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Contemporary Issues in Exposure Assessment Using Biomonitoring

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Abstract

In environmental epidemiology, use of biomonitoring (i.e., trace-level measurement of environmental chemicals or their metabolites in biospecimens) for exposure assessment has increased considerably in past decades. Although exposure biomarkers should reflect a person's exposure to the target chemicals (or their precursors) within a specific timeframe, timing, duration, and intensity of exposures are normally unknown and likely vary within the study period. Therefore, evaluating exposure beyond a single time point may require collecting more than one biospecimen. Of note, collection and sample processing procedures will impact integrity and usefulness of biospecimens. All of the above factors are fundamental to properly interpret biomonitoring data. We will discuss the relevance of the exposure assessment study protocol design to (a) ensure that biomonitoring specimens reflect the intended exposure, (b) consider the temporal variability of concentrations of the target biomarkers, and (c) facilitate the evaluation of accuracy and comparability of biomonitoring results among studies.

Keywords

Biomarker; External quality assessment; Pools; Standard reference material; Variability

Introduction

Epidemiology has used three main tools to quantify chemical exposures: history/questionnaire information; environmental monitoring; and measures of concentrations of the chemicals, their metabolites, or adducts in biological specimens (also known as biomonitoring) [1]. Analytical chemistry advances and technology breakthroughs allow the accurate and precise trace-level quantification in biospecimens of environmental biomarkers [2]. As a result, environmental epidemiologists increasingly use biomonitoring concentrations to estimate chemical exposures within populations [3]. Nevertheless, using

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Compliance with Ethical Standards

Conflict of Interest The author declares that she has no conflicts of interest.

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biomonitoring for exposure assessment is not without challenges including, among others, the nature of the biomarker (e.g., short half-life) and of the exposures (e.g., constant vs episodic) and the adequacy of the sampling process. Therefore, using biomonitoring to optimize the exposure assessment in environmental epidemiology studies will require information on the temporal variability of concentrations of the target biomarkers, particularly for non-persistent compounds, as well as on the timing of collection of the biospecimens. Furthermore, because biomonitoring data can be used to inform chemical risk assessments [3], evaluating aspects of the study design that can impact accuracy and comparability of the biomonitoring results among studies is fundamental.

In this short review, we will provide an overview of factors affecting the design and interpretation of biomonitoring studies in environmental epidemiology.

Interpretation of Biomonitoring Data in Environmental Epidemiology

Biomarker Selection

The scientific community's interest in evaluating exposures to environmental chemicals derives, at least in part, from the potential harmful effects to human health for many of these compounds [3]. Environmental epidemiology relied traditionally on indirect measures of exposure, which included both environmental monitoring and personal exposure history/questionnaire data, to assess human exposure to such environmental chemicals. In the last few decades, however, thanks in part to advances in robotics and analytical chemistry techniques, assessment of exposure using biomonitoring or the targeted assessment of internal dose (i.e., body burden) from trace-level measures of the parent chemical and/or its metabolites in human samples has increased considerably [2].

Interpreting biomonitoring data for environmental epidemiology requires a good understanding of the toxicokinetics of the target biomarkers [1]. Environmental chemicals, after entering the body via ingestion, inhalation, or dermal contact, may or may not be absorbed into the systemic circulation; some chemicals may pass through with no absorption or be absorbed and then excreted. Absorption may depend on the route of exposure. For example, elemental mercury is toxic primarily through inhalation of mercury vapors, but it is only slowly absorbed through the skin, and virtually, no elemental mercury is absorbed through the gastrointestinal tract [4]. Absorbed chemicals can then distribute within the body and, depending on the chemical, can be metabolized, stored in body deposits, circulated or equilibrated with blood concentrations, and ultimately excreted. Any of the body storage or excretion compartments or fluids (e.g., fat, bone, blood, urine, bile, feces, exhaled breath) can serve potentially as a biomonitoring matrix [1, 2].

