Reviewing the variability in urinary concentrations of non-persistent organic chemicals : evaluation across classes, sampling strategies and dilution corrections

Reviewing the variability in urinary concentrations of non-persistent organic chemicals: evaluation across classes, sampling strategies and dilution corrections

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Abstract

Various biomonitoring studies have been carried out to investigate the exposure of populations by measuring non-persistent organic chemicals in urine. To accurately assess the exposure, study designs should be carefully developed to maximise reproducibility and achieve good characterization of the temporal variability. To test these parameters, the intraclass correlation coefficients (ICCs) are calculated from repeated measurements and range from poor (<0.4) to excellent (≥ 0.75). Several studies have reported ICCs based on diverse study designs, but an overview, including recommendations for future studies, was lacking. Therefore, this review aimed to collect studies describing ICCs of non-persistent organic chemicals, discuss variations due to study design and formulate recommendations for future studies. More than 60 studies were selected, considering various chemical classes: bisphenols, pyrethroids, parabens, phthalates, alternative plasticizers and phosphate flame retardants. The variation in ICCs for an individual chemical was high (e.g. ICC of propyl paraben = 0.28 - 0.91), showing the large impact of the study design and of the specific exposure sources. The highest ICCs were reported for parabens (median = 0.52), while lowest ICCs were for 3-phenoxybenzoic acid (median = 0.08) and bisphenol A (median = 0.20). Overall, chemicals that had an exposure source with high variation, such as the diet, showed lower ICCs than those with more stable exposure sources, such as indoor materials. Urine correction by specific gravity had an overall positive effect on reducing the variability of ICCs. However, this effect was mostly seen in the adult population, while specific compounds showed less variation with creatinine correction. Single samples might not accurately capture the exposure to most non-persistent organic chemicals, especially when small populations are sampled. Future studies that examine compounds with low ICCs should take adequate measures to improve accuracy, such as correcting dilution with specific gravity or collecting multiple samples for one participant.

Keywords

Human biomonitoring; intraclass correlation coefficient; urine; temporal variability; emerging contaminants;

1. Introduction

During the past decades, many new chemicals have been introduced into our environment and consumer products, such as alternatives to older, more persistent and sometimes regulated compounds. Brominated flame retardants were substituted by organophosphates, bisphenol A (BPA) was replaced by alternative bisphenols and phthalates were swapped for newer plasticizers. Humans are exposed to these emerging contaminants via various sources, such as air and dust from the indoor environment, food, consumer products and medical devices. Biomonitoring of these chemicals in human biological matrices is a valuable tool to assess internal exposure and potential health risks. Many of these emerging compounds are more polar and less metabolically stable and thus less persistent than their older counterparts, resulting in shorter biological half-lives and substantial variability in their urinary levels, within and between individuals and within and across days. Consequently, urinary concentrations of these emerging chemicals or their metabolites captured through spot sampling likely reflect only recent exposure (Aylward et al., 2014; Aylward et al., 2017; Christiansen et al. 2012; Preau et al., 2010). Environmental exposure to chemicals is constantly changing, causing difficulties in reliably determining total exposure, referred to as the exposome. Understanding the variability in the exposure patterns is crucial to establish time-dependent relationships between exposome and health outcomes, which require rigorous and well-designed studies. When characterizing the individual exposome, the biological half-life of a chemical is an important factor that contributes to the variation in exposure level across time and location. Therefore, determining the variability of exposure over time, considering relevant windows of susceptibility at different stages of life and establishing a sufficient sample size are critical topics to investigate in order to obtain reproducible results (Buck Louis et al., 2019; Chung et al., 2019).

Given the ever-rising number of emerging contaminants humans are exposed to, biomonitoring studies are frequently and increasingly carried out to characterize potential risks to human health. In order to correctly perform risk assessment, it is important that exposure to these relatively new chemicals is accurately characterized. Because of the properties of many of these emerging contaminants, in particular the short half-lives), the study design, together with the resulting sampling campaigns and the number of participants, are of increasing importance to adequately extrapolate the internal human exposure to a broader population. In this context, a single spot (urine) sample, as is common in traditional biomonitoring campaigns, might not be representative to characterize the exposure of an individual. Recently, various efforts have been made to evaluate the reproducibility of biomonitoring measurements (Bastiaensen et al., 2020b; Gys et al., 2021b; Klimowska et al., 2020) or to estimate how many samples are needed per individual to obtain an accurate exposure assessment (Faÿs et al., 2020). However, a clear conclusion on this matter and suggestions for improvement of study design in the future are missing. Furthermore, it is not always feasible to collect human biological samples at multiple times in an epidemiological setting and to repeatedly analyse biomarkers of exposure in a large number of study participants.

The reproducibility of repeated measurements for non-persistent contaminants is often evaluated through the intraclass correlation coefficient (ICC), a frequently used statistical and non-dimensional parameter. ICC is composed of various components and is mathematically computed as the ratio of the between-individual variance to the total variance (i.e., the sum of the between- and within-individual variance components). The equation to calculate the ICC is as follows:

$$ICC = \frac{\sigma^2_{between\ indiv.}}{\sigma^2_{total}} = \frac{\sigma^2_{between\ indiv.}}{\sigma^2_{withi\ \ indiv.\ between\ day} + \sigma^2_{within\ indiv.\ within\ day} + \sigma^2_{between\ indiv.}}$$

A visual representation of the various components that contribute to the ICC value is presented in Figure 1. ICCs can range from zero (indicating low reproducibility over time) to one (indicating high reproducibility and less variability). The reproducibility of measurements, which ultimately is closely related to the ICCs, is usually categorized as poor (<0.40), fair to good (0.40 ≥ ICC > 0.75), and excellent (≥ 0.75) (Rosner, 2010). The lower the ICC for a certain compound is, the higher the probability that a single spot measurement could lead to a misclassification of the internal exposure to this chemical.

Many recent studies have reported ICCs for several chemicals in different study designs and populations, however, the wealth of these ICCs has not yet been used to evaluate variability over different chemical classes and recommend appropriate study designs for a particular population and time window of exposure. Compared to their older, more persistent counterparts, these chemicals are expected to present larger variability and thus classic biomonitoring studies based on one spot sample might result in substantial over- or underestimation of the average exposure of an individual. In this review, we summarize the ICCs obtained in the available studies for specific emerging, non-persistent chemicals and demonstrate how the ICCs and thus variability in concentrations of these chemicals were influenced by different factors, such as timing and duration of sampling, dilution/correction factor of urine, and the characteristics of the study population. We aimed to collect and highlight relevant available data on temporal variability expressed as ICCs for a broad range of (emerging) organic contaminants to allow researchers to optimize study design and interpretation of biomonitoring results for future studies.

2. Methods

The search for relevant papers was performed using PubMed and Web of Science by employing a combination of relevant keywords. The search for each compound class of interest contained the following key words: 'urine' with "variability OR variation OR ICC" and a specific key word related to the individual chemicals in the searched class, including chemical abbreviations. The specific key words are summarized in Table 1. No exclusion criteria for the year of publication were applied during the literature research. However, studies that collected urine samples only during 24 h or one full day were excluded from this

review. The influence of urinary dilution on the variability was evaluated by including concentrations corrected for creatinine levels (CRT), specific gravity (SG) or osmolality (OSM). Information related to the following compound classes (and their metabolites) was investigated: bisphenols, pyrethroids, parabens, phthalates, alternative plasticizers and organophosphate flame retardants. Several other classes, such as neonicotinoids, organophosphate pesticides, polycyclic aromatic hydrocarbon metabolites or triclosan were not included in this review due to data scarcity or knowledge about episodic exposures for some chemicals (e.g. several classes of pesticides).

3. Determinants of ICC values for various classes of chemicals

3.1. Bisphenols

Bisphenols are high-production volume chemicals used to produce polymers employed in various applications such as construction materials, adhesives, housing for electronic equipment, medical devices and protective coatings (Geens et al., 2012). However, they can also be used in their monomeric form as an additive in thermal paper products (Liao and Kannan, 2011; Vervliet et al., 2019). Additionally, due to degradation or incomplete polymerization, residual free bisphenol can leach out of the aforementioned applications and therefore be a source for human exposure (Kovačič et al., 2020). Historically, bisphenol-A (BPA) was used extensively, but due to suspected endocrine disruptive properties, worldwide regulations on its application are implemented (European Food Safety Authority, 2015; Kawamura et al., 2014). This leads to the increasing replacement of BPA with less characterized alternatives, such as other bisphenols. Human exposure and pharmacokinetics of BPA have been studied extensively for BPA, while fewer studies have investigated alternative bisphenols. There is no consensus yet on this topic, but based on the currently available data, it is accepted that exposure routes and behavior of alternative bisphenols are relatively similar to BPA. The main exposure route to bisphenols is thought to be oral ingestion, and absorption is rapid and almost complete. After ingestion, bisphenols are almost completely metabolized to the non-toxic glucuronide metabolite and quickly excreted in urine (half-life < 7-8 h) (Khmiri et al., 2020; Oh et al., 2018; Teeguarden et al., 2015; Thayer et al., 2015). Bisphenols have been detected in various biological matrices, with urine being the matrix of choice to measure internal human exposure. As a consequence of its replacement, internal BPA exposure has decreased in recent years, while extensive internal exposure to alternative bisphenols has recently been reported for the first time in populations (Gys et al., 2020; Gys et al., 2021a).

Variability in bisphenol concentrations

An overview of the 21 available studies that report short- and long-term variability and ICCs for bisphenols is presented in Table S1. BPA has been the most investigated bisphenol in urine, as its temporal variability has been evaluated in eight studies in the general population (Faÿs et al., 2020; Gys et al., 2021b;

Koch et al., 2014; Lassen et al., 2013; Morgan et al., 2018; Townsend et al., 2013; Wang et al., 2019b; Ye et al., 2015), ten papers in pregnant women (Braun et al., 2011; Braun et al., 2012; Casas et al., 2018; Fisher et al., 2015; Guidry et al., 2015; Jusko et al., 2014; Meeker et al., 2013a; Philippat et al., 2013; Vernet et al., 2018; Yazdy et al., 2018), and four in children (Casas et al., 2018; Heffernan et al., 2014; Stacy et al., 2016; Teitelbaum et al., 2008). For BPA, reported ICCs varied widely, from 0.04 to 0.60, depending on the sampling time frame and frequency, the total number of collected samples and the applied urinary dilution correction in the respective study (Gys et al., 2021b; Sakhi et al., 2018). The time frame in which samples were collected differed greatly, ranging from two days to two years, obviously implying a limitation in comparing results from these studies (Koch et al., 2014; Lassen et al., 2013; Morgan et al., 2018; Wang et al., 2019b). Four (Koch et al., 2014; Lassen et al., 2013; Morgan et al., 2018; Wang et al., 2019b) out of eight studies in the general population have shown ICCs of BPA estimated from 24 h-urine sampling in general adult population. Despite differences in the collection method of these daily pooled samples, dilution adjusted (SG or CRT) ICCs between these studies are quite consistent (ICCs 0.15 - 0.28) compared to those based on spot or morning void (MV) urine.

