EVALUATING THE VARIABILITY OF EMERGING NON-PERSISTENT CHEMICALS' URINARY CONCENTRATIONS

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Background

- Many legacy chemicals (e.g. brominated flame retardants, phthalates and bisphenol A) are regulated and **substituted** by new, alternative compounds (e.g. organophosphates, alternative plasticizers and alternative bisphenols).
- **Human exposure** to these emerging chemicals is assessed through biomonitoring studies.
- The introduced alternative chemicals are more polar, less metabolically stable and less persistent, resulting in **shorter half-lives and substantial variability in exposure** and thus in urinary levels.
- The **intra-class correlation coefficient** (ICC) is a non-dimensional parameter often used to evaluate the **reproducibility of repeated measurements**.

Objectives

- Collection of **temporal variability data** for a broad range of (emerging) organic contaminants.
- **Comparison of ICCs** between study designs, study populations, urinary dilution adjustments and compounds.
- Formulation of **suggestions** for future biomonitoring study design and interpretation.

Methodology

- Literature search in PubMed and Web of Science using common key words "urine" with "variability OR variation OR ICC" and specific key words related to the individual chemicals in the investigated chemical classes.

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

Range of ICC

0 poor — **0.4** fair – good — **0.75** excellent — **1**

reproducibility

Compounds	N° of publications
Bisphenols	21
Pyrethroids (metabolites)	9
Parabens	17
Phthalates (metabolites)	23
Alternative plasticizers (metabolites)	9
Phosphate flame retardants (metabolites)	11

Results & discussion

Sampling strategy

- Reported ICCs for individual chemicals **varied greatly between studies** (e.g. propyl paraben ICC ranging from 0.28 to 0.91).
- Spot sampling was compared to collection of morning voids (MV) and 24 h pooled urine. Most studies did not collect repeated samples within a given day, and thus were unable to capture within-day variability.
- **MV** samples are **more concentrated**, leading to **higher ICCs** for a number of chemicals (i.e. BDCIPP, MEP, MnBP, MiBP, MBzP).
- Median ICCs for **24 h pooled** urine were **generally slightly higher** compared to spot samples and MV.

Study population

- Studies reporting ICCs in children are scarce, most studies are carried out in healthy adults and/or students. Studies on pregnant women have a narrower age range and thus less broad ICC distribution.
- Studies on **pregnant women** mostly include **MV** as urine samples were usually collected at prenatal check-up visits.

Urinary dilution adjustment

- Unadjusted concentrations were compared to creatinine- (CRT) and specific gravity-adjusted (SG) levels.
- Dilution adjustment did not significantly affect ICCs of the included chemicals.
- Some CRT-adjusted ICCs < SG-adjusted ICCs, indicating CRT adjustment is not appropriate for all chemicals. **SG is less likely affected by individual phenotype related factors.**

Chemical properties

- The **highest ICCs** were reported for **parabens** (median = 0.52), the **lowest** values for **3-phenoxybenzoid acid** (3-PBA; median = 0.08) and **BPA** (median = 0.20).
- Chemicals present in the **indoor environment and PCPs** (e.g. parabens, LMW phthalates & PFRs) present **higher ICCs** as exposure is relatively **constant** and not subject to frequent changes. Chemicals mainly present in the **diet** (e.g. bisphenols, DEHP metabolites) tend to show exposure **varying daily** and **seasonally**, resulting in higher variability and **lower ICCs**.
- ICCs of compounds with relatively **similar pharmacokinetics** (e.g. BPA and ethyl paraben) can **differ substantially**, indicating that the **exposure route** is the predominant determining factor for reproducibility.

Strengths & limitations

- The first review to demonstrate influence of study population, sampling strategy and urinary dilution adjustment on the ICC of short half-life chemicals.
- ICCs might be influenced by different limits of quantification (LOQ) in the analytical methods and different imputations of concentrations < LOQ.

Conclusions

- The **sampling strategy** and the **main exposure route** are the most important determining factors of temporal variability for a measured chemical.
- If **diet** is the main exposure route, **ICCs will remain low** regardless of study design, urinary dilution adjustment or population.
- Future biomonitoring studies examining compounds with high urinary variability should take **adequate measures** to enable accurate exposure assessment, i.e. **collecting multiple samples or a pooled sample** per participant.

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