolites	based on 2 metabolites	based on 3 metabolites	based on OH-MEHTP	based on 2 metabolites
min	111.0	93.2	102.5	0.1	242.0	79.5	80.6	2.4	102.1
25th per	539.3	532.6	388.3	47.4	864.4	424.9	193.2	435.8	356.1
50th per	941.0	852.7	578.5	91.5	1202.9	648.8	264.3	715.8	548.1
75th per	2507.9	1600.7	991.4	207.4	1836.5	997.6	363.1	1294.6	976.3
95th per	16154.3	4178.1	1756.1	1091.9	3530.7	2521.6	735.1	4706.9	2744.4
max	129546.7	19311.6	5345.2	2837.6	9570.9	52362.9	8432.7	163450.5	56547.8
TDI (ng/kg bw/day)		$1.0x10^4$	$1.0x10^4$	$5.0x10^5$	$5.0x10^4$	$1.5x10^5$	$1.5x10^5$		$1.0x10^6$
% > TDI		6	0	0	0	0	0		0
ratio TDI/95th per		2	6	458	14	59	204		364
RfD (ng/kg bw/day)	$8.0x10^5$	$1.0x10^5$	$1.0x10^5$	$2.0x10^5$	$2.0x10^4$			$1.0x10^6$	$7.0x10^5$
% > RfD	0	0	0	0	0			0	0
ratio RfD/95th per	50	24	57	183	6			212	255
Direct comparison of urinary concentrations with HBM or BE values									
HBM value (ng/mL)		230	190	3000	500 (A)				3000
% > HBM-I value		1.9	0.5	0	0				0
BE value (ng/mL)	18000	2700	200	3800	400 (B)	390 (C)			
% > BE value	0	0	0.5	0	0	0			

435 Tolerable daily intake (TDI) and reference dose (RfD) values were taken from Wittassek et al. (2011); Bhat et al. (2014); Giovanoulis et al. (2016); Lessmann et
436 al. (2016); Kasper-Sonnenberg et al. (2019). HBM values and biomonitoring equivalent (BE) values were taken from Aylward et al. (2013); Apel et al. (2017).
437 The abovementioned HBM-GV_{GenPop} values of MiBP, MnBP, MBzP and the sum of DEHP metabolites for the general population are under development in
438 HBM4EU and not yet confirmed by European authorities. (A) HBM-I value for the sum of OH- and oxo-MEHP. (B) BE value for the sum of cx-MEPP, OH-, oxo-,
439 and MEHP. (C) BE value for cx-MINP only. per: percentile

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