Environmental Research 214 (2022) 113852

Contents lists available at ScienceDirect

Environmental Research

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

Urinary levels of parabens, phthalate metabolites, bisphenol A and plasticizer alternatives in a Belgian population: Time trend or impact of an awareness campaign?

Catherine Pirard [a,b,*], Corinne Charlier [a,b]

[a] Laboratory of Clinical, Forensic and Environmental Toxicology, CHU of Liege, B35, 4000, Liege, Belgium
[b] Center for Interdisciplinary Research on Medicines (CIRM), University of Liege (ULiege), CHU (B35), 4000, Liege, Belgium

ARTICLE INFO

Keywords:
Human biomonitoring
DINCH
phthalates
Parabens
Bisphenols
Adult population

ABSTRACT

A human biomonitoring study was carried out in 2015 within an adult population living in Liege (Belgium). Some phthalate metabolites and parabens were measured in the urine of 252 participants, and information were collected about their food habits, life styles and home environment to identify some predictors of exposure. Concomitantly, an awareness campaign was initiated by the Provincial Authorities of Liege and spread over 2 years. Three years later (2018), 92 of the initial participants provided again urine samples, and the levels of phthalate metabolites, phthalate substitute (DINCH), parabens, bisphenol-A and bisphenol alternatives (bisphenol-S, –F, -Z, -P) were determined and compared to those obtained in 2015 to assess time trends. In 2015, methyl- and ethylparaben were the most abundant parabens (P50 = 9.12 μg/L and 1.1 μg/L respectively), while propyl- and butylparaben were sparsely detected. Except for mono-2-ethylhexyl phthalate and 6-OH-mono-propyl-heptyl phthalate, all other targeted phthalate metabolites were positively quantified in most of the urine samples (between 89 and 98%) with median concentrations ranging between 2.7 μg/L and 21.3 μg/L depending on the metabolite. The multivariate regression models highlighted some significant associations between urinary phthalate metabolite or paraben levels and age, rural or urban character of the residence place, and the use of some personal care products. However, all determination coefficients were weak meaning that the usual covariates included in the models only explained a small part of the variance. Between 2015 and 2018, levels of parabens and phthalate metabolites significantly decreased (from 1.3 to 2.5 fold) except for monoethyl phthalate which seemed to remain quite constant. Contrariwise, all bisphenol alternatives and DINCH metabolites were measured in higher concentrations in 2018 vs 2015 while BPA levels did not differ significantly. However, it was not feasible to unequivocally highlight an impact of the awareness campaign on the exposure levels of the population.

1. Introduction

Parabens are alkyl esters of p-hydroxybenzoic acid used as preservatives in cosmetics, pharmaceutical products, food and food packaging, due to their broad-spectrum antimicrobial properties, stability, low acute toxicity and cost (Soni et al., 2005). They are found individually or in mixture in many everyday life products such like liquid soap, hand and body wash, body lotion, face cream, shampoo, conditioner, foundation, lip and eye makeup, sunscreens, hair products, but also baked food, soft drinks, jams, jellies, sauces, processed vegetables, fats and oils, etc (Błędzka et al., 2014; Dodson et al., 2012; Guo et al., 2014; Soni et al., 2005). Thus human exposure can occur through ingestion, dermal absorption, or inhalation, with personal care products (PCP) considered to be the main sources (Błędzka et al., 2014; Darbre and Harvey, 2008; Soni et al., 2005).

Phthalic acid esters, more commonly called phthalates, are a class of high volume production chemicals. They are used as additives and plasticizers on one hand to increase flexibility, transparency and durability of polyvinyl chloride (PVC) plastics for those with high molecular weights (such like di(2-ethylhexyl) phthalate (DEHP), diisononyl phthalate (DiNP), etc), while on the other hand the low molecular weight ones such like dimethyl phthalate (DMP), diethyl phthalate (DEP) or di-n-butyl phthalate (DnBP) are added as solvent in adhesive, wax and ink, and as humectants, emollients, or skin penetration enhancer in cosmetics and personal care products (Dodson et al., 2012;

* Corresponding author. Laboratory of Clinical, Forensic and Environmental Toxicology, CHU of Liege, B35, 4000, Liege, Belgium.
E-mail address: c.pirard@chuliege.be (C. Pirard).

https://doi.org/10.1016/j.envres.2022.113852
Received 12 May 2022; Received in revised form 4 July 2022; Accepted 6 July 2022
Available online 9 July 2022

Abbreviations:

PCP	personal care products
PVC	polyvinyl chloride
DEHP	di(2-ethylhexyl) phthalate
diNP	diisononyl phthalate
DMP	dimethyl phthalate
DEP	diethyl phthalate
DnBP	di-n-butyl phthalate
BPA	bipshenol-A
ED	endocrine disruptors
EU	European Union
BPF	bisphenol-F
diNCH	Di(isononyl) cyclohexane-1,2-dicarboxylate
HBM	human biomonitoring
PCBs	polychlorobiphenyls
MP	methylparaben
EP	ethylparaben
PP	propylparaben
BP	n-buthylparaben
MEP	monoethyl phthalate
MnBP	mono-n-butyl phthalate
MiBP	mono-iso-butyl phthalate
MEHP	mono-2-ethylhexyl phthalate
5-OH-MEHP	mono-2-ethyl-5-hydroxyhexyl phthalate
5-oxo-MEHP	mono-2-ethyl-5-oxohexyl phthalate
MBzP	monobenzyl phthalate
UPLC-MS/MS	ultra high pressure liquid chromatography-tandem mass spectrometry
OH-MINCH	cyclohexane-1,2-dicarboxylate-mono-(7-hydroxy-4-methyl)octyl ester
cx-MINCH	cyclohexane-1,2-dicarboxylate-mono-(7-carboxylate-4-methyl)heptyl ester
cx-MiNP	7-carboxy-(mono-methyl-heptyl) phthalate
OH-MiDP	6-OH-mono-propyl-heptyl phthalate
MRM	multiple reaction monitoring
BPS	bisphenol-S
BPZ	bisphenol-Z
BPP	bisphenol-P
MSTFA	N-methyl-N-(trimethylsilyl)trifluoroacetamide)
GC-MS/MS	gas chromatography-tandem mass spectrometry
LOQ	limit of quantification
SVHC	Substance of Very High Concern

Guo and Kannan, 2013; Heudorf et al., 2007; Koniecki et al., 2011; Schettler, 2006). Phthalates are therefore present in a wide range of consumer products like building materials, solvents, paints, medical devices, textiles, toys, food contact materials, personal care products and cosmetics, oral medications, etc (Dodson et al., 2012; Halden, 2010; Schettler, 2006; Serrano et al., 2014). The routes of exposure for the general population include ingestion of contaminated food (having been in contact with packaging) or house dust, inhalation or dermal absorption from personal care products, inhalation of indoor air (contaminated by releasing from paints, covering materials for walls and floors), and medical exposure (through dialysis, blood transfusions, or oral medications) (Bekö et al., 2013; Halden, 2010; Koniecki et al., 2011; Schettler, 2006).

Bipshenol-A (2,2′-bis-[4-hydroxyphenyl]propane) or BPA has been mainly used as monomer in the manufacture of polycarbonate plastics and epoxy resins. Numerous consumer products contain BPA, especially food packaging like drinking bottles, food and beverage containers or cans, but also adhesives, toys, water pipes, electric and electronic devices, thermal papers, sport safety equipment, dental cements, etc (Geens et al., 2011; Vandenberg et al., 2007; Von Goetz et al., 2010). Due to its capacity to migrate from the food container into the food, the main BPA's source of exposure for the general population is thought to be dietary ingestion, while inhalation or ingestion of dust, dermal contact and dental sealants would be minor exposure pathways (Geens et al., 2009, 2011; Lakind and Naiman, 2008; Morgan et al., 2011; Vandenberg et al., 2007; Von Goetz et al., 2010; Wilson et al., 2007).