For general population studies in environmental epidemiology, urine and blood are the most common biomonitoring matrices. In general, persistent compounds (chemicals with elimination half-lives of months or years) are commonly measured in blood/blood products, while metabolites of non-persistent compounds (chemicals with half-lives of the order of minutes to hours) are measured in urine [1, 2]. Measuring blood concentrations of non-persistent chemicals may be advantageous to differentiate exposures to the chemical itself or to its environmental degradates or metabolites, particularly when the latter lack specificity

(i.e., can be metabolites of multiple chemicals). For example, benzene in blood is a better exposure biomarker than urinary phenol, catechol, hydroquinone or trans, trans-mucondialdehyde, all non-specific metabolites of benzene [5]. However, in the case of benzene, as for many other pervasive chemicals in the environment such as phthalate diesters, external contamination may occur at various points both during the preanalytical and analytical steps of the biomonitoring process. Contamination would be more prominent for the parent compound (the chemical present in the environment) or its environmental degradates or human metabolites (e.g., hydrolytic phthalate monoesters) than for other metabolites (particularly those that require specific phase I reactions [e.g., P450-mediated oxidations] or phase II reactions) such as oxidative phthalate monoesters or glucuronide conjugates [6]. Therefore, for non-persistent chemicals, in general, measuring the parent compound in blood would require that the analytical method includes fastidious treatment of collection materials to minimize external contamination [7, 8] and is both accurate and sensitive enough to detect transient ultratrace concentrations [1].

In certain cases, however, even with access to such analytical methods, the fast metabolism of the parent compound (e.g., from phthalate diesters to phthalate monoesters), among other reasons, can preclude the usefulness of measures of the parent compound as the exposure biomarker [6, 9]. Lastly, concentrations of the non-persistent parent chemical in blood are often lower than those of its urinary metabolites [10•]. Taken together, the above considerations strongly support using urine as the preferred matrix for the quantification of many non-persistent chemicals for exposure assessment in environmental epidemiology [11].

Variability in Biomarker Concentrations

Other factors impacting the quality and interpretation of biomonitoring data relate to the nature of the biomarker (e.g., temporality) and the adequacy of the sampling process. Biomarker concentrations in spot (i.e., single, untimed) samples can adequately rank a person’s exposure at one given time point, but in environmental epidemiology, exposure biomarkers should ideally reflect a person’s exposure to the target chemicals or their precursors over a period of interest with relevance to the health outcome being studied [11]. Otherwise, variability in biomarker concentrations may result in considerable exposure misclassification and bias associations between exposures and health outcomes toward the null hypothesis. Therefore, to optimize the study design, environmental epidemiologists must rely on information on the temporal variability of concentrations of the target biomarkers. For example, the intra-class correlation coefficient (ICC) describes the agreement of repeated measures over time within a subject. The ICC, defined as the ratio of between-subject variance to total (between- plus within-subject) variance, ranges from 0 (no reproducibility) to 1 (perfect reproducibility). For a given exposure scenario, depending on the temporal variability of concentrations of the target biomarkers (i.e., ICC), a single sample may not be enough to sufficiently characterize a person’s exposure over weeks, months, or years.

A single biomarker concentration for persistent chemicals, those with relatively high ICCs, may adequately represent exposure over time irrespective of whether the exposure is

constant or episodic and of its duration, intensity, or timing [12]. Interestingly, because persistent chemical concentrations are relatively stable over time, provided that the toxicokinetics of the compounds are known, it is possible to estimate concentrations of the biomarkers from known concentrations taken years before assuming no significant intervening exposures [13•]. Being able to predict such concentrations may provide a useful way to increase sample size when costs and logistics of recruitment follow-up may prevent collection of new biospecimens, thus facilitating the exposure and health assessment [13•].

Variability in concentrations is much more pronounced for non-persistent than for persistent chemicals because concentrations of non-persistent chemical biomarkers change rapidly upon exposure [14, 15•]. Therefore, for non-persistent chemicals, the intensity, duration, and recurrence of the exposure and the time passed between exposure and sample collection will impact the reproducibility of the biomarker concentrations [14, 15•]. For certain chemicals, concentrations derived from a single sample may not be sufficient to quantify exposure adequately over time and may require different approaches such as multiple measurements or use of composite (i.e., pooled) specimens.

