Chapter 2
Biomonitoring to Assess Exposures to Mixtures of Environmental Chemicals

Antonia M. Calafat

Abstract In modern societies, humans may be exposed to a wide spectrum of environmental stressors, including mixtures of anthropogenic chemicals. Furthermore, because human exposure does not occur under controlled conditions of dose-response evaluations in animal studies, exposure assessment is complex. Three main tools have been used to assess human exposures: history/questionnaire information, environmental monitoring, and biomonitoring (i.e., measuring concentrations of the chemicals or their metabolites or adducts in human specimens). In this chapter, we will discuss the suitability of biomonitoring data for evaluating exposures to mixtures of environmental chemicals.

Keywords Biomonitoring · Exposure · NHANES · Endocrine disruptors · Environmental chemicals

2.1 Introduction

In the course of their daily routines, humans are exposed to a large number and variety of physical, biological, psychosocial, and chemical stressors. All of these stressors, their timing, and duration along with each person's genetic makeup, diet, and lifestyle can affect human health (Needham et al. 2005a; Birnbaum 2010). Because of the complexity of such exposures and their interactions, understanding the potential effects of the exposures on health requires a multidisciplinary approach—a topic of interest to several scientific fields including, among others, chemistry, ecology, epidemiology, exposure science, pharmacology, risk analysis, statistics, and toxicology (Carlin et al. 2013).

Disclaimer The findings and conclusions in this report are those of the author and do not necessarily represent the official position of the Centers for Disease Control and Prevention (CDC).

A. M. Calafat (✉)
Centers for Disease Control and Prevention, Atlanta, GA, USA
e-mail: aic7@cdc.gov

C. V. Rider, J. E. Simmons (eds.), *Chemical Mixtures and Combined Chemical and Nonchemical Stressors*, https://doi.org/10.1007/978-3-319-56234-6_2

Three main tools have been used to assess chemical exposures: history/questionnaire information, environmental monitoring, and biomonitoring (i.e., measuring concentrations of the chemicals or their metabolites or adducts in human specimens) (Calafat et al. 2006; Sexton et al. 2004; Needham et al. 2005b). Exposure models, covered in the last chapter of this section, usually incorporate information from the three approaches. The use of history/questionnaire data to assess human exposure to environmental chemicals falls within the purview of environmental epidemiology. Indirect measures of exposure (e.g., environmental monitoring) are the subject of the second chapter of this section. In this chapter, we will cover the assessment of internal exposures using biomonitoring.

2.2 Biomonitoring Overview

Biomonitoring is the assessment of internal dose (i.e., body burden) by measuring the parent chemical (or its metabolite or reaction product) in human samples. Biomonitoring, a "gold standard for assessing exposure to chemicals" (Sexton et al. 2004), has many potential uses in the public health context of preventing disease related to people's exposure to chemicals. Biomonitoring can be used to detect and monitor chemical exposures, to assess people's health risk as a result of such exposures, to develop and implement interventions to reduce exposures, and to evaluate the effectiveness of those interventions (CDC 2009; National Research Council 2012).

In some cases, evidence of chemical exposures and their human health effects (e.g., lead poisoning) have been known since antiquity (Waldron 1973; U.S. EPA 1985), although the use of biomonitoring to track lead poisoning did not start until the late 1890s with the screening of factory workers' blood and urine (Sexton et al. 2004). Since then and thanks, in part, to access to and availability of sophisticated analytical chemistry techniques, trace levels of lead and many other chemicals in a person's body can be routinely measured with high precision and accuracy (Angerer et al. 2007; Pirkle et al. 1995).

These scientific and technologic advances along with the increase in global production of chemicals and their use in a myriad of industrial and consumer products starting in the twentieth century (UNEP 2013) have contributed to the remarkable growth of human biomonitoring research in the last few decades (Angerer et al. 2006; National Research Council 2006; Needham et al. 2007). For example, biomonitoring concentrations are increasingly used to categorize exposures (e.g., low, medium, high) within populations to assess internal exposure to environmental chemicals (National Research Council 2012). However, the scenario of chemical human exposures is complex (Table 2.1). First, controlled conditions, as in traditional animal studies based on the administration of a single chemical and identification of potential target organs (Carlin et al. 2013), do not generally apply. Second, intensity, duration, and frequency of the exposures are normally unknown and often changing. Third, the timing of the exposure is seldom known. Fourth,

Table 2.1 Typical scenarios of human vs animal exposures to environmental chemicals

