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Comment on "Optimal Exposure Biomarkers for Nonpersistent Chemicals in Environmental Epidemiology"

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In a recent Brief Communication, Calafat et al. expressed concern that epidemiological studies inappropriately assess exposure to nonpersistent chemicals such as bisphenol A (BPA) and phthalates by measuring chemical concentrations in serum and tissues. They assert that urine is the most scientifically valid matrix and that accurate measurement of other matrices is difficult due to contamination of samples and assays. We believe their assertions require clarification.

The scientifically appropriate matrix is determined by the study objectives. For population studies, we agree urine is an appropriate matrix to initially probe whether exposure to a nonpersistent chemical is associated with a disease or risk factor. However, Calafat et al. appear to target more than population studies. They illustrate the purportedly growing problem of non-urine measurement in epidemiology with a list of 80 studies, cited by PubMed identification numbers (PMIDs), which surprisingly includes pharmacokinetic and experimental studies.

Of these 80 studies, 35 arguably required non-urine matrices to achieve study objectives. For example, in five studies (PMIDs 10716589, 10964036, 11604266, 17661831, 23145999) the subjects were dialysis patients—i.e., people without normal capacity to produce urine. One study used a placenta perfusion system to examine phthalate distribution between maternal and fetal circulation (PMID 17049806). A dog study (PMID 23761051) found unmetabolized BPA was rapidly absorbed into circulation following sublingual administration. A human study (PMID 25337790) exposed participants to BPA-containing thermal receipt paper and found a substantial increase of unmetabolized BPA in serum. It seems inconceivable to us that Calafat et al. would consider such studies inherently flawed.

For chemicals excreted in urine, the urinary concentration provides an estimate of exposure. However, the bioactive form in serum and tissue is what alters physiology. When a nonpersistent chemical is absorbed via the gut, first-pass metabolism by the liver can dramatically reduce the amount of unmetabolized compound reaching the bloodstream as compared with other routes (Søeborg et al. 2014). Therefore, for chemicals in widespread undocumented use—where route-of-exposure information is unavoidably incomplete—one cannot accurately predict the internal concentrations of the unmetabolized compounds with urine measurements and a model that includes only gut absorption. Such models may grossly underestimate internal bioactive dose from non-gut exposures and incorrectly suggest that measurement of higher-than-predicted serum concentrations is due to contamination.

In our view, Calafat et al. suggest that non-urine measurements are invariably contaminated. However, contamination cannot explain the results of the studies by Gayrard et al. (2013) and Hormann et al. (2014), which demonstrated classic pharmacokinetic curves with logical interrelationships between the parent compound and metabolites. Furthermore, the proposition that contamination is unavoidable is contradicted by numerous studies spanning 15 years (vom Saal and Welshons 2014). For example, in a paper coauthored by Calafat (Ye et al. 2013), the authors reported accurately measuring BPA in human serum after identifying and eliminating contamination. Subsequently, Vandenberg et al. (2014) reported a blinded study directed by the National Institutes of Health (NIH) in which several U.S. laboratories accurately measured BPA in human serum spiked by NIH personnel. Arguing that chemical X cannot be measured in tissue Y because of contamination is an odd position to take, given that eliminating sources of contamination is a normal part of the development and validation of any assay—as was clearly described by Ye et al. (2013).

In summary, without further clarification, the Brief Communication by Calafat et al. could easily be interpreted as proposing that human environmental studies of any kind must measure nonpersistent chemicals and metabolites only in urine if they are to be funded and published. Such an interpretation would greatly restrict our ability to move from surface-level exposure measures to internal dose, pharmacokinetics, and *in vivo* pathophysiology. Given the prominence of the authors in environmental health research, this issue needs to be clarified.

The authors declare they have no actual or potential competing financial interests.

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References

Gayrard V, Lacroix MZ, Collet SH, Viguié C, Bousquet-Melou A, Toutain P-L, et al. 2013. High bioavailability of bisphenol A from sublingual exposure. Environ Health Perspect 121:951–956, doi:10.1289/ehp.1206339.

Hormann AM, vom Saal FS, Nagel SC, Stahlhut RW, Moyer CL, Ellersieck MR, et al. 2014. Holding thermal receipt paper and eating food after using hand sanitizer results in high serum bioactive and urine total levels of bisphenol A (BPA). PLoS One 9:e110509, doi:10.1371/journal.pone.0110509.