Of interest, when exposure to the target chemical results from use of personal care products, inter-individual differences in biomarker concentrations are greatest. By contrast, dietary exposures to a given chemical, which may change considerably both within and between days, lead to substantial intra-individual variability of the biomarker concentrations [16•, 17–19, 20•, 21–25]. Therefore, ICCs derived from dietary exposures tend to be lower than those for other exposures (e.g., personal care products use), irrespective of the study population and assessed time period [26–29, 30•, 31–42, 43•, 44–57]. Yet, acceptable variability in biomarker concentrations over time likely exists because background chemical exposures arise from recurring lifestyle routines including diet and use of personal care products [11, 16•, 17, 19, 20•, 21–23, 25] as long as commercial formulations of the chemical-containing products do not change considerably within the study timeframe. Therefore, single concentrations obtained from a sufficient number of persons may adequately describe the study population’s average concentration [11, 15•] even when considerable variability exists at the individual level.

For example, reliability in urinary concentrations of bisphenol A (BPA), a high production volume chemical used in the manufacture of many consumer products, is rather poor (i.e., relatively low ICCs) [28, 29, 40, 48, 57, 58]. Yet, despite this variability, biomonitoring concentrations may identify activities (e.g., consumption of canned soup, handling of thermal receipt paper, consumption of water from certain plastic containers) that result in considerable increases in urinary concentrations of BPA [59–62]. Similarly, biomonitoring data confirm that a person’s use of fragranced products significantly increases urinary concentrations of monoethyl phthalate, a metabolite of diethyl phthalate, which is used extensively in personal care products [63–68]. As expected for exposures resulting from recurrent use of such products, the reproducibility of urinary concentrations of monoethyl phthalate, as measured by the ICC [17, 20•, 26, 29, 30•, 42, 43•, 45, 47, 56, 69], is moderate, and, in general, considerably higher than for biomarkers of chemicals like BPA or di(2-ethylhexyl) phthalate (DEHP) for which food consumption is the main exposure source.

Collection and Storage Protocols Matter

Use of spot urine samples in environmental epidemiology is common because collecting spot samples, including first morning voids, is easier than 24-h collections and thus may facilitate participants' recruitment, compliance, and retention. However, as mentioned above, spot concentrations for short-lived chemicals can show considerable inter- and intra-individual temporal variability, particularly for episodic exposures [11, 15•]. Concentrations of single 24-h urine collections, on the other hand, accurately reflect daily exposure but, much like concentrations of spot samples, cannot represent variability in daily exposures over time, at least for non-persistent compounds such as plastic component chemicals (phthalates, BPA), personal care product chemicals (e.g., parabens, triclosan), pesticides, and polycyclic aromatic hydrocarbons [16•, 17, 19, 20•, 21–23, 25]. The moderate to high correlation of biomarker concentrations in spot samples, including first morning voids, with those from 24-h composites [16•, 17, 19, 20•, 21–23, 25] suggests that collecting 24-h voids may not be advantageous compared to multiple spot collections, at least for exposure assessment purposes. Of interest, when collecting multiple spot samples, because sources and timing of the exposures vary depending on the target chemical, changing the time of collection of spot samples and recording the time of urine collection and time since last void may provide the best reflection of aggregate exposure to environmental chemicals.

Sampling must ensure that the biomarker concentrations reflect contact with the chemicals or their precursor(s) from a person's usual exposures over time and not recent spurious contact with the target chemicals, such as from medical intervention or from specimen contamination [8, 11]. Proper study practices such as the use of blank samples may identify potential external contamination during specimen collection (e.g., field or travel blanks) [8] or laboratory analysis (e.g., laboratory blanks) [70•] but cannot adequately identify contact with the target chemicals shortly before sampling. For example, medical interventions may lead to exposure to ubiquitous chemicals such as DEHP and BPA [71–76]. Concentrations of these chemicals or their metabolites in specimens collected soon after medical treatment would reflect true exposures [11, 77, 78], but because these concentrations would not represent typical daily exposures, they would likely be inconsequential for the purposes of quantifying the exposures during the exposure or health assessments in environmental epidemiology studies.

Unfortunately, for many of the tens of thousands of chemicals commercially used nowadays, exposure sources and pathways are yet unknown. Adequate interpretation of biomonitoring data would benefit from research to identify all relevant exposure sources and pathways particularly for chemicals with widespread commercial and industrial use [8]. In the absence of such information, having detailed records pertinent to the sampling and processing of biomonitoring specimens, including location and timing of specimen collection, will facilitate the interpretation of biomonitoring results. Further, interpretation of biomonitoring data in the peer-reviewed literature would benefit from the explicit presentation of these data in scientific and medical journals that publish biomonitoring research.