These 3 classes of chemicals have the common properties, among others, to be ubiquitously present in our daily environment, and to be suspected or confirmed to act as endocrine disruptors (ED), thus able to exert several adverse health effects in human and wildlife beings. The exposure to these ED has been linked to reproductive impairments and infertility, neurodevelopmental disorders, hormone-dependent cancers, obesity, diabetes, thyroid disorders, oxidative stress, genotoxicity, although the relationships with some of these health endpoints are still controversial (Bledzka at al. 2014;Dabre and Harvey, 2008; Hauser and Calafat, 2005; Heudorf et al., 2007; Katsikantami et al., 2016; Liu et al., 2021; Ma et al., 2019; Rochester, 2013; Soni et al., 2005). Because of the potential health risk related to our exposure to these chemicals, some restrictions and regulations have been progressively implemented worldwide since early 2000's. For instance in the European Union (EU), some phthalates and BPA have been banned or restricted gradually over two decades in toys and childcare products, in food contact materials, in cosmetics, in infant feeding bottles, etc. Thus alternatives have been increasingly marketed and used in many applications. BPA has been replaced by several structurally close analogues such like bisphenol-S (BPS; 4,4′-sulfonyldiphenol) or bisphenol-F (BPF; 4,4′-dihydroxydiphenylmethane) in different industrial applications and everyday products, for instance in lacquers, varnishes, adhesives and glues, dyes, dental sealants, thermal papers, food packaging, can coatings, although their toxicity is still poorly documented and often suggested to be similar (Chen et al., 2016; Kitamura, 2005; Pelch et al., 2019; Rochester et al., 2015; Rosenmai et al., 2014). Di(isononyl) cyclohexane-1,2-dicarboxylate (DINCH) has been used as substitute for high molecular weight phthalates in flexible PVC products including food packaging materials, medical devices, childcare products and toys (Biedermann-Brem et al., 2008; Crespo et al., 2007).

The impact of these chemical regulations has already been captured through human biomonitoring (HBM) studies which highlighted decreasing time trends in human exposure for several restricted or banned chemicals such like organochlorine pesticides (Hardell et al., 2010; Noest et al., 2013; Petrik et al., 2006), perfluorinated compounds (Glynn et al., 2012; Kato et al., 2011), lead (Egan et al., 1976; Lermen et al., 2021; Pollock et al., 2021; Wang et al., 2021); phthalates (Bastiaensen et al., 2021; Koch et al., 2017; Reyes and Price, 2018; Schwedler et al., 2020; Shin et al., 2020; Tranfo et al., 2018; Zota et al., 2014), BPA (Frederiksen et al., 2020; Gyllenhammar et al., 2017; Gys et al., 2021), etc. Beside the actions of the authorities enforcing the manufacturers to reduce their uses of hazardous substances in our everyday life products, the reduction of the population exposure could also be at least partly induced by raising public awareness on the health risks related to chemical exposure. By changing their consumer behaviors, they could create an increasing demand for safer products, thus pressuring the industrials to change the market by replacing hazardous chemicals. The most successful example would likely be the "market shift" within the cosmetics industry initiated by nearly 200 American non-governmental and non-profit organizations constituting The Campaign for Safe Cosmetics. They achieved to get decreased or removed several toxic chemicals in the formulations of personal care products and cosmetics from hundreds American cosmetics industry leaders from 2004 to 2011 (Sarantis et al., 2011). Recently, some HBM

studies demonstrated a decrease of the urinary levels of non-persistent chemicals such like parabens, phthalates or BPA, for people who changed their consumer behaviors following information campaigns where advices to reduce exposure were provided (Dodson et al., 2020; Kim et al., 2021). However, these studies monitored the exposure to the target chemicals over a short time period (maximum 1 month), and the sustainability of the behavioral change and thus of the reduced exposure was not monitored.

In similar perspective, the authorities of the Province of Liege (Belgium) in collaboration with the Clinical, Forensic and Environmental Toxicology lab of the University Hospital of Liege launched an information and awareness campaign, spread over 2014 and 2016, towards the general population on the occurrence of endocrine disruptors in our daily life and the potential associated health risks. A HBM study was concomitantly carried out to assess the current levels of exposure of the adult population of Liege to several ED including both persistent and non-persistent chemicals. Three years later, some of the initial participants were involved again in a follow-up HBM study to assess the long-term impact of such campaign on some non-persistent ED exposure. The levels of mercury and cadmium in the urine samples, and organochlorine pesticides and polychlorobiphenyls (PCBs) in the serum samples collected in 2015 from 252 adults living in Liege were previously reported (Pirard et al., 2018). In the present manuscript are presented on one hand the urinary levels of phthalates and parabens in this population and the identification of some predictors of exposure, and on the other hand the time trends in the exposure of the same population to parabens, phthalates, phthalate substitute, bisphenol-A and several bisphenol alternatives 3 years later.

2. Materials and methods

2.1. Study population and awareness campaign

The timeline of the awareness campaign events, recruitments and chemical analyses is summarized in Fig. 1. In October 2014, a first conference-debate "Environmental pollutants, endocrine disruption and cancer: the point of knowledge" for general public was organized by the Health and Quality of Life Service of the Province of Liege institution (a Belgian public institution) where the problematic of the endocrine disruptors was exposed by a toxicologist, launching the biomonitoring study jointly carried out with the Clinical, Forensic and Environmental Toxicology lab of the University Hospital of Liege and initially focused on cadmium, mercury, organochlorine pesticides, PCBs, phthalates and parabens. Thereafter, the students from Provincial High Schools and the workers of the Province of Liege institution (more than 14,000 people) were informed of the biomonitoring study through a newsletter published on the local intranet. Between February and May 2015, 252 volunteers aged from 18 to 76 years old and living in Liege (Belgium) were recruited. The recruitment process was already detailed elsewhere (Pirard et al., 2018). At the end of September 2015, each participant received own individual results in a letter with some explanations on the chemicals measured, on how to interpret the results, and with some advices to reduce their exposure. Two weeks later (beginning of October 2015), an information session intended to the participants was held to help them to understand and interpret properly their results, and to provide them personal advices to reduce their exposure. In June 2016, a second conference intended for general public was hold ("Contamination of the inhabitants of the Province of Liege by endocrine disruptors, these chemicals capable of upsetting our hormonal balance") to present the global results of the biomonitoring study, parallel to the publication of a brochure on the website of the Province of Liege institution gathering information on chemicals suspected to act as endocrine disruptors, and advice to reduce exposure of each chemicals described. Thus during this awareness campaign spread over 2 years, the participants potentially received information on the targeted substances (toxicity, sources of exposure, advices to reduce exposure) 5 times through different communication channels.

In June 2018, the 252 initial volunteers were contacted again to participate to a second phase aimed to evaluate the potential impact of the awareness campaign. Among them, 92 agreed to participate again, providing between June and September 2018 a urine spot sample collected in 250 mL polypropylene vessel, and answering to a short questionnaire about their feeling concerning the impact of the awareness campaign on their daily behaviours, and about their personal care product and cosmetic uses. All communication documents intended to the participants (inform consents, information leaflets, results letters, etc) used for the present study were strongly inspired from those elaborated during the COPHES/DEMOCOPHES study at the Belgian level.

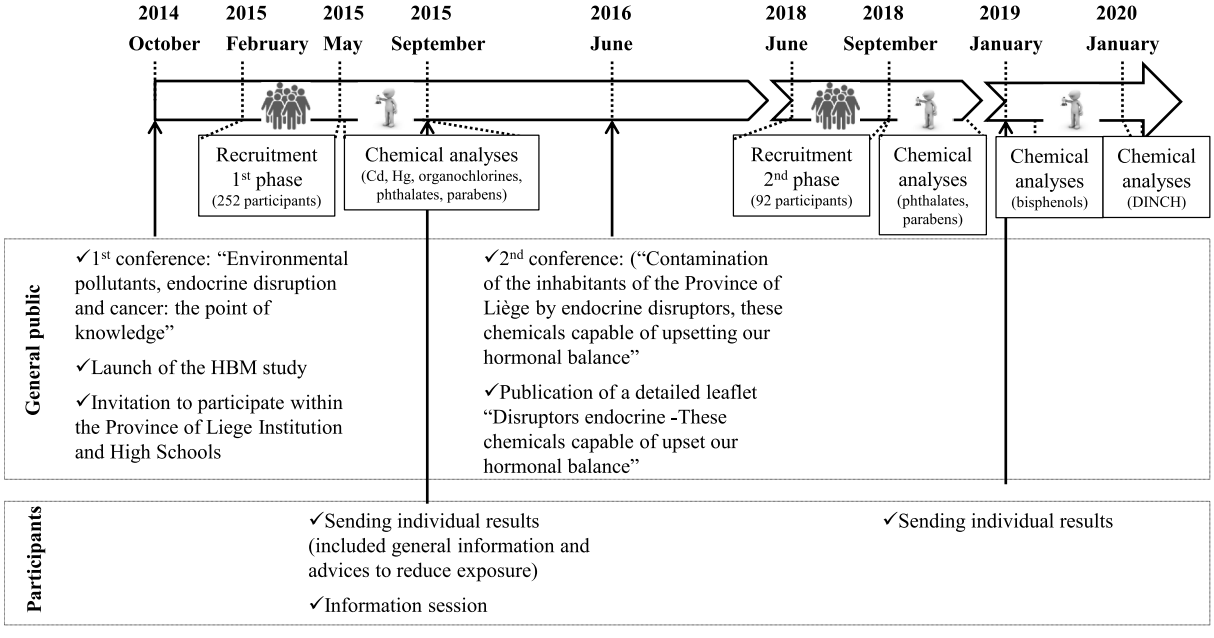

Fig. 1. The timeline of the awareness campaign events, recruitments and chemical analyses.