Søeborg T, Frederiksen H, Andersson A-M. 2014. Considerations for estimating daily intake values of nonpersistent environmental endocrine disruptors based on urinary biomonitoring data. Reproduction 147(4):455–463, doi:10.1530/REP-13-0458.

Vandenberg LN, Gerona RR, Kannan K, Taylor JA, van Breemen RB, Dickenson CA, et al. 2014. A round robin approach to the analysis of bisphenol A (BPA) in human blood samples. Environ Health Glob Access Sci Source 13(1):25, doi:10.1186/1476-069X-13-25.

vom Saal FS, Welshons WV. 2014. Evidence that bisphenol A (BPA) can be accurately measured without contamination in human serum and urine and that BPA causes numerous hazards from multiple routes of exposure. Mol Cell Endocrinol 398(1–2):101–113, doi:10.1016/j.mce.2014.09.028.

Ye X, Zhou X, Hennings R, Kramer J, Calafat AM. 2013. Potential external contamination with bisphenol A and other ubiquitous organic environmental chemicals during biomonitoring analysis: an elusive laboratory challenge. Environ Health Perspect 121(3):283–286, doi:10.1289/ehp.1206093.

Response to "Comment on 'Optimal Exposure Biomarkers for Nonpersistent Chemicals in Environmental Epidemiology'"

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We appreciate the opportunity to respond to the letter from Stahlhut et al. regarding our Brief Communication. We stressed the importance of biospecimen integrity and the potential danger of unrecognized contamination of convenience samples, particularly with ubiquitous environmental chemicals such as bisphenol A (BPA) and phthalates.

We did not discuss the important area of experimental research and specifically pharmacokinetic studies, although we based our argument partly on knowledge of concentration changes in various compartments post-exposure. We agree that information from pharmacokinetic models is quite valuable and note that experimental studies that use isotope-labeled materials are not susceptible

to extraneous contamination. Such experimental studies do not support using polar metabolites, such as unmetabolized BPA, as biomarkers in epidemiologic studies (Thayer et al. 2015). For example, even in situations that may result in exposures higher than background levels, such as handling cash register receipts, BPA serum concentrations are below or near the detection limit and much lower than urinary concentrations (Thayer et al. 2016).

The figure in our Brief Communication revealed the sharp increase in the number of publications using blood-based polar biomarkers over the past 15 years, especially etiologic studies. Our main point was that urine is the most dependable biomonitoring matrix for population research, a position that Stahlhut et al. also support in their letter.

Target-organ dose may inform biological models, but measuring this dose is not always possible, although it can be inferred from pharmacokinetic studies. For environmental epidemiology, reliable measurements in urine can be used to quantify exposures.

A suitable exposure biomarker involves more than detecting the analyte with precise and accurate methods. For pervasive chemicals and particularly for archived samples, specimen integrity must be confirmed. This is true for any matrix, including urine (Guidry et al. 2015; Koch et al. 2012), to ensure valid results.

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References

Guidry VT, Longnecker MP, Aase H, Eggesbo M, Zeiner P, Reichborn-Kjennerud T, et al. 2015. Measurement of total and free urinary phenol and paraben concentrations over the course of pregnancy: assessing reliability and contamination of specimens in the Norwegian Mother and Child Cohort Study. Environ Health Perspect 123(7):705–711, doi:10.1289/ehp.1408325.

Koch HM, Kolossa-Gehring M, Schroter-Kermani C, Angerer J, Bruning T. 2012. Bisphenol A in 24 h urine and plasma samples of the German Environmental Specimen Bank from 1995 to 2009: a retrospective exposure evaluation. J Expos Sci Environ Epidemiol 22(6):610–616, doi:10.1038/jes.2012.39.

Thayer KA, Doerge DR, Hunt D, Schurman SH, Twaddle NC, Churchwell MI, et al. 2015. Pharmacokinetics of bisphenol A in humans following a single oral administration. Environ Int 83:107–115, doi:10.1016/j.envint.2015.06.008.

Thayer KA, Taylor KW, Garantziotis S, Schurman S, Kissling GE, Hunt D, et al. 2016. Bisphenol A, bisphenol S, and 4-hydroxyphenyl 4-isoprooxyphenylsulfone (BPSIP) in urine and blood of cashiers. Environ Health Perspect 124(4):437–444, doi:10.1289/ehp.1409427.