In pregnant women, urinary BPA variability has been estimated from spot urine samples, MVs or daily pools and resulted in ICCs ranging from 0.07 to 0.60. In all but one of these studies, ICCs estimated based on dilution-adjusted spot urine were lower than non-adjusted spot urine (Braun et al., 2011; Braun et al., 2012; Casas et al., 2018; Fisher et al., 2015; Guidry et al., 2015; Jusko et al., 2014; Meeker et al., 2013a; Philippat et al., 2013; Vernet et al., 2018; Yazdy et al., 2018). Due to physiological changes occurring throughout pregnancy, urinary dilution status may vary depending on the trimester in which samples were collected (Lee et al., 2021). In children, two studies have evaluated the influence of urinary dilution correction on the variability of urinary BPA concentrations. In both publications, it was reported that the ICC increased when a correction with CRT was applied (Stacy et al., 2016; Teitelbaum et al., 2008). Despite the number of studies that have assessed temporal variability of urinary BPA, so far no consensus had been established on the most suitable study design for urine sampling in order to achieve a reliable exposure assessment of BPA. However, this literature overview finds that a high variability could in general be observed for urinary BPA concentrations, regardless of study design, population or dilution correction.

For alternative bisphenols, data on temporal variability of repeated measurements is scarce, with very few publications available per compound for the BPA analogues, BPAP, BPF and BPS (Gys et al., 2021b; Vernet et al., 2018; Wang et al., 2019b). Variability of urinary BPAP concentrations has been studied just once and proved to be high for spot samples (ICC 0.09) when not corrected for urinary dilution (Gys et al., 2021b). For BPF, ICCs ranged from <0.01 (over the course of 12 weeks) to 0.44 (over 5 days) in different adult study populations (Faÿs et al., 2020; Gys et al., 2021b; Wang et al., 2019b). From these three studies, no conclusion could be drawn on the influence of the sample type (spot versus MV) on the reproducibility of urinary BPF concentration. The variability of BPS concentrations in urine was assessed in three studies as well, showing

differing but low reproducibility, with ICCs varying from <0.01 (over 5 days) to 0.20 (over 19 weeks) (Faÿs et al., 2020; Gys et al., 2021b; Vernet et al., 2018).

Despite the differences in study design and time frame, the outcomes of this small number of studies indicate that temporal variability is high for alternative bisphenols and collecting only one sample per participant could result in a misclassification of exposure. In addition, there is no consistent relation between the sampling timeframe (ranging from 5 days up to 26 weeks) and the ICC for these compounds. These differences between studies might partially be explained by the differing extent of application of these emerging compounds between regions, and thus strongly varying exposure patterns. Furthermore, the reported results of the abovementioned studies depend greatly on the included compounds and their respective limits of quantification, in particular for the alternative bisphenols. Correcting for the dilution of urine samples using the CRT or SG yields slightly higher ICCs (Gys et al., 2021b; Vernet et al., 2018). However, this comparison between urinary dilution adjustments has been carried out only in two studies and more data is needed to confirm the differences in the adjustment procedures.

3.2. Synthetic pyrethroids

Synthetic pyrethroids (SPs) are a group of insecticides commonly used around the world. They are more stable when exposed to sunlight than their natural precursors - pyrethrins (Bradberry et al., 2005; Kaneko, 2010; WHO, 2005). Due to their high insecticidal activity, low acute toxicity to mammals, and low persistence in the environment, SPs are widely used for crop protection, as well as in medical and animal care products. Furthermore, SPs are recommended by the WHO for the treatment of mosquito bednets in tropical countries for malaria vector control (WHO, 2021). Although SPs are found to be relatively safe for humans (e.g., compared to organophosphate insecticides), a higher urinary concentration of SP metabolites has been recently linked to neurodevelopmental and behavioral problems in children (Oulhote and Bouchard, 2013; Viel et al., 2015) and to abnormal reproductive parameters in adults (Jurewicz et al., 2020a; Jurewicz et al., 2015; Jurewicz et al., 2020b; Meeker et al., 2008; Meeker et al., 2009; Radwan et al., 2015). Recently, the concern about the safety of SPs has been emphasized by including pyrethroids on the list of prioritized substances provided by HBM4EU Initiative (Hbm4Eu, 2018). Dietary intake is considered a significant route of exposure to pyrethroids. However, non-dietary factors, such as dust ingestion, inhalation of indoor air and dermal exposure due to the use of insecticides on household pets, seem to play an additional and important role in exposure of humans to SPs (Morgan et al., 2007; Rodzaj et al., 2021; Yoshida et al., 2021). After entering the human body, pyrethroids are rapidly absorbed, metabolized, and eliminated in the urine as phase-II conjugates or in free form (Kaneko, 2010; Ratelle et al., 2015a; Ratelle et al., 2015b; Sams and Jones, 2012).

The most frequently quantified pyrethroid metabolites in human biomonitoring studies are non-specific metabolites, such as 3-phenoxybenzoic acid (3PBA) and cis/trans-3-(2,2-dichlorovinyl)-2,2-dimethyl-(1-

cyclopropane) carboxylic acid (cis/trans-DCCA) (Barr et al., 2010; Garí et al., 2018; Oulhote and Bouchard, 2013; Viel et al., 2015; Wielgomas et al., 2013; Ye et al., 2016). As these are common metabolites of several SPs, they are widely employed in the assessment of aggregated exposure to SPs. Since the pyrethroid metabolites are primarily excreted by kidneys, urine has become the primary biological matrix used in human biomonitoring studies. However, short urinary elimination half-lives of SP metabolites (< 7 h) (Ratelle et al., 2015a; Ratelle et al., 2015b; Sams and Jones, 2012) make the exposure assessment challenging.

Temporal variability in synthetic pyrethroids concentration

The literature search on the temporal variability in the urinary excretion of SP metabolites resulted in 9 papers describing short- and long-term variability of 3PBA urinary concentration in general populations (Faÿs et al., 2020; Klimowska et al., 2020; Li et al., 2019a; Lin et al., 2021; Morgan et al., 2016; Wielgomas et al., 2013), pregnant women (Barkoski et al., 2018) and children (Attfield et al., 2014; van Wendel de Joode et al., 2016). Nevertheless, only 3 papers reporting long-term studies included other metabolites, such as cis- and trans-DCCA (Attfield et al., 2014; Klimowska et al., 2020; Li et al., 2019a). Although different sampling strategies were employed in each study, the results are consistent for most SP metabolites.

In general, a high variability was observed for urinary concentrations of 3PBA with ICCs ranging from 0.00 to 0.35 (Attfield et al., 2014; Barkoski et al., 2018; Faÿs et al., 2020; Li et al., 2019a; Lin et al., 2021; Morgan et al., 2016; van Wendel de Joode et al., 2016). The reproducibility was only slightly improved when SG- and CRT-adjustment was applied. Similarly, the type of sample (spot, MV, or 24 h) increased only slightly the ICCs. On the contrary, however, two studies presented higher reproducibility for SP metabolites with ICCs ranging from 0.35 to 0.91 (Klimowska et al., 2020; Wielgomas et al., 2013). The overview of available studies reporting ICCs for SP metabolites is presented in Table S2.

A recent study on longitudinal temporal variability showed consistently high ICCs for three target SP metabolites (ICCs: 0.75-0.91) (Klimowska et al., 2020). The study relied on the monthly collection of one or two complete 24 h urine samples over 12 consecutive months. The benefit of this sampling design is that biomarker concentration in a 24 h sample represents an average daily exposure level, and thus is less susceptible to the intra-day fluctuations in chemical urinary excretion (Aylward et al., 2014). Interestingly, a similar low variability (high ICC) was observed for 3PBA in a short-term study when all urine spot samples were collected by seven adult volunteers over seven consecutive days (Wielgomas et al., 2013). In that study, the concentration of 3PBA was examined in each urine void, MV, and 24 h urine sample prepared by pooling all voids provided on a given day. Similar ICCs were obtained for spot and simulated 24 h samples (ICC: 0.60 and 0.68, respectively), whereas lower reproducibility was observed for MVs (ICC: 0.35). However, the highest ICCs occurred in spot (ICC: 0.85) and 24 h samples (ICC: 0.80) after adjustment to CRT level. Based on these results, Wielgomas (2013) concluded that a single random urine sample adequately represents the average exposure level to 3PBA precursors over a 7-day period.

In contrast to these findings, when only four random spot samples were collected over a week, the variability was rather high (ICCs: 0.01-0.05) (Lin et al., 2021). Likewise in another study, collection of two MVs, bedtime voids or 24 h samples over a week did not improve the reproducibility (ICCs: 0.00-0.21) (Morgan et al., 2016). The discrepancies among the various short-term studies may be due to differences in sampling strategy and the number of participants, since only seven individuals contributed to the former one, whereas 43 and 50 individuals participated in the latter two studies, respectively. On the other hand, Pleil and Sobus (2013) defined the number of measurements per person as a reliable indicator for ICC quality (Pleil and Sobus, 2013). In the study provided by Wielgomas (Wielgomas et al., 2013) participants collected averagely 5.7 samples daily giving about 40 spots over seven days. Only two long-term studies included similar number of individual spot samples, up to 40 samples per person over 44 days (Li et al., 2019a) or 43 samples per person over six months (Faÿs et al., 2020). However, it is expected that exposure level, from both diet and indoor environment, over short period is much less diversified than over several weeks or months. Interestingly, slightly higher ICCs in the range of 0.29-0.35 were computed from results in morning and bedtime voids collected by children at least three months apart (Attfield et al., 2014; van Wendel de Joode et al., 2016).