2.2. Analytical methods

2.2.1. Paraben, phthalate metabolite and DINCH biomarker measurement

Methylparaben (MP), ethylparaben (EP), propylparaben (PP), n-buthylparaben (BP), monoethyl phthalate (MEP), mono-n-butyl phthalate (MnBP), mono-2-ethylhexyl phthalate (MEHP), mono-2-ethyl-5-hydroxyhexyl phthalate (5-OH-MEHP), mono-2-ethyl-5-oxohexyl phthalate (5-oxo-MEHP), and monobenzyl phthalate (MBzP) were determined between May and June 2015 in urine of the 252 initial participants, and between August and November 2018 in urine collected for the second phase of the study, according to the method validated by Dewalque et al. (2014). Briefly, 3 mL of urine samples were enzymatically hydrolyzed using Helix pomatia glucuronidase, and extracted by solid phase extraction using Bond Elut Certify LRC cartridges. The final determination was performed using ultra high pressure liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) in negative electrospray mode.

Cyclohexane-1,2-dicarboxylate-mono-(7-hydroxy-4-methyl)octyl ester (OH-MINCH), cyclohexane-1,2-dicarboxylate-mono-(7-carboxylate-4-methyl)heptyl ester (cx-MINCH), 7-carboxy-(mono-methyl-heptyl) phthalate (cx-MiNP), and 6-OH-mono-propyl-heptyl phthalate (OH-MiDP) were measured in January 2020 in the urine samples collected in 2015 and 2018 for the 92 individuals who participated to both studies, using the above-described analytical procedure used for phthalate metabolites and parabens, but updated with the following small adaptations. Native OH-MINCH, cx-MINCH, cx-MiNP and OH-MiDP (purchased from Cambridge Isotope Laboratories, Andover, MS, USA) were added in the stock standard solutions, as well as their labeled homologues ($^{13}C_4$) in the internal standard solutions (also purchased from Cambridge Isotope Laboratories). Moreover, the following multiple reaction monitoring (MRM) transitions were monitored: 313.2 > 152.9 and 317.2 > 156.9 for respectively native and labeled OH-MINCH; 327.2 > 173.2 and 331.2 > 173.1 for respectively native and labeled cx-MINCH; 321.0 > 173.0 and 325.0 > 173.0 for respectively native and labeled cx-MiNP; and 321.0 > 173.0 and 325.0 > 124.0 for respectively native and labeled OH-MiDP. For all these targets the acquisition windows were enlarged (1 min on either side of the retention time of the analytical standard) to ensure to include all peaks corresponding to the isomer mixtures.

2.2.2. Bisphenol measurements

The measurement of BPA, BPF, bisphenol-S (BPS), bisphenol-Z (BPZ) and bisphenol-P (BPP) in the urine samples collected in 2015 and 2018 from the volunteers participating to both phases was performed in the beginning of 2019 using an analytical method previously described (Pirard et al., 2012) but slightly modified. The enzymatic hydrolysis and the SPE extraction were similar, but the further purification and derivatization steps were modified. Briefly, urine samples (3 mL) were enzymatically hydrolyzed with β-glucuronidase and sulfatase in a sodium acetate buffer (pH 5) for 30 min at 40 °C, extracted by solid phase extraction (Oasis HLB SPE cartridge) followed by liquid-liquid extraction using ethyl acetate, and then derivatized using MSTFA (N-Methyl-N-(trimethylsilyl)trifluoroacetamide). The final determination was carried out using gas chromatography-tandem mass spectrometry (GC-MS/MS) operating in MRM using electronic impact as ionization mode. Among the 92 urine samples collected in 2015 and 2018, 86 and 90 samples respectively had remaining high volume enough to perform bisphenol analyses. The detailed analytical procedure including sample preparation and GC-MS/MS conditions is reported in the Supplementary Data.

2.2.3. Quality assurance

Each unknown sample sequence consisted of a calibration curve (spiked LC/MS grade water or synthetic urine) extracted as real samples, 1 reagent blank, two home-made Quality Controls (spiked water or synthetic urine at low and high levels), one reference material sample obtained from previous German External Quality Assessment Scheme for Analyses in Biological Materials (G EQUAS; material 14/15 for BPA, and material 9 for phthalate metabolites), and N = 30 unknown samples. Because the calibration curves built form spiked water or synthetic urine were extracted as real samples, they took into account the potential lab background contamination which thus was automatically subtracted during the quantification process. For BPA, BPS, and MEHP, the intercept of the curves did not pass through zero reflecting the background input from the lab in the extracted curve samples. The reagent blanks were used to ensure that the lab contamination was under control. The calculated concentrations of all markers measured in the reagent blanks for all sequences of unknown samples were either equal to zero or at most equal to LOQ/3. Detailed results related to QC are provided in Supplementary Data (Table S1).

The lab is regularly participating for phthalate metabolites and BPA to G EQUAS organized twice a year by the Institute and Out-Patient Clinic for Occupational, Social and Environmental Medicine of the University Erlangen-Nuremberg (http://www.g-equas.de/info.htm), and for BPA, BPF, BPS, and BPZ to the External Quality Assessment Scheme for Organic Substances in Urine (OSEQAS), organized twice a year by the "Institut national de santé publique du Québec, Centre de toxicologie du Québec" (https://www.inspq.qc.ca/en/ctq/eqas/oqesas/description). Moreover, the lab successfully participated to several HBM4EU QA/QC programs and was qualified as "HBM4EU lab" for the analyses of BPA, BPS, BPF, and for all phthalate metabolites measured within this study. Both DINCH metabolites were also determined in few samples from the HBM4EU ICI/EQUAS study on DINCH biomarkers and the results obtained were compared to the assigned values to check that all peaks belonging to the biomarkers were properly integrated and to ensure accurate measurement.

The integrity of the samples over the whole study period was tested by adapting a strategy developed within the HBM4EU project. Phthalate metabolites and parabens were measured in 2021 in 10 samples (5 low and 5 high levels) previously collected and analyzed in 2015 (stored at −20 °C during these 6 years). The correlation between the first and second measurements was tested by Spearman rank (r) correlation, and appeared to be high for all phthalate metabolites and parabens (r values ranged between 0.972 and 0.996). The differences in absolute values (expressed as the percentage change between the second measurement and the mean of both measurements) did not exceed 25% except for MEP (for which 1 measurement in 2021 was 29% lower than previously measured). The arithmetic means of the percentage changes ranged between −4.6% and −8.0% according to the compound considered (and +4.0% for MEP) meaning that the second measurements were on average slightly lower than the first ones, although for each compound some samples were overestimated while some others were underestimated during the second round of measurements. These differences between results obtained in 2015 and 2021 would thus likely come from analytical variations rather than chemical degradation, and would therefore demonstrate the stability of these compounds under the storage conditions. Because the stability of DINCH metabolites seems to be comparable to phthalate metabolites (Mol et al., 2022; Silva et al., 2013), the urinary DINCH metabolite levels and by extrapolation the bisphenol levels were assumed to be stable under the present storage conditions although it could not be demonstrated.

2.2.4. Statistical analyses

The descriptive statistics for all 3 DEHP metabolites were reported separately, and together (DEHP metab) by summing the molar concentrations of each metabolites (concentration divided by molecular weight) and multiplied this molar sum by the average molecular weight of the DEHP metabolites (288 g/mol) (Zota et al., 2014). For inference statistics oxidized metabolites (5-OH-MEHP and 5-oxo-MEHP) were summed because being highly correlated (Shin et al., 2020). The levels measured below the limit of quantification (LOQ) were replaced by half the LOQ value (Hornung and Reed, 1990). The normality of the

distribution of each biomarker level was evaluated using the Shapiro-Wilk test. Since all chemicals showed a highly skewed distribution, nonparametric tests were applied.