A good understanding of the sampling and processing practices is highly relevant when using archived samples for which limited information related to collection and storage may exist. In such situations, at least for non-persistent chemicals, evaluating the ratio of

conjugated vs non-conjugated (i.e., free) species may provide useful insight as to whether external contamination or degradation of the biomonitoring specimen occurred during the collection or storage period [8, 57, 79–81]. This approach was applied to the quantification of BPA and other phenols in archived samples collected as part of two European programs, the German Environmental Specimen Bank (ESB) [79] and the Norwegian Mother and Child Cohort Study (MoBa) [57]. BPA is rapidly and almost completely (>90 %) conjugated in phase II biotransformation before excretion in urine [82]. Therefore, external contamination may be assessed from measuring both concentrations of total (conjugated plus free combined) as well as free BPA to identify samples in which the ratio of free/total species is out of the expected range [57, 79–81]. Following this approach, investigators determined that neither contamination nor degradation of the ESB samples occurred [79]. By contrast, the much higher ratio of free/total species compared to normal physiological ranges strongly suggests that BPA contaminated the MoBa urine samples, likely from the use of a urinary preservative [57, 83]. Similarly, evidence suggested external contamination with several parabens from the use of the preservative, but not with other phenols such as the antibacterial triclosan. These findings document the usefulness of measuring total and free biomarker concentrations to assess external contamination of specimens with ubiquitous compounds such as parabens, certain phenols, and phthalates [8, 57, 79–81]. These findings also stress the relevance of promoting a close dialog among laboratory and field researchers from the onset of the study because use of certain preservatives may result in contamination and also interfere with analytic procedures [57, 83].

Use of quality control (QC) materials is an integral component of quality standards for laboratory testing [84]. QC materials, including blanks, are analyzed in each analytical batch along with study samples to ascertain precision and reproducibility of laboratory results. Every batch must meet set QC criteria, or the samples within the batch must be reanalyzed [70•, 84, 85]. In addition to these internal laboratory quality standards, biomonitoring protocols increasingly include screening of collection materials to minimize contamination during sample collection [75, 86]. However, biomonitoring protocols seldom include requirements to monitor (1) potential contamination during handling, storage, and shipping before analysis (e.g., field blanks) [83]; (2) reproducibility of the sampling (e.g., blind duplicates) [87, 88]; or (3) independent checks on laboratory accuracy and precision (e.g., blind samples) [57, 89]. Of interest, these requirements can provide useful information to ensure reliable laboratory measurements through time in epidemiology studies that may span several years. High-purity solvent(s) placed in a sample container and labeled and processed as the biological study samples can serve as a field blank. Blind duplicates are duplicate study samples, preferably split from the same sample container. Blind (matrix) samples can be obtained from commercial sources or collected by field staff and prepared (e.g., mixed well), in quantities sufficient to last for the duration of the project; blind samples may be pools or individual samples. Like field blanks, both blind duplicates and blind samples must be prepared by someone other than the laboratory staff who will perform the analytical measurements and processed (e.g., labeled, stored) as the study samples. Appropriate use of field blanks, blind duplicates, and blind samples interspersed among the study samples can (a) facilitate epidemiologists' evaluation of the integrity of laboratory results and (b) assist

laboratory and field staff in identifying sources of error and to implement corrective measures [88, 90].

Comparability of Biomonitoring Data: Standard Reference Materials and External Quality Assessment Programs

General population human biomonitoring programs, including existing nation-wide initiatives in North America, Europe, and Asia, can provide the most comprehensive assessment of populations' exposure to select environmental chemicals [91–94, 95•, 96–101] and also can potentially inform chemical risk assessments [3]. In addition to nation-wide general population programs, biomonitoring has also been increasingly used in environmental epidemiology for studies of birth cohorts and cohorts of other specific population groups.