Since low ICCs were calculated for most studies, a few authors attempted to calculate number of samples required to achieve a satisfactory estimate of the individual's average 3PBA concentration over a defined period of time (Fäys et al., 2021; Li et al., 2019a; Lin et al., 2021; Morgan et al., 2016). The number of samples that would be required for reliable participant's classification ranged from 14 (Lin et al., 2021) to 800 (Morgan et al., 2016) for spot samples collected over a week and bedtime voids over 6 weeks, respectively.

3.3. Parabens

Parabens, a group of esters of *p*-hydroxybenzoic acid with a broad spectrum of activity against microorganisms, are commonly applied as preservatives in foods, personal care products (PCPs) and cosmetics, and pharmaceutical products. Their widespread use is also attributed to several beneficial features, such as relative safety of use, chemical stability, sufficient solubility in water, and no perceptible odor or taste (Błędzka et al., 2014). Nevertheless, antimicrobial activity, as well as the toxicity of parabens, are directly proportional to the chain length of the ester group, thus more than one ester is usually used in a single product. The combination of methyl (MeP) and propyl (PrP) ester is utilized most frequently (Błędzka et al., 2014; Guo et al., 2013). The main concern about parabens relates to their weak estrogenic activity and potential to disturb the human endocrine system; however, the available data considering this issue remains inconclusive (Sccs, 2011; Sccs, 2021).

Following oral administration, parabens are rapidly absorbed from the gastrointestinal tract and then metabolized by non-specific esterases to *p*-hydroxybenzoic acid (Błędzka et al., 2014; Soni et al., 2005). Only

a relatively small fraction of the absorbed dose (< 20%, depending on paraben) is excreted in urine as a parent compound in free form or as conjugates with glucuronic acid and sulfate (half-life < 7 h) (Moos et al., 2016; Shin et al., 2019). Parabens are also partially absorbed through the skin, which is important since the use of PCPs is regarded as the greatest contributor to the paraben burden, whereas diet is mentioned as the second exposure source for humans (Canada, 2019; Huang et al., 2021; Moos et al., 2015; Pollack et al., 2018; Smarr et al., 2017).

Variability in paraben concentrations

In total, 17 studies describing temporal variability in urinary excretion of parabens in general population (Dewalque et al., 2015; Engel et al., 2014; Huang et al., 2021; Kim et al., 2020b; Koch et al., 2014; Nishihama et al., 2018; Pollack et al., 2016; Sakhi et al., 2018; Smith et al., 2012; van der Meer et al., 2021), pregnant women (Casas et al., 2018; Guidry et al., 2015; Li et al., 2019b; Meeker et al., 2013a; Philippat et al., 2013; Vernet et al., 2018; Yazdy et al., 2018) and children (Casas et al., 2018; Kim et al., 2020b) were retrieved from the literature search. ICCs for two parabens (MeP and PrP) were reported in all studies. Butylparaben (BuP) was excluded from variability assessment in six studies due to the low detection frequency (<60%), whereas EtP was not included in five study protocols. An overview of available studies reporting ICCs for parabens is presented in Table S3. Overall, ICCs ranged from 0.02 to 0.92 across all studies indicating very poor to excellent reproducibility. Correction of urinary paraben concentrations by either SG- or CRT-normalization only slightly improved ICCs. An increase in ICCs was obtained when FMVs or 24 h urine samples were used instead of spot samples. Nevertheless, ICCs obtained within a single study were rather similar for all parabens.

High variability (or low ICCs) was observed for all studies in which a small number of samples was collected over a longer period of time. Low ICCs were obtained for two random spots (ICCs < 0.30) (Engel et al., 2014) and two 24 h urine samples (ICCs < 0.42) (van der Meer et al., 2021) collected from adults at least two years apart. Higher ICCs were reported in other longitudinal studies in which repeated spot samples were provided by non-pregnant women and male adults over less than five months (ICCs 0.28-0.68) (Dewalque et al., 2015; Nishihama et al., 2018; Pollack et al., 2016). However, lower variability for MeP and EtP was observed in men (ICCs 0.56-0.58) than women (ICCs 0.40-0.43) (Dewalque et al., 2015; Nishihama et al., 2018; Pollack et al., 2016) which may be due to a different pattern of PCPs use.

Two intervention studies on short-term variability in paraben urinary concentrations have been recently published (Huang et al., 2021; Koch et al., 2014). In both studies, urine collection was carried out during two periods of high and one period of low exposure level (intervention period) when participants used typical cosmetics and PCPs with or without parabens, respectively. Huang et al. (2021) assessed the variability separately for each of the three 6-day periods and found that the ICCs generally were in close agreement between all periods, even though paraben concentrations were at least 3-fold lower in samples collected

during the intervention period (Huang et al., 2021). The lowest variability in ICCs was obtained for spot samples after CRT-adjustment of concentrations by a toxicokinetic model (TK-model) (Huang et al., 2021). Koch et al. (2014) observed an increase in ICCs in the 24 h urine (ICCs 0.72-0.92) comparing to spot urine samples (ICCs 0.39-0.82). However, in this study a large within-individual variability of the paraben exposure levels was observed, which combined with a large variation between individuals, may explain relatively high ICCs (Koch et al., 2014).

A few studies in pregnant women have been conducted under three slightly different settings. Regardless of the study design, poor to moderate reproducibility was observed (ICCs 0.24-0.64). The simplest study design relied on collection of one random spot sample provided at three times during gestation and resulted in ICCs in the range of 0.31-0.64 (Li et al., 2019a; Meeker et al., 2013a; Philippat et al., 2013). Furthermore, no increase in ICCs was observed when one weekly pool consisting of seven daily pools were provided in each trimester (ICCs 0.36-0.54) (Casas et al., 2018) or repeated spot samples every 3-4 gestational weeks (ICCs 0.24-0.62) (Guidry et al., 2015; Yazdy et al., 2018). Moreover, there was no difference in variability throughout pregnancy when assessment was based on three random spot samples (ICCs 0.40-0.85) or three weekly pools (ICCs: 0.33-0.86) (Vernet et al., 2018).

Although the variability of paraben concentrations in adults has been extensively studied, data on ICCs in children are still scarce. The short-term analysis of daily pools collected from 6-11 year old children during four consecutive days showed a good reproducibility (ICCs 0.58-0.68) which decreased in long-term analysis when two weekly pools were provided six months apart (ICC < 0.31) (Casas et al., 2018). Due to the differences in the metabolism and use of PCPs, which are considered to be the main source of exposure to parabens, data on variability in adults should not be extrapolated to children.

3.4. Phthalates

Phthalates are the principal plasticizers for polyvinyl chloride (PVC) and are used for a wide range of materials at low cost. While high molecular weight phthalates, such as dibutyl phthalate (DBP), butylbenzyl phthalate (BBzP), di-2-ethylhexyl phthalate (DEHP), and di-isononyl phthalate (DiNP), were used for food contact materials and other plastic products, the low molecular weight phthalates, such as dimethyl phthalate (DMP) and diethyl phthalate (DEP), were added in PCPs as fragrances and additives (Malveda et al., 2018). The main source of exposure to phthalates was thought to be diet due to migration from plastic food packaging or containers (Wormuth et al., 2006). However, due to the increasing use of plastics for many other applications and because of the leaching of phthalates into indoor and outdoor environments, ingestion of dust, inhalation, and dermal absorption from PCPs are also important exposure routes. Adverse health effects of phthalates on the endocrine system (eg. diabetes, obesity, thyroid hormone), asthma and allergies, reproductive system (eg. precocious puberty, decreased anogenital distance, decreased sperm

quality) and neurodevelopment (eg. ADHD) have been reported from both experimental and epidemiological studies (Chang et al., 2021).

The concentrations of phthalate metabolites from single spot urine are generally used to evaluate exposure levels to phthalates. However, the elimination of phthalate diesters in urine is relatively fast and their half-lives are short. Elimination of DnBP, DiBP, DEHP, and DiNP in urine after a single dose occurs within 24 h (DnBP and DiBP), 2-4 h (DEHP), and 48 h (DiNP) (Koch and Angerer, 2007; Koch et al., 2004; Koch et al., 2012) have been reported in healthy human volunteers. In addition, the half-lives of the first elimination phase of DnBP, DiBP, and DEHP metabolites are approximately 2.6 h, 3.9 h, and 2 h, respectively. In the terminal phase of elimination, the half-lives of DEHP and DiNP metabolites are approximately 5 h and 12-18 h, respectively. However, because humans are continuously exposed to phthalates via various sources, phthalates are categorized as "pseudo-persistent" chemicals.

Variability in phthalate concentrations

Twenty-three papers discussing the temporal variability in phthalate metabolites were retrieved from the literature search. The description of these studies and the ICCs for phthalate metabolites can be found in Table 2. Metabolites of low molecular weight phthalates, such as MEP, MnBP, MiBP, and MBzP have a good ICC (ICC > 0.4), while those of the high molecular weight phthalates, such as DEHP metabolites have a poor ICC (ICC < 0.4). This difference can be attributed to the difference in applications. As MEP, MnBP, and MiBP are contained in PCPs, they are used daily and have little variation in the usage patterns, resulting in more constant internal exposure levels. For the higher molecular weight phthalate metabolites, such as metabolites of DEHP, their main exposure source is represented by food and food contact materials, which are prone to have a more varied usage. Moreover, gender does not have a significant impact on the ICCs of phthalates (Dewalque et al., 2015; Fromme et al., 2007).

In a comprehensive study of the short term variability of concentrations in adults (Bastiaensen et al., 2020a), dilution was adjusted using two different methods: uncorrected, and correcting for SG and CRT on the same adult urine samples. The correction had a large effect on the highest ICCs for the CRT-correction, which is in line with the ICCs of two other studies in the adult population (Table 2). Apart from dilution, both MV and spot urine samples were collected, showing higher ICCs for MV samples. Additionally, Frederiksen et al. also included 24h-sampling, for which similar ICCs were found compared to MV, with higher ICCs for DEP, DBP and BBzP. Across studies, there is no difference between different sampling methods, likely due to the high variability. Based on the current data, it is advisable to use MV samples. As the collection of 24 hour urine is more complex and the small increase of low molecular mass phthalates might not warrant the added complexity.