2.2.4.1. First set of results: phthalate metabolites measured in the 252 initial urine samples collected in 2015. The statistical analyses performed on the results obtained from the samples collected during the first phase of the study (levels of phthalate metabolites and parabens measured on 252 samples collected in 2015 as well as the answers to the first complete questionnaire) were performed using the SAS 9.4 statistical software (SAS Institute, Cary, NC, USA). Multiple regressions adjusted for gender and age (as continuous variable) were conducted to test the association between log-transformed biomarker levels (to obtain a less skewed distribution) and each covariate detailed in Supplementary Data (Table S2), except for PP and BP because of their low frequencies of quantification. A question about blood donation or perfusion in the last 24 h was asked but not used in the statistical models because of the very few positive answers. All covariates were tested for both women and men together, but some of them were additionally tested for women only (i.e. use of makeup removal, nail polish and nail polish remover, number of makeup products) or men only (use of shaving gel or foam, aftershave). Then multivariate regression models were constructed with covariates which were roughly correlated to the biomarker levels ($p<0.1$) in the univariate analyses. Statistical significance was set at $p<0.05$.

2.2.4.2. Second set of results: levels of all markers measured in the urine samples from the 92 volunteers participating in both 2015 and 2018 campaigns. The time trends in the exposure of parabens, phthalates, DINCH, BPA, BPF, BPS, BPZ and BPP were assessed by comparing using Statistica 12 (Dell Software, France) the urinary levels measured in the urine samples collected in 2015 for the 92 volunteers participating to both campaigns, and in the levels measured in the urine samples collected in 2018 from these same 92 individuals. The differences between the chemical levels measured in the samples collected in 2015 and 2018 were assessed by Wilcoxon matched pairs test for both gender considered together and separately.

3. Results

3.1. Characteristics of study populations

The main characteristics of the initial volunteers recruited in 2015 were previously detailed (Pirard et al., 2018). Briefly, the 252 participants were aged from 18 to 76 years old and were equally distributed between women and men (127 and 125 respectively), between age groups (18–29, 30–39, 40–49, 50–59, >60), and between the urban or rural character of their residence place. Some information about the 92 volunteers who participated at the second phase in 2018 are gathered in Table 1. Among them 36%, predominately women, reported to have attended at least at one conference during the awareness campaign or read the brochure published on the website, 27% declared to have changed some of their daily behaviors to reduce their exposure to endocrine disruptors not only focused on phthalate, paraben or bisphenol exposure (i.e. food consumption or food handling/process, cosmetic or PCP uses, tobacco status, etc), and 29% declared to have changed specifically their cosmetic or PCP uses, again more often women than men. Even if the number of participants is quite low, the fact that a higher number of female participants are interested to reduce their pollutant exposure compared to males is consistent with what was observed during a Swiss study where women seemed to have a higher risk perception of chemicals (Dickson-Spillmann et al., 2011).

Table 1
Involvement of the population participated to both HBM phases (2015 and 2018) towards the awareness campaign.

	Total N (%)	Men N (%)	Women N (%)
All	92 (100)	43 (46.7)	49 (53.3)
Age			
Mean ± SD (yrs)	49.0 ± 10.2	46.6 ± 11.2	49.4 ± 9.3
Range (yrs)	22–79	22–77	25–72
Conference attendance			
Yes	33 (35.9)	12 (13.1)	21 (22.8)
Change in daily behaviour			
Yes	30 (32.6)	9 (9.8)	21 (22.8)
Change in PCP or cosmetic use			
Yes	27 (29.3)	8 (8.7)	19 (20.6)

3.2. Urinary phthalate metabolite levels and predictors of exposure for the 252 initial participants recruited in 2015

Table 2 gathers the frequencies of quantification (levels above LOQ) and the levels of phthalate metabolites and parabens (geometric means, percentiles 5, 25, 50, 75, 95, and minimum and maximum levels) measured in the 252 initial urine samples collected in 2015. As expected MP was the most frequently detected and the most abundant measured among parabens, followed by EP. PP and BP were less detected with respectively 25 and 11%. The results of the multivariate regression models built with covariates roughly correlated in the univariate analyses to phthalate metabolite and paraben levels are gathered in Table 3. MP levels were significantly higher in women compared to men in the univariate regressions but this difference disappeared in the multivariate models. MEHP and MBzP levels decreased with increasing age while of MP and EP levels increased, with statistical significance in both univariate and multivariate models. Among the dietary behaviours or specific food consumption within the last 24 h (related to the packaging), only the consumption of some frozen food packed in carton was significantly associated for oxidized DEHP metabolites and MnBP (and borderline significantly for MEP), but only 8 participants (3%) reported to have eaten such food. MEP was not associated with cosmetic and PCP uses recorded except the application of sunscreens in the past 24 h (positively), the frequency of use of shaving products (positively, borderline significance) and the frequency of paraben-free PCP use (negatively). The urinary levels of DEHP oxidized metabolites and MEHP were positively associated with respectively makeup products and artificial nails. Higher levels of MnBP and MBzP (borderline significant) were measured in the urine of the participants living in urban area.

3.3. Time trend for marker levels measured in the urine samples from the 92 volunteers participating in both 2015 and 2018 campaigns

Table 4 gathers the levels of parabens, phthalate metabolites, DINCH metabolites and bisphenols in the urine samples collected in 2015 and 2018 from the volunteers participating to both campaigns, while Fig. 2 presents the levels measured in 2015 and 2018 for women and men separately (P5, P50, P95 and p-value) for parabens and phthalate metabolites. For most compounds (MP, EP, PP, MnBP, MBzP, DEHP metabolites, and OH-MiDP), the decrease in urinary levels was more pronounced and/or only significant for women.

4. Discussion

4.1. Urinary phthalate metabolite levels and predictors of exposure for the 252 initial participants recruited in 2015

The profile of phthalate metabolites was similar to the one usually reported, with high detection rates for all metabolites (a bit lower for MEHP), and a wide range of concentrations measured. Compared to the results previously observed in a quite similar Belgian adult population (living in Liege) recruited 2 years earlier (Dewalque et al., 2014), the urinary levels of parabens in the present study are 2–2.5 times lower, the

Table 2
Number of participants (N), LOQ, frequencies of quantification (levels above LOQ), geometric means (GM), percentiles 5, 25, 50, 75, 95, and minimum and maximum levels, measured in the 252 initial urine samples collected in 2015. All concentrations are expressed in μg/L.

	N	LOQ	N > LOQ	GM	P5	P25	P50	P75	P95	Min-Max
		(μg/L)	(%)	(μg/L)	(μg/L)	(μg/L)	(μg/L)	(μg/L)	(μg/L)	(μg/L)
Parabens										
MP	252	0.79	86.1	7.64	<LOQ	1.40	6.59	30.03	248.06	<LOQ-11655.00
EP	252	0.30	74.2	1.28	<LOQ	<LOQ	1.00	3.75	37.12	<LOQ-854.10
PP	252	0.36	25.0	0.50	<LOQ	<LOQ	<LOQ	0.24	41.73	<LOQ-1444.00
BP	252	1.00	11.1	0.61	<LOQ	<LOQ	<LOQ	<LOQ	2.97	<LOQ-23.10
Phthalate metabolites										
MEP	252	0.94	97.2	25.35	1.91	9.40	24.35	65.58	405.42	<LOQ-1852.35
MnBP	252	0.99	96.4	15.26	1.94	8.31	17.50	31.98	81.96	<LOQ-203.70
MBzP	252	0.61	86.9	2.96	<LOQ	1.30	3.12	6.43	28.02	<LOQ-155.80
5-oxo-MEHP	252	0.53	94.0	2.73	<LOQ	1.40	2.81	5.79	13.79	<LOQ-72.80
5-OH-MEHP	252	0.43	97.2	4.06	0.78	2.00	4.10	8.50	19.90	<LOQ-132.70
MEHP	252	0.62	61.1	0.98	<LOQ	<LOQ	0.90	2.20	6.35	<LOQ-52.30
DEHP metab	252	–	–	7.67	0.76	3.33	7.71	16.30	39.62	<LOQ -255.67