Chemical-dependent Variable	Human	Animal
Dose	Low? (known?)	High (controlled/ known)
Intensity	Unknown	Known
Timing	Variable (known?)	Fixed
Frequency	Unknown, likely episodic yet chronic	Known
Pathway	Multiple (known?)	Single and identifiable
Chemicals	Many (known?) Metabolites?	Single (mixtures)
Target organ	Accessible? (known?)	Accessible

exposure routes and sources are numerous and, at times, even unknown. Finally, in a world where more than 80,000 chemicals are used in commerce (Bell and Edwards 2015), people are exposed to "cocktails" (multiple/mixtures) of chemicals. Therefore, mixtures encompass the large majority of environmental or background chemical exposures, even in situations when other exposures to mainly single chemicals or chemical classes may occur (e.g., accidental exposures). The fact that all of the above considerations would apply to each of the individual components of the mixtures may further complicate the interpretation of human biomonitoring data. Nevertheless, because biomonitoring per its nature provides an aggregate measure of exposure, biomonitoring has the potential to provide invaluable information for the exposure assessment of chemical mixtures.

2.3 Analytical Aspects of Biomonitoring

Biomonitoring relies on a targeted analysis to provide a quantitative measure of the amount of a chemical or chemicals present in the human body. These chemical biomarkers can be markers of exposure, effect, or susceptibility (National Research Council 2006). As defined by the World Health Organization (WHO), a biomarker of exposure is a "chemical or its metabolite or the product of an interaction between a chemical and some target molecule or cell that is measured in a compartment in an organism," a biomarker of effect is "a measurable biochemical, physiologic, behavioral, or other alteration in an organism that, depending on the magnitude can be recognized as associated with an established or possible health impairment or disease" (e.g., DNA adduct), and a biomarker of susceptibility is "an indicator of an inherent or acquired ability of an organism to respond to the challenge of exposure to a specific chemical substance" (e.g., glucose-6-phosphate dehydrogenase deficiency) (National Research Council 2006). In this chapter, we will focus on biomarkers of exposure.

The success of a biomonitoring approach greatly depends on the adequate selection of the exposure biomarkers, the matrix, and the analytical method (Needham et al. 2007). Knowledge of the physicochemical properties of the target chemicals is important in the choice of exposure biomarkers (e.g., parent compound vs metabolite) and biomonitoring matrix. In general, persistent compounds are commonly measured in blood or blood products, while metabolites of nonpersistent compounds (chemicals with half-lives of the order of hours) are measured in urine (Needham et al. 2007). Measuring blood concentrations of nonpersistent chemicals may be possible when the blood is collected soon after the exposure and if the analytical method is sensitive enough to detect the much lower blood concentrations of the chemical than of its metabolites in urine (Needham and Sexton 2000).

Because exogenous chemicals are present in the biological matrix at much lower concentrations than other endogenous compounds, biomonitoring methods generally include steps to (a) preconcentrate the target analytes and eliminate unwanted matrix components and (b) separate the target analytes from each other and from residual matrix constituents before quantification. The chemical nature of the biomarker and availability of instrumentation can impact the choice of preconcentration (e.g., liquid-liquid extraction, solid-phase extraction) and separation (e.g., chromatography) techniques. For example, separation of volatile organic chemicals is generally achieved by gas chromatography, while liquid chromatography separates nonvolatile organic compounds; nonvolatile organic compounds may also be amenable to gas chromatography after suitable chemical derivatization (Needham et al. 2005c). For human biomonitoring of organic chemicals, isotope-dilution mass spectrometry is generally considered the gold standard quantification technique (Needham et al. 2005c; WHO 2011). Other techniques (e.g., enzyme-linked immunosorbent assay [ELISA], fluorescence) may have the required sensitivity but generally lack adequate analytical selectivity and specificity (WHO 2011).

Biomonitoring methods, rooted in their analytical chemistry foundation, must be sensitive (i.e., capable of accurately measuring small amounts of a given substance in a sample (Saah and Hoover 1997)), selective and specific (i.e., able to measure one particular substance, rather than others in a sample (Saah and Hoover 1997)), and accurate and precise at trace levels (Needham et al. 2005c; Calafat and Needham 2009). Thanks to the scientific and technical advances in robotics and analytical instrumentation in the past few decades, such methods have become increasingly common in many laboratories (Angerer et al. 2007). In addition, biomonitoring methods should preferably use minimal matrix volume, be high throughput, show sustained reproducibility, and concurrently quantify multiple biomarkers. To achieve such characteristics, biomonitoring requires highly trained staff, top quality analytical standards (often custom-synthesized), and the use and maintenance of state-of-the-art instrumentation and facilities. Because of the uniqueness of these resources, biomonitoring is relatively expensive. Nevertheless, despite cost and other challenges associated with the interpretation of biomonitoring data (e.g., study design, communication of results), the use of biomonitoring in environmental public health is on the rise (National Research

Council 2012, 2006; Albertini et al. 2006; Morello-Frosch et al. 2015). Specifically, the possibility of measuring multiple chemicals simultaneously in a small amount of biospecimen makes biomonitoring uniquely suited to study human exposures to chemical mixtures and the potential effects of such exposures on health.