When dilution adjustment was investigated in urine of pregnant women collected across pregnancy, SG-correction resulted in similar ICCs as uncorrected urine, while CRT-correction resulted in lower ICCs (Table 2).

Although there is no comparative study, studies of periods longer than 12 weeks (or one pregnancy trimester) have lower ICCs than studies with ICCs of shorter timeframes, indicating that single measurements are not a good predictor for exposure during whole pregnancy. Most of the studies that examined ICCs from spot urine samples throughout pregnancy at multiple time points until delivery have concluded that more than one measurement at different times of day is required to get an accurate exposure assessment, particularly when diet is the main source of exposure to the chemicals of interest (Adibi et al., 2008; Cantonwine et al., 2014; Fisher et al., 2015; Valvi et al., 2015). On the other hand, it is also necessary to consider which exposure windows of pregnancy are most appropriate to use for the factor being examined when a study design that prospectively examines the association with maternal exposure concentrations showed low reproducibility.

While many studies have been performed for adults and some on pregnant women, temporal variability studies for phthalate metabolites on children are scarce, with only 3 reported studies. These studies were carried out in the US (Teitelbaum et al., 2008; Watkins et al., 2014) and the EU (Casas et al., 2018). Watkins et al. studied both short term (average two weeks) and long term (1-5 years) variability for MEP, cx-MEPP and MBzP and reported poor ICCs for all three compounds among 1-5 years old children (Watkins et al., 2014). ICCs of MEP and MBzP were lower in children than in adults. Creatinine correction on the children's samples did not improve the ICCs. Moreover, no improvement was seen when comparing the short term variability of 2 weeks with the long-term variability of one year. This suggests that especially for younger children like during infancy, toddlers, and preschool age, a single spot urine sample may be a reasonable measure of short-term (daily) exposure to phthalates that are linked to routine behaviour (e.g., frequently use of certain products). However, such sampling design may not adequately capture exposure over weeks or months, since diet, PCPs use, and routine behaviour change dramatically over the first years of life. These findings are confirmed by Casas et al., which presented higher reliability of short-term (between-day) than long-term (> 6 months) for metabolites of DEP, DnBP, DiBP, and BBzP, which are present in PCPs (Casas et al., 2018).

3.5. Alternative plasticizers

Due to endocrine disrupting potential and adverse effects in particular on children, the use of several phthalates, such as DEHP, DBP, BBzP, has been restricted in plastic toys and childcare articles, as well as in food contact materials by international legislation (ECHA, 2012; 2018). Terephthalates (e.g. di-2-ethylhexyl terephthalate-DEHTP), adipates (e.g. di-2-ethyl-hexyl adipate-DEHA), bis-(2-propylheptyl) phthalate (DPrHpP), and di-(iso-nonyl)-cyclohexane-1,2-dicarboxylate (DINCH), are used as alternative plasticizers for the traditional phthalates. The most used adipate is DEHA, which is used as a plasticizer for PVC, surface coatings, and rubber (BASF Technical information).

Half-lives of DPrHpP, DEHTP, DINCH, and DEHA have been reported as 6-8 h (DPrHpP), 7 h (DEHTP), 10-18 h (DINCH), and 2.1-2.8 h, respectively (Koch et al., 2013; Leng et al., 2014; Lessmann et al., 2018; Nehring et al., 2020). Human biomonitoring studies have reported that positive temporal trends have been

424 determined for the DINCH metabolites in the Swedish and the Danish general population (Frederiksen et al.,
425 2020; Gyllenhammar et al., 2017), suggesting a worldwide increase of DINCH exposure over time. In general,
426 these alternative plasticizers are considered safer alternatives to DEHP and other traditional phthalates.
427 However, recent epidemiological studies have reported adverse effects of alternative plasticizers in early life;
428 e.g., increased serum total T3 in Swedish pregnant women (Derakhshan et al., 2021), increased risk of
429 preterm birth (Zhang et al., 2020), lower total testosterone among general U.S men age ≥40 y (Woodward et
430 al., 2020) and higher free testosterone among general US women age >20 y (Long et al., 2021).
431
432 ***Variability in alternative phthalate and plasticizer concentrations***
433 As opposed to the traditional phthalates, fewer studies on the ICCs of alternative phthalates and
434 plasticizers were performed. Therefore, only ten studies could be collected, as shown in Table S4 and S5.
435 Only two studies have calculated ICCs in children, although they are a more sensitive group, as well as have
436 different metabolization and elimination capabilities compared to adults (Watkins et al., 2014). Moreover,
437 most studies have only focused on metabolites of two alternative phthalates, DINCH and DINP, with
438 metabolites of DINP being the most studied compounds. Only one AP metabolite, mono(2-ethyl-5-
439 hydroxyhexyl) terephthalate (OH-METHP), had fair to good reproducibility (ICC > 0.4), and all other measured
440 AP metabolites had poor reproducibility (ICC < 0.4) with among them the DINP, DIDP and DINCH metabolites.
441 DEHTP, the parent compound of OH-METHP, has similar applications to DEHP (phthalates), but has higher
442 reproducibility, probably due to specific toxicokinetic properties.
443 The metabolites of APs that were most studied are all secondary metabolites. However, Fajis et al.
444 (2020) also studied the primary metabolites of DINP and DINCH (Faÿs et al., 2020). They found that MINP
445 (ICC: 0.27) has a slightly higher ICC than Cx-MINP (ICC: 0.21) and OH-MINP (ICC: 0.09) (Table S4). For DINCH,
446 they found smaller differences with MINCH (ICC: 0.11) and oxo-MINCH (ICC: 0.10) which were lower
447 compared with OH-MINCH (ICC: 0.14) and cx-MINCH (ICC: 0.19) (Table S5). In the only comparative ICC study
448 on the general population (Bastiaensen et al., 2020a), the dilution adjustment by either CRT or SG increased
449 the ICCs when compared with unadjusted ICCs. Additionally, MV samples had slightly higher ICCs compared
450 to spot samples.
451 Comparative studies on the ICCs in pregnant women and children are scarce. Only three studies are
452 comparative, comparing no dilution adjustment with either SG or CRT. From these studies, it seems that ICCs
453 are unaffected by urinary SG- or CRT-correction. However, short term variability in children increased for
454 CRT-correction (Table S5). Additional comparisons and recommendations could not be drawn for the
455 alternative plasticizers due to the limited data collected. Comparative ICC studies applying different
456 biomonitoring parameters or focusing on specific risk groups are needed to allow for further clarification.
457
458 **3.6. Phosphate flame retardants and plasticizers**

Phosphate flame retardants and plasticizers (PFRs) are a class of chemicals widely used in commercial products, such as textiles, plastics, electronic devices, food contact materials, paints and furniture. PFRs were introduced as alternatives to brominated flame retardants, although toxicological studies have demonstrated potential adverse effects, such as endocrine disruption of these replacement chemicals. The release of PFRs from consumer products has resulted in the contamination of the indoor and outdoor environment, which could lead to significant exposure to humans as a result of dust or food ingestion, inhalation or dermal absorption. Indoor dust is an important exposure source for PFRs, in particular for children who spend more time indoors, have more frequent hand-to-mouth activities and have lower body weights compared to adults (Araki et al., 2014; Heffernan et al., 2014; Hoffman et al., 2014). According to recent studies, dietary intake is of equal or greater importance for human exposure to PFRs due to higher average food consumption (Kim et al., 2020a; Poma et al., 2017; Poma et al., 2018; Xu et al., 2015). Another exposure route to PFRs is the inhalation of contaminated air, with the main contributors being PFRs with higher vapor pressures (Wong et al., 2018; Xu et al., 2016; Zhou et al., 2017). These results indicate that exposure routes can be divergent relative to the various physicochemical properties of individual PFRs.

PFRs are well absorbed and distributed after oral dosage. PFRs have a weak association with lipid-rich tissues which suggest they are metabolized and rather excreted than accumulated in the body (Hou et al., 2016). Studies on the toxicokinetics of PFRs are limited, but they are consistent with short half-lives ranging from 0.7 to 24h (Bui et al., 2017; Hou et al., 2016; van der Veen and de Boer, 2012). Although PFRs were also be reported in whole blood, serum and plasma (Hou et al., 2020; Wang et al., 2020), the preferred matrix for human biomonitoring is urine, because of the rapid metabolism and excretion of PFRs (Hou et al., 2016). Regarding the temporal variability of PFR biomarkers in urine, the fast metabolization and excretion suggest that a single urinary measurement would capture only recent exposure (of previous few days), while poor reproducibility between measurements points to episodic exposure.

Variability in PFR concentrations

Several studies investigating ICCs of PFRs in general population (adults, pregnant women and children) are summarized in Table S6. Only PFR biomarkers with reports in more than two studies were listed there. Several biomarkers, such as 5-HO-EHDPHP, DoCP+DpCP, BCIPP, or EHPHP, with reported ICCs in only one study, are not included in the overview Table S6 and in the discussion.

For pregnant women, the ICC range for PFR biomarkers indicate low reproducibility in the late pregnancy (Percy et al., 2020), with CRT-normalized ICCs slightly lower than the unadjusted ICCs (Table S6).This suggests that a single measurement during pregnancy cannot accurately predict the exposure to PFRs throughout the whole pregnancy. Additionally, pregnant women experience plasma volume expansion and altered renal function (Cheung and Lafayette, 2013), which can lead to increased variation in the concentrations of PFR biomarkers. Romano et al. and Hoffman et al. (2017) found good reproducibility for urinary PFR metabolites

possibly due to more stable exposure sources, sampling years, higher population homogeneity and even study design and population size (Hoffman et al., 2017; Romano et al., 2017).

Meeker et al. (2013) reported moderate to strong reproducibility between measurements of DPHP and BDCIPP in adult men who did not experience significant physiological changes between sampling times (Meeker et al., 2013b). The ICCs of PFR metabolites in males were > 0.35, whereas in females they were between 0.05 and 0.19 (Wang et al., 2019a), indicating that a higher variability of PFR metabolites in females than in males, probably due to sex-specific physiology and lifestyle factors (e.g., physical activity and PCP use).