levels of DEHP metabolites and MnBP are 2–3 fold lower, while the MEP and MnBzP levels are similar in the urine of both presently and formerly recruited populations. Because the exposure of the worldwide population to these endocrine disruptors was demonstrated to be age and/or gender dependent likely due to difference in lifestyle habits (food consumption, cosmetic uses, time spent indoors, etc) (Bastiaensen et al., 2021; Dewalque et al., 2014; Geens et al., 2014; Hartmann et al., 2015; Giovanoulis et al., 2016; Lim, 2020; Park et al., 2019; Saravanabhavan et al., 2013) and has been decreased since the early 2000s (Bastiaensen et al., 2021; Kim et al., 2021; Koch et al., 2017; Reyes and Price, 2018; Tranfo et al., 2018; Wittassek et al., 2007; Zota et al., 2014), the results obtained were compared with those from some large scale studies carried out on mixed-gender adult populations recruited within a similar time period (between 2012 and 2016) and gathered in Table 5. The urinary levels of parabens in the present Belgian adult population were similar to those measured in the urine of some French and Dutch populations (Balicco et al., 2019b; Fillol et al., 2021; Van der Meer et al., 2021), but considerably lower than those reported from Australia (Heffernan et al., 2015), Canada (Health Canada, 2017) or the United States (CDC, 2019) where the chemicals in PCP and cosmetics are drastically less regulated than in Europe (Sarantis et al., 2011). The higher urinary levels of parabens measured within the Norwegian RHINESSA study (Vindenes et al., 2021) would at least partly be explained by the later implementation of the 2014's EU regulation on parabens in Norway (Vindenes et al., 2021), the younger study population, and the different patterns of PCP and cosmetic uses. The levels of phthalate metabolites in the urine of our Belgian adult participants were globally close to the results reported from the Netherland, Norway, and the United States (CDC, 2019; Giovanoulis et al., 2016; Van der Meer et al., 2021), except for MnBP which showed lower levels in the urine of the US population, nearly twice higher levels than those observed in Germany (Koch et al., 2017), but far lower than levels measured in a French population.

In the univariate regressions, MP levels were significantly higher in women compared to men but this difference disappeared in the multivariate models demonstrating that the usual difference observed between women and men for parabens would be due to some gender-dependent habits such like the use of cosmetics (Calafat et al., 2010; Kiani Feizabadi et al., 2020; Honda et al., 2018; Kang et al., 2016; Moos et al., 2015; Zhao et al., 2021). The associations observed between the levels of some phthalate metabolites and parabens, and the age of the participants were previously observed (Dewalque et al., 2014). Although this relationship used to be inconsistent in the literature (Fromme et al., 2007; Giovanoulis et al., 2016; Park et al., 2019; Ye et al., 2008), a positive association between paraben levels and age has been frequently reported (Calafat et al., 2010; Frederiksen et al., 2013; Kang et al., 2016; Giovanoulis et al., 2016; Zhao et al., 2021). Nevertheless the increased use of PCP and cosmetics with age suggested as an attempt of explanation in most of these studies could not be assumed in the present work because the correlation was significant using the multivariate models which took into account the number and the frequency of uses of these products. However, it's likely that the type of PCP and cosmetic used would change with age, and thus the paraben exposure would evolved. Moreover, it's still unclear how the paraben bioavailability, pharmacokinetics and metabolic pathways would differ according to age or other personal characteristics.

Unexpectedly, although diet is thought to be the main source of exposure for high molecular weight phthalates (Schettler, 2006), none of the food consumption (except the consumption of some frozen food packed in carton) was associated to phthalate metabolite levels. Also surprisingly, MEP was associated with very few cosmetic and PCP uses, whereas DEP is commonly added to PCP and cosmetics such like hair products, makeup and foundation, lotion, hand soap, shampoo, shaving products, deodorant, perfume, etc (DiGangi and Norin, 2002; Dodson et al., 2012; Gkrillas et al., 2021; Guo and Kannan, 2013; Helm et al., 2018; Houlihan et al., 2002; Koniecki et al., 2011), and a large number of studies already demonstrated the association between MEP urinary levels and the use of such products (Berger et al., 2019; Cantonwine et al., 2014; Ding et al., 2019; Duty et al., 2005; Fisher et al., 2019; Nassan et al., 2017; Pagoni et al., 2022; Qin et al., 2021; Romero-Franco et al., 2011; Runkel et al., 2020; Wallner et al., 2016; Watkins et al., 2014). The use of DEHP and other phthalates in cosmetics and PCP was banned in EU or North America for many years (Regulation EC 1223/2009; Koniecki et al., 2011). However, DEHP has been detected in low concentrations in some perfumes, deodorants, skin toners, nail polishes, shaving cream, lipsticks, or hair products (Dodson et al., 2012; Guo and Kannan, 2013; Helm et al., 2018; Koniecki et al., 2011) likely due to the transfer from plastic packaging to content or as impurity. Thus the positive association observed between the urinary levels of DEHP metabolites, and makeup products and artificial nails was not surprising and was consistent with other previous studies (Romero--Franco et al., 2011; Qin et al., 2021; Runkel et al., 2020). Finally, the difference in some phthalate metabolite levels according to the urban or rural character of the residence place observed in the present study seemed similar to what was observed in the urine of Egyptian girls (Colacino et al., 2011) or Indian men (Pant et al., 2008), while other studies reported contradictory results (Blount et al., 2000; Park et al., 2019). This difference (or not) would come from different lifestyle adopted by city and country dwellers, such like dietary habits, use of plastic products, time spent indoor, etc, which would be related to the country or region, the age class (adults or children), the socioeconomic status etc, resulting in apparent discrepancies between studies. The lower MEP levels measured in the urine of participants using paraben free PCP, the negative association between DEHP metabolite and MBzP levels with the frequent use of aftershave, or between MEP levels and the presence of PVC decoration at home could not rationally be explained

Table 3
Results of the multivariate regression models (R^2 of the regression, β, Standard Error and p-value) built with the covariates correlated in the univariate analyses (with $p < 0.1$) and the logarithm of the phthalate metabolite and paraben concentrations.

	MEP ($R^2 = 0.151$)		Sum oxidized DEHP ($R^2 = 0.239$)		MEHP ($R^2 = 0.246$)		MBzP ($R^2 = 0.111$)	
Variable	β ± SE	p-value	β ± SE	p-value	β ± SE	p-value	β ± SE	p-value
Intercept	2.93 ± 0.45	<.001	1.91 ± 0.34	<.001	1.24 ± 0.50	0.014	1.81 ± 0.33	<.001
Gender (woman vs man)	0.02 ± 0.32	0.955	−0.52 ± 0.28	0.070	−0.53 ± 0.29	0.068	−0.14 ± 0.22	0.522
Age (years)	0.01 ± 0.01	0.729	−0.00 ± 0.01	0.857	***−0.02 ± 0.01***	***0.006***	***−0.01 ± 0.01***	***0.013***
Residence area (urban vs rural)							0.31 ± 0.17	0.063
Food consumtion in the last 24h								
Frozen food packed in carton (yes vs No)	0.76 ± 0.42	0.069	***0.85 ± 0.31***	***0.008***	0.47 ± 0.30	0.123		
Frozen food wrapped in plastic (yes vs No)	−0.11 ± 0.24	0.662	−0.36 ± 0.21	0.093	−0.12 ± 0.20	0.547		
Canned food (yes vs No)					−0.39 ± 0.27	0.145		
Catering or fast-food type foods (yes vs No)	0.44 ± 0.29	0.136						
Use of cosmetics and PCP								
Hand soap (>5x/day vs < 2/day)					0.05 ± 0.40	0.896		
Hand soap (3–4x/day vs < 2/day)					−0.11 ± 0.39	0.779		
Shower gel, bath or soap (frequency)							0.13 ± 0.09	0.136
Deodorant or perfume (frequency)	0.05 ± 0.09	0.562						
Shampoo (frequency)					−0.06 ± 0.03	0.083		
Makeup removal (frequency)			−0.01 ± 0.04	0.817	−0.02 ± 0.04	0.661		
Shaving gel or foam (frequency)	0.10 ± 0.06	0.061						
Aftershave (frequency)			***−0.14 ± 0.04***	***0.002***	***−0.12 ± 0.04***	***0.008***	***−0.12 ± 0.05***	***0.013***
Makeup products (number)	0.12 ± 0.08	0.121	0.08 ± 0.07	0.239	***0.15 ± 0.07***	***0.031***		
Lotions and creams for body and face (number)							−0.09 ± 0.06	0.110
Paraben free PCP (yes vs No)	***−0.51 ± 0.22***	***0.022***						
Sunscreen in the last 24 h (yes vs No)	***1.12 ± 0.53***	***0.037***						
Wearing artificial nails (yes vs No)	0.76 ± 0.54	0.162	***1.22 ± 0.48***	***0.012***				
Miscellaneous								
Home renovation in the last year (yes vs No)			0.22 ± 0.18	0.211				
PVC frames or paneling at home (yes vs No)	***−0.52 ± 0.20***	***0.011***						
Daily time spent in new car (>1 h/d vs < 1 h/d)	0.40 ± 0.20	0.053	−0.27 ± 0.20	0.179	−0.19 ± 0.19	0.320		