For all of these initiatives and studies, scientists and policy makers rely on biomonitoring exposure information to identify at-risk populations and knowledge gaps and to understand the potential impact of chemical exposures on health to support sound policies to limit or track exposures. Therefore, comparing biomonitoring data amongst these programs is of public health interest. However, because each program relies on its own study design, which includes choice of the study population, procurement and type of biospecimens, and selection of analytical methods, to ensure scientifically meaningful comparisons, evaluating aspects of the biomonitoring programs design that can impact comparability of data is key [102]. First, differences in the analytical method accuracy or the degree to which the result of a measurement conforms to the correct value may affect the comparability of biomonitoring results among programs. Two main tools can be used to check the accuracy of the analytical methods: (a) traceability to National Institute of Standards and Technology (NIST) standard reference materials (SRM) [103] and (b) participation in external quality assessment (EQA) programs [104].

SRMs are certified reference materials issued under NIST trademark that are well characterized using state-of-the-art methods for the determination of chemical composition and/or physical properties. In the past few decades, NIST, in collaboration with leading international laboratories, has developed SRMs in urine, blood, or milk for a range of chemical classes including both inorganic and organic chemicals [105, 106•, 107, 108]. For these SRMs, certified values are typically based on the combination of results from two or more independent methods. Whenever possible, incorporating these SRMs in laboratory QC programs can ensure the accuracy, traceability, and comparability of biomonitoring measurements among studies. Regrettably, SRMs are only available for a limited number of chemical agents and biological matrices. Because accurate and precise quantitative measures of environmental chemical biomarkers are at the core of any biomonitoring program, having access to a wider range of SRMs in relevant biological matrices would greatly benefit biomonitoring research.

EQA, a system for objectively checking a laboratory's performance using an external agency or facility, allows for comparison of a laboratory's testing to a peer group of laboratories or a reference laboratory [104]. Participating in EQA programs helps to assure comparability of results from different laboratories and that a laboratory can produce reliable results by the

following: (a) allowing comparison of performance and results among different laboratories, (b) providing early warning for systematic problems associated with laboratory operations, (c) providing objective evidence of testing quality, (d) indicating areas that need improvement, and (e) identifying training needs [104].

Biomonitoring laboratories can use EQA programs, such as those administered by the Centre de Toxicologie du Québec (CTQ, https://www.inspq.qc.ca/en/ctq/eqas) and the University of Erlangen-Nuremberg (http://www.g-equas.de/default.htm), to identify laboratory practice problems, thus allowing for appropriate corrective action. For example, thanks to their participation in EQA programs, the CTQ and US Centers for Disease Control and Prevention (CDC) laboratories identified inaccuracies with commercial phthalate metabolite standards used as calibrators [95•, 109]. Both laboratories issued correction factors for the affected standards that, when applied to previously acquired measurements, corrected for the inaccuracy of the standards to supply accurate and comparable results.

Continuing and expanding EQA programs to include additional compounds would, similar to developing other SRMs, strengthen biomonitoring research. Of interest, however, EQA assesses only the accuracy of the analytical method and cannot detect all other unrelated problems, particularly those pertaining to pre- and post-analysis steps (e.g., external contamination, specimen degradation) that could compromise the integrity of the specimen. Therefore, other QC checks, such as those described in the previous section, must exist to identify these scenarios, thus facilitating the implementation of measures to isolate and track such situations and minimize as much as possible their recurrence and impact [8, 70•]. Otherwise, even valid (i.e., accurate, precise) analytical measures on compromised specimens can lead to erroneous interpretation of biomonitoring results.

Conclusions

The number of epidemiology studies including an exposure assessment biomonitoring component continues to increase. Therefore, programs that allow for the evaluation of accuracy and comparability of results among studies are critical to interpret biomonitoring data for both exposure and risk assessment purposes. Moreover, proper use and interpretation of biomonitoring depend in large part on the study objectives which, in turn, dictate the study design. Adequate selection of the study population, procurement and type of biospecimens, and choice of analytical methods are key to a successful biomonitoring initiative. Biomonitoring provides an integrated measure of exposure to chemicals from all sources and routes. Therefore, biomarkers should be selected to minimize contamination arising from collection, processing, or analysis procedures to best represent usual personal exposures and not recent, adventitious, or extraneous exposures. When properly used, biomonitoring data can be reliably used to estimate internal doses in environmental epidemiology studies.

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