Because MV samples are more concentrated, some PFR metabolites had higher reproducibility in MVs than spot samples (Hoffman et al., 2014; Meeker et al., 2013b; Wang et al., 2019a). Measurements of BDCIPP showed good reproducibility in MVs (ICC range 0.44 – 0.88), but fair reproducibility in spot samples (ICC range 0.35 – 0.62). Demographic characteristics (e.g., gender and BMI) of the study population can also be responsible for the variation (Wang et al., 2019a). Wang et al (2021) also noticed a higher reproducibility in some PFR metabolites among individuals with a higher BMI, probably due to differences in dietary consumption, physical exercise, and metabolism kinetics (Wang et al., 2021).

The urinary concentrations of PFR metabolites in Asians showed higher variability (lower ICCs: 0.20–0.26) than in Caucasians (higher ICCs: 0.32–0.67). There was no significant difference in variability of PFR metabolite concentrations between the age groups of 30–40 y (ICC: 0.34–0.87) and >40 y (ICC: 0.17–0.70) (Wang et al., 2019a). Individuals with BMI > 25 kg/m^2 showed a low ICC for BBOEP (ICC: 0.04), which suggested that overweight or obese individuals may show higher variability in the urinary concentrations of some PFR metabolites.

The inter-day variability for DPHP (ICC: 0.54, 95% CI: 0.37–0.74) was similar to those reported in urine from pregnant women (ICC: 0.6, 95% CI: 0.4–0.7) (Hoffman et al., 2014), healthy adults (ICC: 0.51, 95% CI: 0.43–0.63) (Hoffman et al., 2015) and women (ICC: 0.42, 95% CI: 0.36–0.50) (Romano et al., 2017). Overall, urinary PFR metabolite concentrations exhibited a moderate temporal reproducibility and CRT-adjustment slightly improved the reproducibility.

Fair to good reproducibility was found for BCIPHIPP (SG-corrected ICC: 0.60), and BDCIPP (0.59) when spot samples of five consecutive days were considered. Lower ICCs were observed for DPHP (0.30), EHPHP (0.23) and 5-HO-EHDPHP (0.40) which suggest that concentrations of these compounds varied more during the study period (Bastiaensen et al., 2020a). When only MV samples were considered, the reproducibility improved for BDCIPP, BCIPHIPP and 5-HO-EHDPHP (SG-corrected ICCs of respectively 0.66, 0.69 and 0.60), whereas the ICCs of DPHP (0.15) and BBOEHEP (0.36) decreased.

For the most frequently measured PFR metabolites, the urinary BDCIPP showed moderate-to-strong temporal reproducibility, whereas ICCs for DPHP were lower, indicating a larger variation over time (Table S6). The reproducibility of measurements of PFR metabolites is not only influenced by exposure to

corresponding parent compounds, but may also be affected by their kinetics of absorption, distribution, metabolism and elimination (Aylward et al., 2014). The suggested longer half-lives of chlorinated PFRs in humans compared to aryl- and alkyl-PFRs (Wang et al., 2020) agree with the better reproducibility over time for BCIPHIPP and BDCIPP compared to other metabolites (Bastiaensen et al., 2020a).

The relatively high variability in the DPHP concentrations (ICCs < 0.40 for most studies) is probably attributable to the fact that DPHP is a metabolite of several parent PFRs (e.g., TPHP, EHDPHP, bisphenol A bis (diphenyl phosphate) and resorcinol bis(diphenyl phosphate)). The largest contribution to the total variance of urinary DPHP concentrations was the within-day variance in most studies. A higher diurnal variation of DPHP is possibly due to inconsistent exposure to multiple sources. TPHP and EHDPHP were found to be the main contributors to dietary exposure in foodstuffs which is more heterogeneous from day-to-day. Similar findings have been reported for di(2-ethylhexyl) phthalate (DEHP) and bisphenol A (BPA) for which diet is likely the main source of exposure; the short-term variation within an individual is generally greater than the variation between individuals (resulting in low ICCs). PFR metabolites with more continuous and stable sources had fair-to-good reproducibility (ICCs > 0.40).

Bastiaensen et al (2021) was the only study to sample healthy adults who provided all spot urine samples during five consecutive days, to allow the study of diurnal variations and calculate short-term ICCs of PFRs metabolites (Bastiaensen et al., 2020a). However, since age is a predictor of PFR exposure (Van den Eede et al., 2015), the generalizability of ICCs from adults to children or adolescents is limited due to differences in exposure patterns (related to lifestyle) and potential differences in metabolism (Aylward et al., 2014).

4. Discussion

This is the first review demonstrating the influence of specific factors, such as study populations (adults, pregnant women, and children), sampling strategies (spot, MV, and 24 h), and type of urinary dilution adjustments (non-adjustment, CRT-adjustment, and SG-adjustment) on the ICCs of wide range of short half-life chemicals: bisphenols, pyrethroids, parabens, phthalates, alternative plasticizers, and PFRs.

Reflection on ICC values

All studies included in this review used ICC values as a frequently used statistical and non-dimensional parameter to evaluate the reproducibility of repeated measurements for a selection of non-persistent chemicals (Figure 1). Observed differences in the ICCs between studies may result from several reasons: 1) the experimental design (how often and for what period of time samples are collected from the same study participants), 2) sampling (MV, spot or 24 hours), 3) the pattern of exposure in a given geographical area or country/population, 4) the ratio of the number of samples taken from the same participants to the number of participants and/or 5) combinations of these components. In turn, these differences in ICCs may result from the method of calculating the ICC, although (Pleil et al., 2018) showed that different methods of

564 calculating the variance components had little effect on the ICCs. These authors concluded that the precision
565 of ICC estimates is mostly affected by the distribution of the samples, the number of repeated
566 measurements, and the total number of samples. However, even for similar study designs, ICCs may vary
567 between the studies with the following possibly contributing to these findings: 1) different limits of
568 quantification (LOQs) in the applied analytical methods, which influence the detection frequency and the
569 distribution of the measurements. 2) various strategies for imputation of concentrations < LOQ, which in turn
570 might contribute to the ICC variability in particular for chemicals with a low detection frequency in the
571 studied population, depending on the cut-off applied for calculating the ICC in the respective study.
572
573 **Variation across chemical classes and study populations**
574 Figure 2 and Table S7 show the variation in ICCs for all short half-life chemicals or their metabolites
575 included in this review, divided per type of sampled population. Expectedly, the largest number of
576 publications on variability of urinary concentrations were available for the legacy chemicals, such as BPA and
577 MEP. The ICCs of particular chemicals, such as parabens (MeP, EtP, and PrP), low molecular weight phthalate
578 metabolites (MEP, MnBP, and MBzP) and BDCIPP tended to be relatively higher in the adult population than
579 in pregnant women (Table S7). In addition, median ICCs of MEP in adult population were significantly higher
580 than in children. Yet, they also presented a broader range of ICC values possibly an influence of the specific
581 study designs. On the other hand, BPA and 3-PBA showed the lowest ICCs in both adults and pregnant women.
582 Median ICCs of MEHP, oxo-MEHP, and DEHP showed also low ICCs (< 0.4) in both adults and pregnant women.
583 Chemicals related to the diet as a main exposure source, e.g. BPA, 3-BPA, and metabolites of DEHP, have
584 shown lower ICCs regardless of study population. On the other hand, contaminants with specific indoor
585 exposure sources, i.e. the flame retardant TDCIPP, and the chemicals related to PCPs, such as parabens and
586 metabolites of DEP and MBzP, showed higher ICCs. This indicates that even for chemicals presenting
587 relatively similar human kinetics, such as BPA and EtP, a substantial difference in ICC can be observed. This
588 is likely due to the more regular or continuous indoor exposure in comparison to erratic diet-related exposure
589 routes and indicates that the exposure route of the respective compound is one of the most important
590 determining factors of temporal variability. However, the potential variation in urinary excretion factors
591 throughout different stages of life for metabolites of AP and PFRs has not been investigated yet.
592 In addition, most of the studies reporting ICCs were conducted on healthy adult populations and/or
593 students, while the studies focused on children were scarce. In the studies on pregnant women, urine
594 samples were usually collected at the time of prenatal checkup visits, hence MV urine was the most common
595 type of collection strategy. Furthermore, the age range in the pregnant women group is not broad and,
596 therefore, the distribution of ICCs in pregnant women is narrower than in adult population.
597
598 **Sampling strategy**

Generally, evidence suggests that the use of a single urinary measurement to predict exposure to chemicals with short half-lives may lead to classification errors. The collection of multiple urine samples and the inclusion of information on the sampling strategy, time of collection, and demographic characteristics may provide a more complete approach to assess exposure to various chemicals. However, as shown in Figure 3 and Table S8, only the ICCs of BPA showed a significant improvement from spot sampling to 24 h sampling (p= 0.008). MeP and OH-MEHP in spot sampling showed borderline significant differences with 24 h and MV sampling, respectively (MeP: p= 0.100; OH-MEHP: p= 0.053). However, for most chemicals, the ICCs have been similar irrespective of sampling strategies (spot, MV, or 24 h), except BDCIPP. ICCs of BDCIPP were higher for MV sampling compared to spot sampling (p= 0.005). It should be noted that the divergence in the estimated ICCs for each chemical/metabolite across the studies included in this review could partially be explained by the heterogeneity in the sampling strategy (e.g., sampling frequency and time of collection). Most of the studies did not collect repeated samples within a given day, and thus were unable to properly capture the within-day variability, which may account for the largest proportion of the total variation for many metabolites. Besides, the variation in the ICCs between studies may be partly attributable to differences in the sampling strategy. Because MV samples are more concentrated and the time since the previous void is usually the longest, low molecular phthalate metabolites, such as MEP, MnBP, MiBP, and MBzP had higher reproducibility (higher ICCs, but not statistically significant) in MVs than spot samples (Figure 3). Despite the differences in the procedures of composing pooled samples (e.g. 24 h urine by collecting all complete urine voids over a whole day, or daily pools by combining equal aliquots over urine voids over a whole day) between studies, these pooled samples were grouped under “24 h” regardless of the exact strategy to avoid obtaining too many different types of samples.

The differences in the ICCs among various urine collection strategies were mostly determined by the properties of the respective chemicals (Table S8). For example, ICCs of BPA, 3-PBA, and parabens in 24 h urine were higher than in spot urine, while those of phthalate and PFR metabolites were higher in MV urine than in spot urine. Moreover, the variation in the ICCs of 3-PBA was rather wide across the various studies (e.g. ICC 0.13 – 0.80, CRT adjusted 24 h urine). In general, the median ICCs in 24 h urine had a tendency to be slightly higher than for the other two sampling strategies (p = 0.14; ANOVA). The 24 h urine collection has been suggested as the standard sampling strategy for assessing exposure to environmental pollutants which are eliminated in urine within 24 h (Wang et al., 2016). Indeed, the predictive power of a single spot sample for same-day 24 h urine collection was relatively low for several chemicals (e.g. BPA and PFR metabolites), thereby suggesting that a single spot sample might not be appropriate for substituting the 24 h urine collection. However, the long-term temporal variability of such measurements has not yet been investigated.