	MnBP ($R^2 = 0.181$)		MP ($R^2 = 0.243$)		EP ($R^2 = 0.170$)	
Variable	β ± SE	p-value	β ± SE	p-value	β ± SE	p-value
Intercept	4.18 ± 0.90	<.001	0.15 ± 0.42	0.731	−1.39 ± 0.54	0.011
Gender (woman vs man)	−0.14 ± 0.23	0.559	0.34 ± 0.34	0.313	−0.30 ± 0.35	0.387
Age (years)	−0.01 ± 0.01	0.239	***0.02 ± 0.01***	***0.009***	***0.03 ± 0.01***	***0.004***
Residence area (urban vs rural)	***0.54 ± 0.21***	***0.010***				
Food consumtion in the last 24h						
Frozen food packed in carton (yes vs No)	***0.91 ± 0.37***	***0.016***			0.81 ± 0.49	0.101
Frozen food wrapped in plastic (yes vs No)	−0.21 ± 0.24	0.375			−0.01 ± 0.27	0.998
Canned food packed (yes vs No)						
Catering or fast-food type foods (yes vs No)						
Use of cosmetics and PCP						
Antibacterial hand sanitizer (<2/day vs 0x/day)			0.39 ± 0.31	0.208		
Antibacterial hand sanitizer (>2/day vs 0x/day)			0.17 ± 0.32	0.591		
Hand soap (>5x/day vs < 2/day)						
Hand soap (3–4x/day vs < 2/day)						
Shower gel, bath or soap (frequency)						
Lip balm (frequency)			0.18 ± 0.11	0.085	0.20 ± 0.11	0.063
Deodorant or perfume (frequency)						
Shampoo (frequency)						
Makeup removal (frequency)						
Shaving gel or foam (frequency)						
Aftershave (frequency)	−0.08 ± 0.05	0.111				
Nail polish remover (frequency)			0.63 ± 0.42	0.135		
Bath salts or foam (frequency)			0.13 ± 0.08	0.125	***0.16 ± 0.08***	***0.039***
Makeup products (number)			0.13 ± 0.10	0.195	***0.29 ± 0.10***	***0.004***
Lotions and creams for body and face (number)			0.11 ± 0.10	0.283	0.01 ± 0.09	0.972
Paraben free PCP (yes vs No)					***−0.57 ± 0.26***	***0.028***
Sunscreen in the last 24 h (yes vs No)			***1.88 ± 0.63***	***0.003***		
Wearing artificial nails (yes vs No)						
Miscellaneous						
Home renovation in the last year (yes vs No)						
PVC frames or paneling at home (yes vs No)						
Daily time spent in new car (>1 h/d vs < 1 h/d)	−0.26 ± 0.24	0.276				

and would likely be due to chance or to unconsidered confounding factors.

Many studies have demonstrated increased urinary levels of parabens, mainly MP, with the use of PCP and cosmetics such like body and hand washes, shaving products, sunscreens, deodorant and other fragrance products, lip makeup and/or balm, foundation, lotion, face and hand creams, etc (Berger et al., 2019; Ding et al., 2019; Fadaei et al., 2021, Hajizadeh et al., 2020; Harley et al., 2016; Hong et al., 2021; Kang et al., 2016; Nassan et al., 2017; Sakhi et al., 2017; Vindenes et al., 2021). Thus in the present study, it was unexpected that only very few associations were observed between cosmetic and PCP uses and MP urinary levels. It was also surprising that only the urinary levels of EP decreased with the use of paraben free PCP, while MP levels seemed to be not affected. Moreover, the determination coefficients of the multivariate regression models for all biomarkers (parabens and phthalate metabolites) were weak meaning that the covariates included in the

Table 4
Comparison between marker levels measured in the samples collected in 2015 and 2018 from volunteers participating to both campaigns (in μg/L).

	N		LOQ	N > LOQ (%)		P50 (μg/L)		P75 (μg/L)		P95 (μg/L)		
	2015	2018	(μg/L)	2015	2018	2015	2018	2015	2018	2015	2018	p-value
Parabens												
MP	92	92	0.79	83.7	83.7	9.12	3.56	65.13	11.68	251.61	128.92	***0.002***
EP	92	92	0.30	77.2	62.0	1.08	0.58	5.48	2.16	37.12	18.75	***0.002***
PP	92	92	0.36	25.0	28.3	<LOQ	<LOQ	<LOQ	0.54	50.54	15.84	0.118
BP	92	92	1.00	9.8	4.3	<LOQ	<LOQ	<LOQ	<LOQ	2.92	<LOQ	0.347
Phthalate metabolites												
MEP	92	92	0.94	95.7	97.8	21.25	20.37	62.85	57.34	320.46	689.67	0.629
MnBP	92	92	0.99	97.8	97.8	18.96	11.81	28.81	25.31	63.18	76.97	***0.021***
5-oxo-MEHP	92	92	0.53	92.4	85.9	2.67	1.92	5.05	3.93	12.90	7.76	***0.045***
5-OH-MEHP	92	92	0.43	96.7	96.7	3.75	2.89	8.30	5.90	17.04	12.84	0.175
MEHP	92	92	0.62	62.0	47.8	1.11	<LOQ	2.14	1.23	6.61	3.75	***0.002***
DEHP metab	92	92	–	–	–	7.45	4.72	15.31	10.92	36.22	24.09	-
MBzP	92	92	0.61	89.1	81.5	3.20	1.85	5.83	3.41	18.49	12.86	***0.002***
cx-MiNP	87	90	2.00	95.6	91.1	3.71	3.40	6.57	6.39	38.28	14.55	0.504
OH-MiDP	87	90	2.00	31.0	27.8	<LOQ	<LOQ	1.38	1.10	4.81	2.40	***0.037***
DINCH metabolites												
OH-MINCH	87	90	2.00	24.1	35.6	<LOQ	<LOQ	<LOQ	4.76	10.31	35.99	***0.032***
cx-MINCH	87	90	2.00	19.5	34.4	<LOQ	<LOQ	<LOQ	2.76	9.13	24.30	0.309
Bisphenols												
BPA	86	90	0.29	74.4	77.8	0.82	0.79	1.52	1.58	3.26	7.96	0.492
BPS	86	90	0.09	24.4	45.6	<LOQ	<LOQ	<LOQ	0.25	0.56	1.59	***0.005***
BPF	86	90	0.07	38.4	57.8	<LOQ	0.12	0.11	0.39	0.67	1.41	***0.001***
BPZ	86	90	0.06	10.5	22.2	<LOQ	<LOQ	<LOQ	<LOQ	0.12	0.85	***0.036***
BPP	86	90	0.09	1.2	16.7	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	0.72	***0.005***

statistical models only explained a small part of the variance (less than 25%), and thus main sources of exposure were not taken into account. The apparent miss of factor impacting significantly the paraben body burden of our population could also resulted from a misclassification of the exposure because the questions about cosmetic and PCP uses remained quite general, and the information collected did not included the brand nor the content in parabens of the products used.

4.2. Time trend for marker levels measured in the urine samples from the 92 volunteers participating in both 2015 and 2018 campaigns

As shown in Table 4, the exposure to all parabens (not significantly for PP and BP) and phthalate metabolites decreased for our participants between 2015 and 2018, including the former phthalate alternatives to DEHP (OH-MiDP, and cx-MiNP not significantly), but except MEP for which urinary levels seemed to remain quite constant. Some studies already demonstrated that providing personalized information on own chemical exposure and how to reduce it could result in lower body burden levels of the aware population (Dodson et al., 2020; Kim et al., 2021). Although in the present study each participant received after the first campaign the results of the analyses of his own biological samples and advices to reduce his exposure to the chemicals measured, it's not clear how far this awareness campaign launched between 2015 and 2018 in the province of Liege really positively affected their daily exposure. On one hand, while more women reported to be concerned by their exposure to endocrine disruptors (by being present at the different conferences and/or by changing their daily habits following the awareness campaign), a stronger decrease was observed for women vs men for most of the chemicals measured (as observed Fig. 2). Moreover, for instance for MP, EP or PP, all the participants showing in 2015 a urinary level above the P90 (mentioned in the personalized letters) saw their levels drastically decreased in 2018 (results not shown), except one individual for whom similar or higher levels were measured. The stable trend observed for MEP could be explained by the lack of labelling requirement for this compound thus making avoidance difficult for the consumers (Dodson et al., 2020; Helm et al., 2018). On the other hand, the variation of the levels measured in 2015 and 2018 for parabens was compared between participants who reported to have changed their behavior in terms of cosmetic uses vs those who have not (results not shown), and did not significantly differ (the impact of the change in daily cosmetic use was not investigated for the other markers considered as less related to cosmetics). Note that no detailed information was collected about the nature of this change. Furthermore, such decreases in phthalate and paraben exposure for a same individual over a several year period were already reported within a Dutch population between 2009 and 2016 (Van der Meer et al., 2021), albeit no particular sensitization was done between the two measurements. The limitation of paraben content in cosmetics which was implemented for all products available on the EU market from the end of July 2015 (see Table 6), i.e. 2 months after the first phase recruitment, could fairly explain the drastic decrease measured for all esters.