2.4 Interpretation of Biomonitoring Data

Biomonitoring provides information on the concentrations (i.e., amount) of select chemicals that were absorbed into the body after contact between the chemicals—or their precursors—and the body (Needham et al. 2005b). Noteworthy, such concentrations are in the range of trace levels (compared to the generally higher concentrations of the chemicals in the environment) and integrate all environmental pathways and routes (e.g., food, water, air, dust, product use). Furthermore, using biomonitoring concentrations to estimate exposure can pose study design challenges related both to the nature of the biomarker (e.g., specificity, temporality) as well as to the adequacy of the sampling process.

Specificity of the Biomarker Interpreting biomonitoring data requires a good understanding of the toxicokinetics of the target biomarkers. In general, relying on the concentrations of the most abundant biomarker for a given chemical will likely minimize exposure misclassification. For example, di-isononyl phthalate (DINP) metabolizes into mono-isononyl phthalate (MINP) before forming several oxidative metabolites which are the major DINP metabolites in urine (Koch and Angerer 2007). In general population settings, using urinary concentrations of MINP may underestimate exposure to DINP because MINP represents only a minor fraction (~2%) of the DINP excreted in urine compared to the oxidative metabolites (~44%). In fact, exposure to DINP in approximately 82% of Americans would have been misclassified based on the concentrations of the insensitive biomarker MINP, highlighting the importance of selecting a priori the best biomarkers for the intended purposes of the study (Calafat et al. 2011). An additional benefit of measuring phthalate oxidative metabolites is that they cannot be formed as a result of external contamination with the parent phthalate (Koch and Calafat 2009), thus also increasing the specificity of the measurement. In general, when a compound is converted to multiple metabolites, the quantification of all metabolites provides the best biomonitoring approach for exposure assessment. Depending on the aims of the study, exposure categorization can then be based on the concentrations of the individual biomarkers (e.g., four di (2-ethylhexyl) phthalate [DEHP] metabolites) and/or their sum (e.g., sum of all measured DEHP metabolites) (Dales et al. 2018; Kasper-Sonnenberg et al. 2017; Sathyanarayana et al. 2016; Huang et al. 2016; Axelsson et al. 2015; Ferguson et al. 2014; Guo et al. 2014; Kim and Hong 2014; Larsson et al. 2014; Mervish et al. 2014; Watkins et al. 2014; Zhang et al. 2014; Kim et al. 2013; Park et al. 2013; Tellez-Rojo et al. 2013; Upson et al.

2013; Braun et al. 2012; James-Todd et al. 2012; Kasper-Sonnenberg et al. 2012; Teitelbaum et al. 2012; Frederiksen et al. 2011; Romero-Franco et al. 2011).

The fact that several chemicals can metabolize into the same end product may also complicate the interpretation of biomonitoring data. For example, a number of synthetic pyrethroid insecticides are converted to 3-phenoxybenzoic acid (Leng et al. 2003). Therefore, the presence of 3-phenoxybenzoic acid in urine suggests exposure to pyrethroids, but 3-phenoxybenzoic acid concentrations per se cannot pinpoint the specific pyrethroid(s) to which exposure occurred. Similarly, certain chemicals (e.g., organophosphate insecticides) may degrade in the environment, and exposure could be to both the parent compound and the preformed degradate (e.g., dialkylphosphates) (Needham et al. 2005a; Barr et al. 2004). Yet, biomonitoring concentrations of degradates will reflect exposure to both the parent chemical and the preformed metabolites. In the above scenarios, interpreting the concentrations of the biomarkers may be challenging, particularly when the bioactivity of the precursors/parent compounds and their corresponding degradates or non-specific metabolites differ (Duggan et al. 2003). Nonetheless, use of these "non-specific" urinary biomarkers can still provide useful information about cumulative exposure to the parent class of compounds (e.g., pyrethroids, organophosphates).

Temporality of the Biomarker Exposure biomarkers should reflect a person's exposure to the target chemicals or their precursors within a specific time period (e.g., pregnancy) (Calafat et al. 2015). However, with a few exceptions of defined patterns of exposure, such as scheduled tasks in occupational settings (Arnold et al. 2013), the timing, duration, and intensity of chemical exposures are generally unknown and likely different for each chemical in a mixture. As a result, even though biomarker concentrations can accurately rank a person's exposure at a single time point, to evaluate exposure over weeks, months, or years may require different approaches.