Influence of correction method

Figure 4 and Table S9 show the variation in the ICCs for chemicals with short half-lives or their metabolites in spot urine between non-adjusted vs CRT-adjusted vs SG-adjusted concentrations. Most of the chemicals with low ICCs (< 0.4) continue to show low reproducibility following adjustment for SG and/or CRT. However, as for EtP and PrP, the distribution of ICCs for CRT-adjusted urine were slightly higher than for non-adjusted urine ($p < 0.2$; Dunn's test). CRT-adjusted ICCs of parabens (MeP, EtP, and PrP) were not significantly different from those of SG adjusted ICCs. On the other hand, CRT-adjusted ICCs of MEP and MEHP were slightly lower than those for SG ($p < 0.5$). According to Table S8, non-adjusted ICCs of MeP, EtP, PrP, MEP, MiBP, MBzP, and BDCIPP showed fair to good median ICCs ($0.40 \geq ICC > 0.75$), which > 0.4 regardless the dilution adjustment type. This suggests that dilution adjustments of urine concentrations do not significantly affect the ICCs of most of the chemicals included in this review.

Data presented in Figure 4 includes all population groups (adults, pregnant women, and children). SG is a measure of the relative density of urine specimens to water and solely depends on the molecular size and weight of analytes in the urine. On the other hand, CRT-correction was more likely to be affected by age, gender, BMI, diet, season and lifestyle variations, which would add other sources of variability, Therefore, the comparisons of ICCs according to CRT-adjustment should have been also stratified by the age group. However, due to limited numbers of studies on each chemical with study population and types of dilution adjustment, we could not consider further statistical analyses. Furthermore, CRT-correction might not be appropriate for some metabolites, because they can be conjugated in the liver as glucuronides or sulfates and are actively excreted by the renal tubules, while CRT is excreted mostly by glomerular filtration. SG is less likely to be influenced by individual phenotype related factors compared to CRT. The results of the comparison also showed that CRT-adjustment slightly improved the ICCs only for EtP and PrP, which suggests that the dilution adjustment did not improve the reproducibility.

Exposure sources

The ICCs can be impacted by differences in the exposure sources and routes of various chemicals, between classes, but also within classes for different times and locations of sampling. For example, among the chemical classes targeted in this review, parabens, MEP, MnBP, MiBP, and BDCIPP had higher ICCs compared to the other chemicals. Parabens and low-molecular weight phthalates can be present in PCPs, which are used daily and usually not frequently changed. Depending on the type of PCP, chemicals present in PCPs will absorb through the skin, which is usually less efficient and slower in comparison to e.g. oral exposure. The presence of the stratum corneum is the factor that limits the absorption of chemicals through the skin. This makes the skin a buffer zone that averages the variability of the external exposure, since the absorption rate through the skin might be slower than the dynamics of external exposure changes. This phenomenon can explain the relatively high and reproducible ICCs reported for urinary parabens (2008; Aylward et al., 2020). BDCIPP, For TDCIPP, a flame retardant used in polyurethane foam, the indoor

environment is the main exposure source. Since the indoor environment does not change frequently, BDCIPP, a metabolite of TDCIPP, would have relatively constant internal exposure levels, which in turn will result in higher ICCs. On the other hand, for chemicals such as BPA and DEHP metabolites, the main exposure source is the diet, which tends to vary both daily and seasonally, resulting in higher variability and thus lower ICCs. In addition, absorption from the gastrointestinal tract is usually rapid and, in combination with an efficient and fast metabolism and elimination, it contributes to the large variability in the urinary excretion of these metabolites.

Overall recommendations

We hypothesized that study population (age group), timing of urine collection, and dilution adjustment will have a significant influence on the ICCs of various chemicals with short-lives. However, the information summarized in Figures 2-4 and in Tables S7-S9, indicates that the variability in urinary concentrations is largely determined by the nature and properties of the measured chemical or its metabolite. Moreover, our comparisons in Tables S7-S9 clearly show that the ICCs (reproducibility) did not dramatically improve according to study population, sampling strategies, or dilution adjustments. However, our comparisons are not restricted to the same study design, but include studies conducted in various study designs. Therefore, it should be kept in mind that the results from our comparisons may differ from similar comparisons restricted to studies with the same study design. For example, neither study population nor dilution correction was considered in Figure 3. Also, the number of the studies with 24 h sampling was limited, and thus the statistical power was not sufficient to make adequate comparisons. Interpretation of Figures 2-4 should be made with caution. Even for chemicals with relatively similar human pharmacokinetics (e.g. BPA and EtP), a substantial difference in the ICCs can be observed, which indicates that the predominant determining factor for the ICCs is the exposure route.

Based on the available knowledge, we suggest that, for some chemicals, the reproducibility in the ICCs can be improved by collecting multiple samples per participant within the same day, including MV. In adults, the collection of only MV samples and correcting for urine dilution might be a good and practical alternative for biomonitoring studies investigating exposure to short-lived chemicals, if the collection of multiple samples is not an option. However, in that case, special attention should be paid to biomarkers which have a higher short-term temporal variability or low ICCs, such as DPHP, BPA, MINCH or MEHP. ICCs of PCP-related chemicals, such as parabens, MEP, MiBP, MBzP and BDCIPP had high and reproducible ICCs (ICCs > 0.40). Moreover, restricting the sampling design onto the MV collection would miss or underestimate exposures at other time points, such as the morning use of cosmetics or breakfast/lunch exposures, etc …. On the other hand, the ICCs of some chemicals (e.g. BPA, 3-PBA) were rather low (ICCs < 0.40) regardless of sampling strategies, dilution adjustments, and study population, meaning that a high variability in the concentrations is observed due to the erratic nature of exposure. Therefore one single spot sample might not capture the

variation of such compounds, especially those largely influenced by dietary intake. Yet, extreme concentration values and other influencing factors (such as variable between-day diets) are averaged out in biomonitoring studies with a large number of individuals. Therefore, reports that calculated BPA intake from single spot urine samples of sufficiently large populations are considered good estimations of the average population exposure (Covaci et al., 2015).

The collection of 24 h pooled urine or complete voids with the determination of volume for spot samples would allow for more detailed exposure reconstruction by reverse dosimetry. However, this sampling strategy might not be feasible for most studies and a compromise should be sought. It is recommended for the chemicals with lower ICCs that the sampling strategy in future studies is adapted also to the nature and identity of the chemicals which need to be investigated and their characteristics (half-life, metabolism, urinary excretion patterns, etc) and that it includes the collection of MV urine samples and the measurement of specific gravity for concentration-adjustment to minimize temporal variability. Our recommendations may guide researchers to optimize the study design and interpretation of biomonitoring results for future studies, taking into account the reproducibility of each targeted chemical.

Lastly, ICCs included in this review are estimated based on mathematically estimated formula, which may sometimes lead to misuses of ICCs in a variety of disciplines, including the evaluation of health measurement scales. Bobbak et al. (2018) suggested the estimation of ICCs using an Bayesian approach with hierarchical regression and variance-function modeling, which leads to estimates that are a better reflection of a measurement scale's reliability, while maintaining ease of interpretation. Although all ICCs in this review have been estimated using the "traditional" assumptions, researchers should take into account the limitations of mathematically estimated ICCs and should carefully interpret the chemical reliability.

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734 **Table 1.** The compound class specific keywords used in literature searches and the resulting number of publications.
735 Common keywords for each search were: urine, variability or variation, and ICC
736

Compounds	Specific key words	Number of publications
Bisphenols	bisphenols or individual compounds or their acronyms (e.g., BPA, BPF, BPS)	21
Pyrethroids	pyrethroids or pyrethroid metabolites	9
Parabens	paraben, parabens or individual compounds	17
Phthalates	phthalates or the acronyms of individual compounds and their metabolites	23
Alternative plasticizers	alternative plasticizers or the acronyms of individual compounds and their metabolites (e.g., TOTM, DINCH, OH-MEHA)	9
Phosphate flame retardants	phosphate flame retardants or the acronyms individual compound and their metabolites (e.g., BDCIPP, DPHP,DNBP, BCEP)	11

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739 **Table 2.** Intraclass correlation coefficients for phthalate metabolites from different studies.
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Reference	Sampling region	Sample type	Dilution adjustment	N	Time frame	MEP	cx-MPP	MnBP	MiBP	MBzP	MEHP	oxo-MEHP	OH-MEHP	cx-MEPP
General population: men and/or women														
Hauser et al. 2004	US	Spot	SG	11^{M}	13 weeks	0.43		0.71		0.55	0.54			
Fromme et al. 2007	Germany	MV	CRT	50	1 week			0.45	0.44	0.58	0.34	0.24		
Baird et al. 2010	US	MV	CRT	60^{F}	2 weeks	0.48		0.34		0.53	0.37	0.33		
Peck et al. 2010	US	MV	CRT	45^{F}	3 weeks	0.61		0.55	0.51	0.64	0.22	0.19		
Preau Jr et al. 2010	US	Spot	CRT	8	1 weeks	0.77								
Braun et al. 2012	US	Spot	SG	137	5 weeks	0.56		0.40	0.36	0.35	0.11			
Meeker et al. 2012	US	Spot	-	269	5 weeks	0.49					0.13	0.14		
Frederiksen et al., 2013	Denmark	24 h	-	33^{M}	7 weeks	0.51				0.59	0.19		0.09	
	Denmark	MV	OSM	33^{M}	7 weeks	0.35				0.35	0.23		0.22	
	Denmark	MV	-	33^{M}	7 weeks	0.33				0.31	0.21		0.21	
	Denmark	Spot	OSM	33^{M}	1 week	0.68				0.39	0.51		0.15	
	Denmark	Spot	-	33^{M}	1 week	0.65				0.38	0.37		0.19	
Townsend et al. 2013	US	MV	CRT	80^{F}	104 weeks	0.44		0.45	0.29		0.16	0.46	0.45	0.47
Dewalque et al. 2015	Belgium	Spot	CRT	351	16 weeks	0.55		0.46	0.64	0.37	0.28	0.20	0.20	
Sun et al. 2017	UK	24 h	-	47	13 weeks	0.12		0.14		0.55	0.26	0.00	0.00	0.00
	UK	24 h	CRT	47	13 weeks	0.10		0.18		0.64	0.30	0.00	0.01	0.02
Faÿs et al. 2020	France and Luxembourg	Spot	-	16	26 weeks	0.51				0.48	0.21	0.24	0.24	0.29
Bastiaensen et al. 2020	Belgium	Spot	-	10	5 days	0.46		0.17	0.49	0.55	0.39	0.11	0.16	0.29
	Belgium	Spot	SG	10	5 days	0.59		0.32	0.70	0.72	0.49	0.09	0.19	0.48
	Belgium	Spot	CRT	10	5 days	0.67		0.44	0.75	0.79	0.55	0.23	0.30	0.64
	Belgium	MV	-	10	5 days	0.69		0.30	0.74	0.77	0.60	0.17	0.36	0.44
	Belgium	MV	SG	10	5 days	0.70		0.42	0.81	0.85	0.65	0.21	0.35	0.53
	Belgium	MV	CRT	10	5 days	0.75		0.43	0.79	0.86	0.67	0.44	0.42	0.65
Pregnant women														