Regarding phthalates, a downward trend in exposure was observed worldwide since the early 2000s (Bastiaensen et al., 2021; Kim et al., 2021; Koch et al., 2017; Reyes and Price, 2018; Tranfo et al., 2018; Wittassek et al., 2007; Zota et al., 2014) also likely resulting from the several restrictions on phthalate uses implemented in Europe these past decades (Table 6), and more specifically their updated in the REACH Candidate List of Substance of Very High Concern (SVHC) based on endocrine disrupting properties and reprotoxicity (ECHA candidate list, 2021). The dependence of the time trend for phthalate exposure with the regulations implemented was also consistent with the stable urinary level observed for MEP since until now DEP has escaped from the main restrictions in EU (EC 201-550-6).

As expected and already observed (Frederiksen et al., 2020; Gyllenhammar et al., 2017; Kasper-Sonnenberg et al., 2019; Schütze et al., 2014; Silva et al., 2013), the urinary levels of the DINCH metabolites increased between 2015 and 2018 (not significantly for cx-MiNP) likely resulting from the increasing use of DINCH as substitute for high molecular phthalates (Giovanoulis et al., 2016; Kasper-Sonnenberg et al., 2019; Schütze et al., 2014). However, the levels measured in the urine of our participants seemed to be higher for both metabolites than those reported from a German population recruited in 2017 (Kasper-Sonnenberg et al., 2019), or from a US population in 2016 (CDC, 2019), but this comparison should be interpreted with caution because of the lower sensitivity of our analytical method. Similarly, all bisphenol alternatives were measured in higher concentrations in 2018 vs 2015 although these concentrations remained low compared to BPA, and higher urinary levels of BPS and BPF were reported from France (Balicco et al., 2019b;

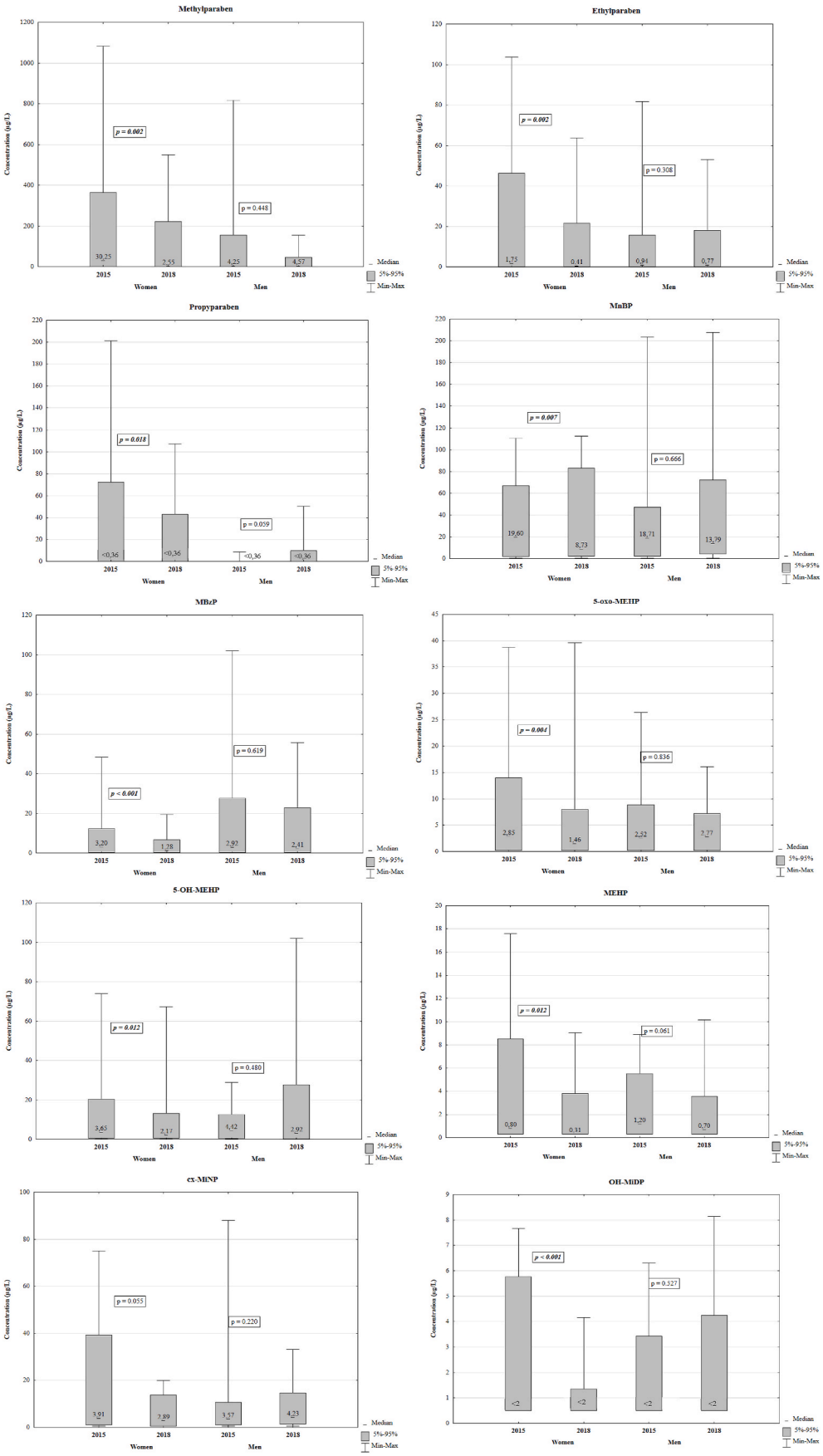

Fig. 2. Concentrations of parabens and phthalate metabolites measured in 2015 and 2018 for women and men separately (P5, P50, P95 and p-value).

Table 5
Comparison of urinary phthalate metabolite and paraben levels (measured in the present HBM with some international studies.

Country	Years	N	Cohort	Population (age)	MP (μg/L)	EP (μg/L)	PP (μg/L)	BP (μg/L)	MEP (μg/L)	MBzP (μg/L)	MnBP (μg/L)	DEHP metab. (μg/L)	References
Belgium	2015	252	-	Adults (>18 yrs)	6.59	1.00	<0.36	<1.00	24.4	3.12	17.5	7.71	Present study
Belgium	2013	194	–	All (1–85 yrs)	16.1	1.70	1.20	<1.00	34.3	5.50	33.3	17.6	Dewalque et al., 2014
The Netherlands	2014–2015	500	Lifeline	Adults (>18 yrs)	4.81	0.76	0.21	<0.06	31.5	2.01	12.5	10.6	Van der Meer et al., 2021
France	2014–2016	600–897	Esteban	Adults (18–74 yrs)	6.75	1.04	<0.50	<0.50	52.0*	6.0*	18.5*	17.6*	Balicco et al., 2019b
Czech	2013	201	FANTOM	Adults (18–65 yrs)	–	–	–	–	14.2	–	36.9	21.0	Müllerová et al., 2016
Germany	2015	60	ESB	Adults (20–30 yrs)	–	–	–	–	13.5	1.20	8.00	8.50	Koch et al., 2017
Norway	2013–2014	61	–	Adults (20–66 yrs)	–	–	–	–	24.2	3.50	13.4	10.5	Giovanoulis et al., 2016
Norway	2014–2015	496	RHINESSA	Adults (18–47 yrs)	19.3	1.71	1.72	0.11	–	–	–	–	Vindenes et al., 2021
Korea	2012–2014	6478	KoNEHS	Adults (>19 yrs)	–	–	–	–	–	3.63	31.6	40.5	Park et al., 2019
Autralia	2012–2013	2400	–	All (0- >60 yrs)	232	33.5	60.6	4.32	–	–	–	–	Heffernan et al., 2015
USA	2015–2016	1690	NHANES	Adults (>20 yrs)	31.7	<1.00	4.00	<0.10	29.0	3.70	9.80	9.90	CDC (2019)
Canada	2014–2015	2564	CHMS	All (3–79 yrs)	15.0	<0.90	2.00	<0.30	–	–	–	–	Health Canada (2017)

* geometric mean

Table 6
Regulations on phthalates, parabens and BPA at the EU level.