Adibi et al. 2008	US	Spot	-	28	6 weeks	0.30		0.62	0.54	0.66	0.35	0.34	0.36	0.33
	US	Spot	CRT	28	6 weeks	0.21		0.55	0.48	0.65	0.25	0.22	0.23	0.21
Catonwine et al. 2014	Puerto Rico	Spot	-	139	6 weeks	0.43	0.23	0.41	0.35	0.37	0.35	0.26	0.25	0.20
	Puerto Rico	Spot	SG	139	6 weeks	0.44	0.20	0.44	0.34	0.41	0.36	0.25	0.24	0.19
Ferguson et al. 2014	US	Spot	SG	1181	27 weeks	0.47	0.36	0.57	0.52	0.61	0.30		0.21	0.31
Fisher et al. 2015	Canada	Spot	-	80	24 weeks	0.38	0.21	0.30		0.23	0.16	0.22	0.18	
	Canada	Spot	SG	80	24 weeks	0.38	0.19	0.32		0.24	0.12	0.20	0.15	
	Canada	Spot	-	80	12 weeks	0.34	0.23	0.30		0.23	0.32	0.22	0.18	
	Canada	Spot	SG	80	12 weeks	0.33	0.21	0.35		0.20	0.23	0.20	0.15	
Valvi et al. 2015	Spain	Spot	CRT	391	21 weeks	0.23		0.19	0.20	0.24	0.18	0.07	0.06	0.19
Yazdy et al. 2018	US	MV	SG	19	20 weeks	0.68								
Shin et al. 2019	US	MV	SG	188	3 weeks	0.58	0.08	0.36	0.38	0.60	0.36	0.32		0.37
Philippat et al. 2021	France	Spot	SG	454	28 weeks	0.61		0.58	0.60	0.63	0.42	0.37	0.35	0.39
Children														
Teitelbaum et al. 2008	US	Spot	-	$35^{(6\text{-}10y)}$	26 weeks	0.26	0.21	0.35	0.28	0.62	0.29	0.23	0.24	
	US	Spot	CRT	$35^{(6\text{-}10y)}$	26 weeks	0.18	0.13	0.14	0.21	0.47	0.26	0.19	0.22	
Watkins et al. 2014	US	Spot	-	$283^{(1\text{-}5y)}$	1 year	0.36	0.20			0.26				
	US	Spot	CRT	$283^{(1\text{-}5y)}$	1 year	0.35	0.19			0.25				
	US	Spot	-	$136^{(1\text{-}3y)}$	2 weeks	0.32	0.31			0.34				
	US	Spot	CRT	$136^{(1\text{-}3y)}$	2 weeks	0.29	0.25			0.36				
Casas et al. 2018	Europe	Spot	CRT	$152^{(6\text{-}11y)}$	24 weeks	0.38		0.36	0.52	0.57	0.67	0.69	0.65	0.69

MV - morning void, BV - bedtime void, 24 h - 24 hour pooling of urine samples, CRT - creatinine, SG - specific gravity, OSM - osmolality, N - number of participants, M - male, F - female, 1-3y - 1 to 3 years of age

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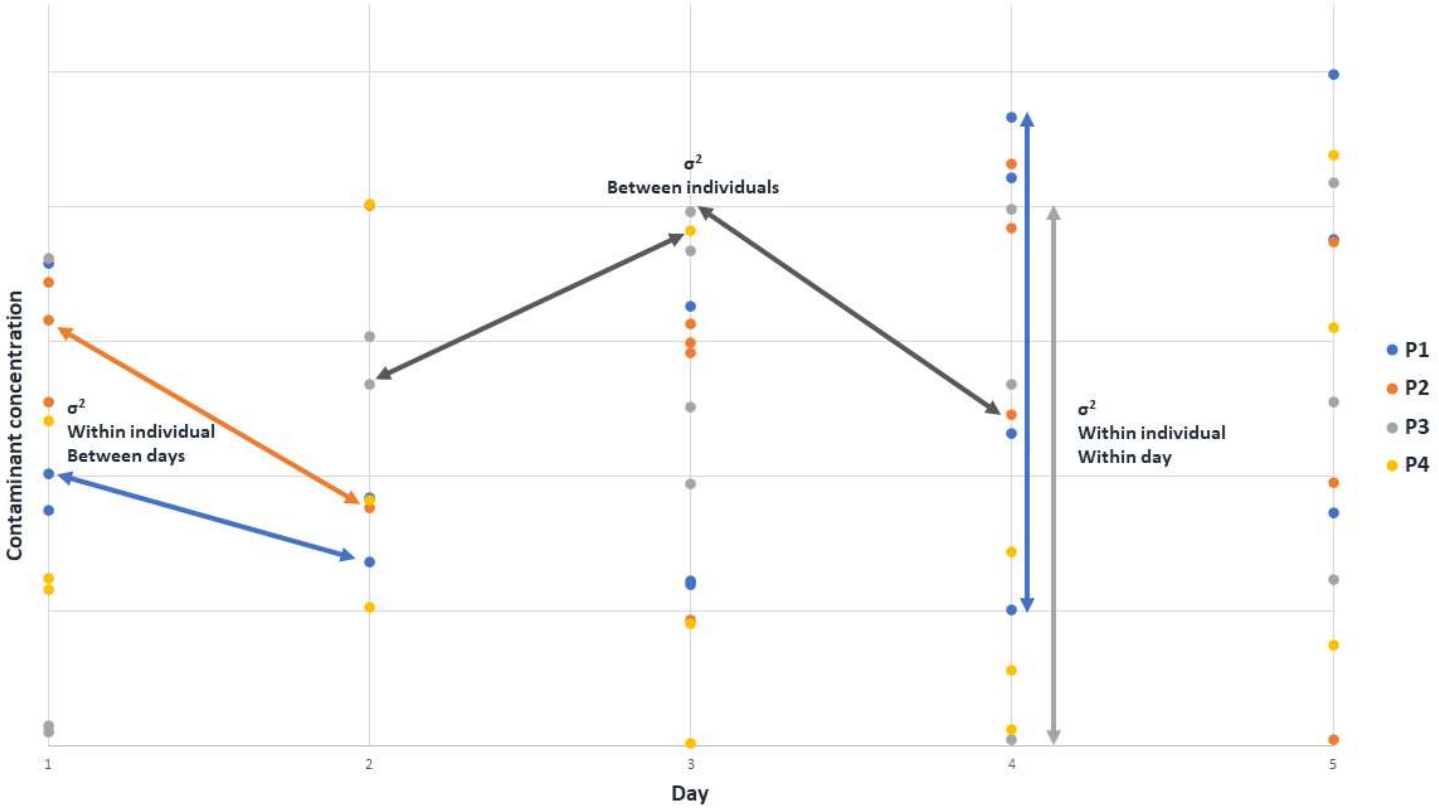
742 Figure 1: Graphical representation of variance components and the formula used to calculate intraclass correlation coefficients (ICCs).



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744 $$ICC = \frac{\sigma^2_{between\ indiv.}}{\sigma^2_{total}} = \frac{\sigma^2_{between\ indiv.}}{\sigma^2_{within\ indiv.\ between\ day} + \sigma^2_{with\quad indiv.\ withi\quad day} + \sigma^2_{between\ indiv.}}$$