Chemicals targeted	Years	Actions	Regulations n°
Phthalates			
DEHP, DnBP, BzBP, DINP, DiDP, DnOP	1999	Restrictions in toys and childcare intended to be placed in mouth (<3 years)	EC/815/1999
DEHP, DnBP, BzBP, DiNP, DiDP, DnOP	2006	Inclusion in the list of substances subject to authorization within REACH	EC/1907/2006
DEHP, DnBP, BzBP, DiNP, DiDP, DnOP	2006	Restrictions in toys and childcare (<0.1%)	EC/84/2005
DEHP, DnBP, BzBP, DiDP, DiNP	2007	Restrictions in food contact materials with exceptions (migration limits)	EC/19/2007
DEHP, BzBP, DnBP	2009	Ban in cosmetics	EC/1223/2009
DEHP, DnBP, BzBP, DiDP, DiNP	2011	Restrictions in food contact materials (migration limits)	EU/10/2011
DEHP, DnBP, BzBP, DiBP	2014	Inclusion as SVHC list (within REACH)	ED/108/2O14
DEP	2015	No need for regulatory action	EC 201-550-6
DEHP, DnBP, BzBP, DiBP	2017	Inclusion in the SVHC list as substances toxic for reproduction	Amending EC/ 1907/2006
DEHP, DnBP, BzBP, DiBP	2017	Inclusion in the SVHC list as endocrine disruptors	ED/30/2017
DEHP, DBP, BBP and DIBP	2019	Restriction in EEE (<0.1%)	EU/863/2015
DEHP, DnBP, BzBP, DiBP	2020	Restrictions in any plastics with few exceptions (<0.1%)	Annex EC/322/ 2018
Parabens			
MP, EP, PP	2011	Restrictions in food contact materials (migration limits)	EU/10/2011
MP, EP, PP, BP	2014	Restrictions in cosmetics (<0.4% for single paraben, <0.8% for mixtures)	EU/358/2014
Bisphenols			
BPA	2006	Inclusion in the list of substances subject to authorization within REACH	EC/1907/2006
BPA	2009	Ban in cosmetics	EC/1223/2009
BPA	2011	Restrictions in food contact materials (migration limits)	EU/10/2011
BPA	2011	Ban from infant feeding bottles	EU/8/2011
BPA	2017	Inclusion in the SVHC list as substances toxic for reproduction	Amending EC/ 1907/2006
BPA	2017	Inclusion in the SVHC list as endocrine disruptors	ED/30/2017
BPA	2017	Restrictions in toys and childcare intended to be placed in mouth (migration limits)	EU/898/2017
BPA	2018	Restriction in food contact materials (decreased migration limits)	EU/213/2018
BPA	2020	Restriction in thermal paper (<0,02%)	EU/2235/2016

Fillol et al., 2021), Norway (Vindenes et al., 2021) or US (CDC, 2019). On the other side, steady BPA level was observed between 2015 and 2018 contrariwise to the worldwide general trend highlighted this last decade (CDC, 2019; Frederiksen et al., 2020; Gyllenhammar et al., 2017; Gys et al., 2021; Huang et al., 2018; Van der Meer et al., 2021) and despite the different EU regulations aimed to restrict BPA uses and set in the same time frame than those related to phthalates (Table 6). Nevertheless, compared to a similar study previously carried out in Liege in 2011 (Pirard et al., 2012), the urinary median concentration measured was roughly three times lower (0.79 μg/L in 2018 vs 2.46 μg/L in 2011). The median levels measured and thus the difference observed within this time period were very close the those reported for Belgian adolescents recruited within the FLEHS cycles (from Northern part of Belgium) in 2008–2009 and 2017–2018 (Gys et al., 2021). The more pronounced

decrease compared to earlier period (before 2011) could support that the implementation of migration limits in food contact materials (EU/10/2011) was more effective in reducing human exposure to BPA than other more recent policy actions gathered in Table 6 (e.g. the inclusion in the SVHC list as endocrine disruptors), unless the interval between the latest policy action (2017) and the sample collection (2018) was a bit tight to observe any influence. Another explanation could be that the pressure of the public opinion alerted by the heated controversial debate about the safety of BPA within the EU and several media campaigns against BPA (around 2010) would prompt manufacturers to anticipate regulations and thus begin to market earlier products BPA-free labeled.

4.3. Study limitations

It should be mentioned that this study suffered from several limitations. First, the use of urinary spot samples to assess the exposure of such non persistent chemicals with short biological half-lives used to be questionable. The variability of urinary levels of phthalate metabolites, parabens and BPA has been already extensively studied and fair to poor reproducibility depending on the chemicals has been reported (Aylward et al., 2017; Bastiaensen et al., 2020; Dewalque et al., 2015; Frederiksen et al., 2013; Fromme et al., 2007; Hauser et al., 2004; Koch et al., 2014; Lassen et al., 2013; Teitelbaum et al., 2008). If several strategies have been suggested to reduce the potential resulting misclassification including the collection of multiple spots (individually or pooled), the use of 24 h-pooled urine, the collection of the first-morning void, the adjustment for creatinine content or for specific gravity (Bastiaensen et al., 2020; Casas et al., 2018; Frederiksen et al., 2013; Perrier et al., 2016; Philppat and Calafat., 2021; Valvi et al., 2015), none seemed to perfectly compensate the high intra-individual variability for some chemical levels and the unadjusted measurement in single spot samples is, up to now, the most used strategy when the sampling size is large enough. Because the size of the present studied population is not so large, the statistical analyses to test the concentration variations between 2015 and 2018 were also performed on creatinine adjusted levels, and if for few targets, the results were slightly different (results not shown), the main trends and conclusions remained similar. Secondly, the population recruited was not fully representative of a general Belgian population in terms of age (adults only), socio-economical status, of geographical distribution (covered a local area around Liege), due to the small size of the population who participated to both measurement campaigns, and because the recruitment was carried out on a voluntary basis (with no other incentive than obtain personal results) thus was biased with a higher proportions of already concerned individuals. The covariates included in the regression models to identify some predictors of exposure were a priori selected and did likely not cover all potential sources, thus other confounders should be missed (as highlighted by the weak determination coefficients of the multivariate regression models). Moreover, some questions administrated were very general and unspecific, e.g. about cosmetic and PCP uses, resulting in the miss of exposure sources.

5. Conclusion

This study provided on one hand the levels of exposure to phthalates and parabens in 2015 in a general Belgian adult population living in Liege (Southern part of Belgium) and tried to identify some predictors of exposure among daily habits or demographic characteristics. On the other hand, the temporal trends following an awareness campaign were assessed for parabens, phthalates and substitute (DINCH), and for BPA and bisphenol alternatives (BPS, BPF, BPZ and BPP).

The main findings of the initial campaign were firstly that the paraben levels observed in the urine of our participants were close to those reported from other European countries where similar regulations were set. Secondly the covariates included in the regression models and a priori selected based on the major known routes of exposure only explained a small part of the variance for phthalate metabolite and paraben urinary levels, advocating for further studies on the current sources of exposure for both chemical families.

The second part of this study consolidated the decrease in phthalate and paraben exposure observed worldwide since the 2000s within the general population, likely at least partially due to the several EU regulations implemented, and an increase exposure for substitutes (DINCH and bisphenols other than BPA). It was not feasible to unequivocally highlight a possible impact of the awareness campaign on the exposure levels of the population, but one third of the participants reported to have changed their habits to reduce their daily exposure to chemicals. If this kind of awareness campaign towards potential harmful substances could be enlarged to other larger-scale populations, one's can hope that this could result in an increasing consumer demand for safer products and thus to a market change.

Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethical approval

This protocol was approved by the Hospital Faculty Ethics Committee of the University of Liege (B707201422894).

Credit author statement

Catherine Pirard: Conceptualization; Validation; Investigation; Writing – original draft. Corinne Charlier: Conceptualization; Supervision

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2022.113852.

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