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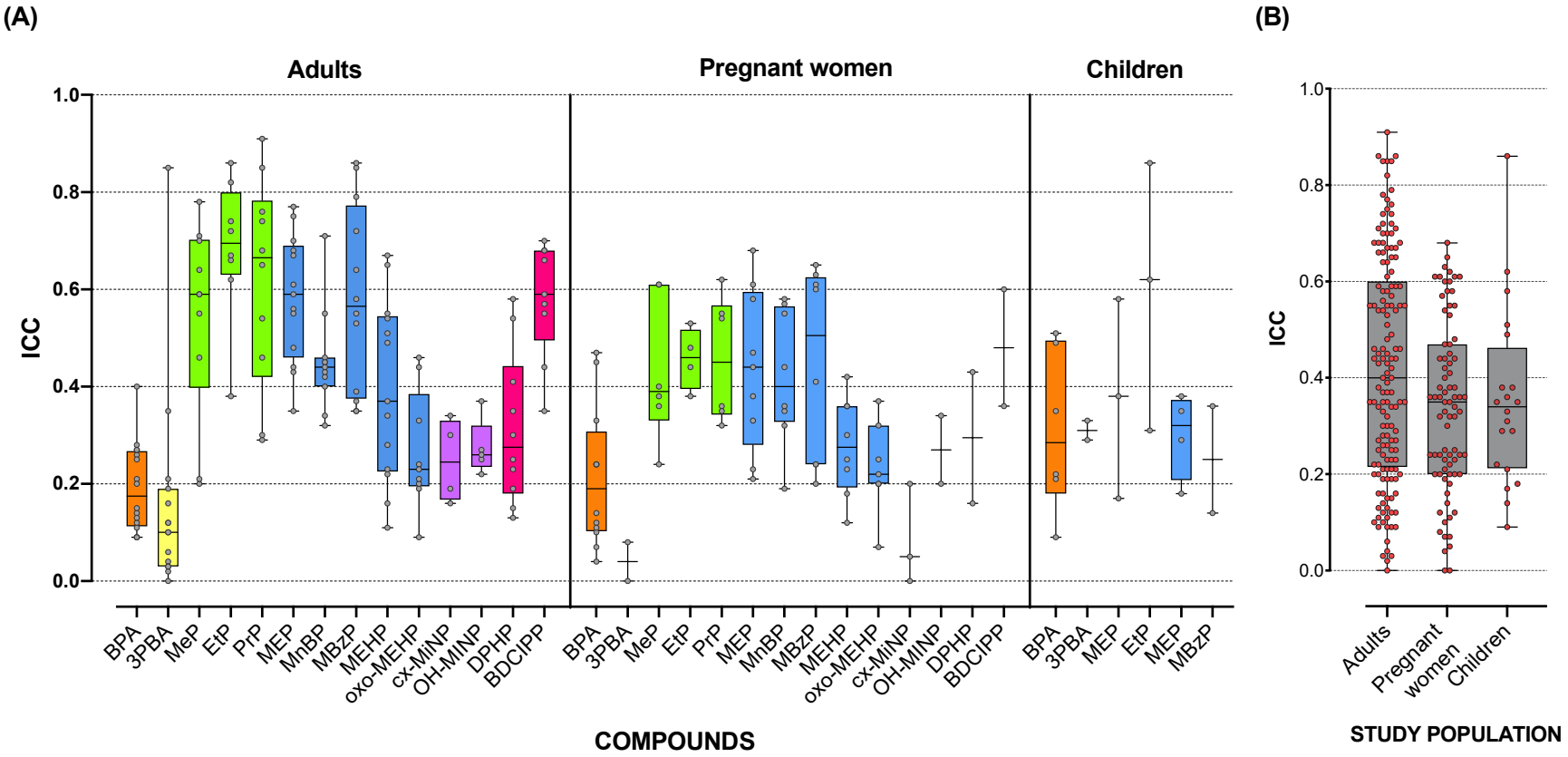
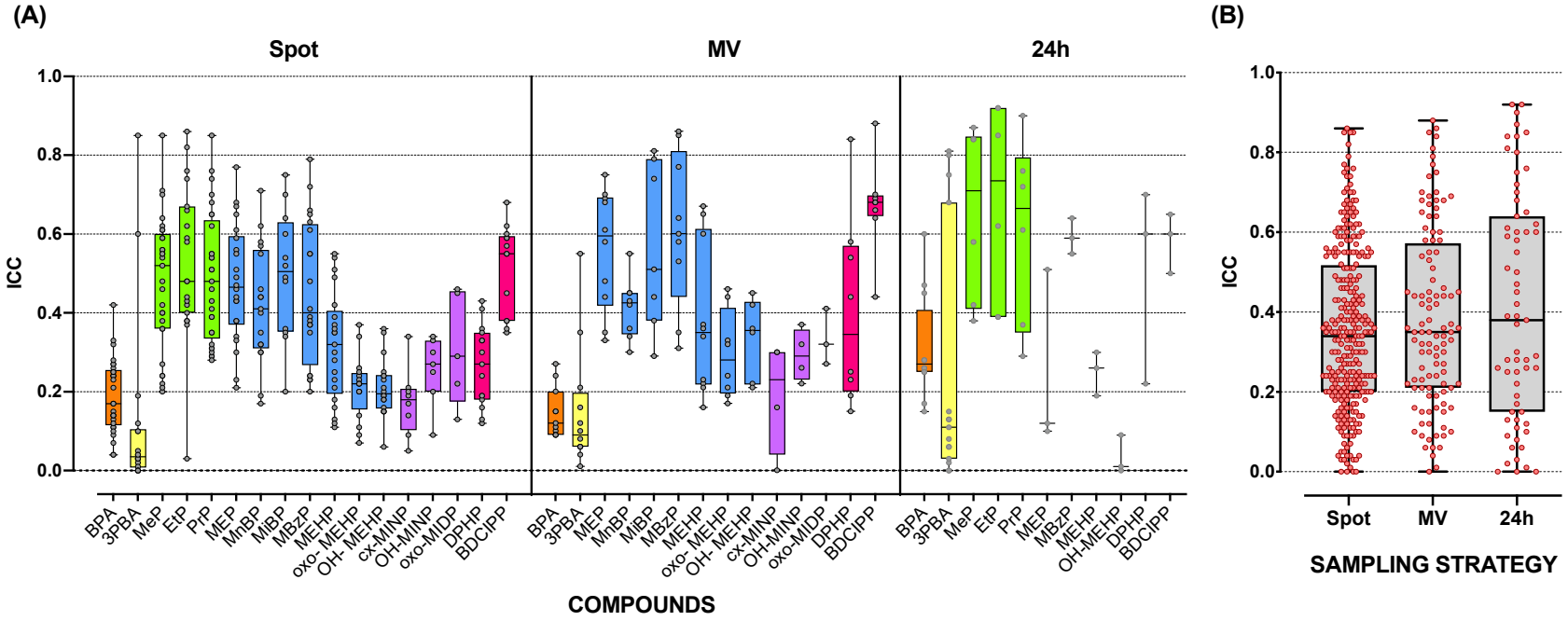
Figure 2. Variation in the ICCs for short-lives chemicals or their metabolites of adult study population to pregnant women and children.



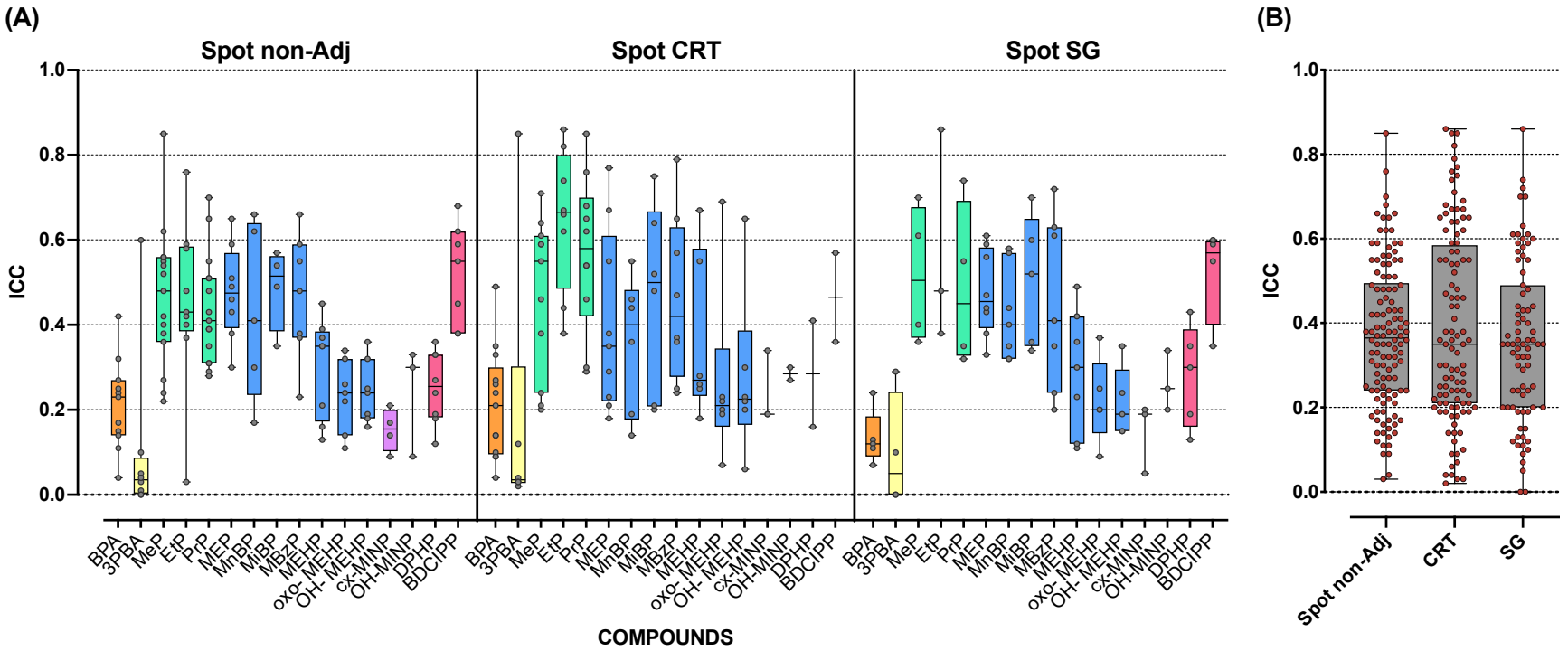
(A) ICCs of each class of compound; (B) Each class of compound was summarized according to study population. Boxplots show median and interquartile range, and upper and bottom bars represent max and minimum, respectively. Each dot represents an individual ICC from the studies included in this review. Selected data is spot/MV and CRT/SG adjustment (excluded 24 h urine and non-adjustment). Y-axis shows the ICCs of selected studies. X-axis displays short-lives chemicals or their metabolites stratified by study population: adults, pregnant women, and children.

Figure 3. Variation in the ICCs for short-lives chemicals or their metabolites in spot urine compared to morning void and 24h urine.



(A) ICCs of each class of compound; (B) Each class of compound was summarized according to sampling strategies.
Boxplots show median and interquatile range, and upper and bottom bars represent max and minimum, respectively. Each dot represents an individual ICC from the studies included in this review. Studies of adults and pregnant women were included (not considering dilution adjustments). Y-axis shows the ICCs of selected studies. X-axis displays short-lives chemicals or their metabolites stratified by methods of urinary collection.

Figure 4. Variation in the ICCs for short-lives chemicals or their metabolites in spot urine between non-adjusted vs creatinine vs specific gravity-normalized urine concentrations.



(A) ICCs of each class of compound; (B) Each class of compound was summarized according to urinary dilution methods. Boxplots show median and interquatile range, and upper and bottom bars represent max and minimum, respectively. Each dot represents an individual ICC from the studies included in this review. Studies of adults, pregnant women, and children are included. Y-axis shows the ICCs of selected studies. X-axis displays short-lives chemicals or their metabolites stratified by urinary dilution adjustments.

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