In general, for persistent compounds, the timing of the exposure relative to sample collection is not critical. Regardless of the nature of the exposure (i.e., constant vs episodic), its duration, intensity, or timing, a single biomarker concentration at a given time point adequately represents exposure over an extended time (e.g., years) because persistent compounds have relative long elimination half-lives (Needham et al. 2005a; Meeker et al. 2009; Makey et al. 2014). Nonetheless, in certain situations, more than one sample may be needed. For example, chemical-specific toxicokinetics, including transplacental transfer or distribution into breast milk, can result in biomarker concentration changes which, in turn, could impact long-term exposure estimates obtained using a single sample collected during pregnancy or lactation (Adetona et al. 2013; Hooper et al. 2007; Glynn et al. 2012; Kato et al. 2014).

Variability in concentrations is much more pronounced for nonpersistent than for persistent chemicals because concentrations of the target biomarkers for non-persistent chemicals increase and decay rapidly in blood and urine after exposure

(Needham et al. 2005a, 2008; Needham and Sexton 2000; Aylward et al. 2014). Therefore, the intrinsic short half-life (e.g., hours) of nonpersistent chemicals, the nature of the exposure (i.e., intensity, duration, recurrence), and the time passed between exposure and collection of the biomonitoring matrix will impact the reproducibility of the biomarker concentrations (Needham et al. 2005a; Needham and Sexton 2000; Aylward et al. 2014). The timing, duration, and intensity of recurrent activities including use of personal care products or diet—likely pathways of exposure to environmental chemicals—generally change not only between days but even within a day and result in individual variability in concentrations of nonpersistent chemical biomarkers (Aylward et al. 2017; Koch and Angerer 2007; Preau et al. 2010; Teeguarden et al. 2011; Ye et al. 2011; Koch et al. 2004, 2005, 2012, 2013, 2014; Frederiksen et al. 2013; Li et al. 2010; Lassen et al. 2013; Fromme et al. 2007). Assuming a recurrent exposure of constant intensity and duration, this variability will increase as the half-life of the target chemical becomes shorter and the exposure becomes more infrequent (Aylward et al. 2014). The real situation, though, is not as simple: exposures likely recur but at unknown times, and with variable duration and intensity. Moreover, the variability of concentrations will differ for the individual components of chemical mixtures. Nevertheless, because background chemical exposures arise from everyday activities (e.g., food consumption, product use), acceptable biomarker variability over time exists although a person's concentration of a nonpersistent chemical will vary considerably (Calafat et al. 2015; Koch et al. 2014; Preau et al. 2010; Ye et al. 2011; Frederiksen et al. 2013; Li et al. 2010; Lassen et al. 2013; Bradman et al. 2013; Wielgomas 2013). Therefore, biomarker concentrations of a single sample—representing each person's variable exposure scenario—obtained from a large number of individuals can adequately characterize a population's average concentration over extended time because every person's exposure (represented by the biomarker concentration in his/her single sample) would contribute to the mean and extent of exposure (categorized from the mean and range of biomarker concentration, respectively) of the overall population (Calafat et al. 2015; Aylward et al. 2014). This principle is at the foundation of population-based or nation-based biomonitoring programs discussed later in this chapter.

In environmental epidemiology, the intrinsic variability in biomarker urinary concentrations may result in considerable exposure misclassification and bias associations between exposures and health outcomes toward the null hypothesis. Therefore, optimizing the design of exposure assessment in epidemiological studies will require information on the temporal variability of concentrations of the target compounds, particularly for nonpersistent compounds. Determining exposure over weeks, months, or years may require multiple measurements or use of composite (i.e., pooled) specimens to minimize this variability (Ferguson et al. 2014; Adibi et al. 2008; Bertelsen et al. 2014; Braun et al. 2011; Braun et al. 2012; Cantonwine et al. 2014; Engel et al. 2014; Hauser et al. 2004; Irvin et al. 2010; Lewis et al. 2014, 2015; Mahalingaiah et al. 2008; Meeker et al. 2012; Peck et al. 2010; Philippat et al. 2013; Quiros-Alcala et al. 2013; Smith et al. 2012; Teitelbaum et al. 2008; Watkins et al. 2014; Whyatt et al. 2012; Baird et al. 2010; Valvi et al. 2015; Hoppin et al.

2002; Townsend et al. 2013; Heffernan et al. 2014; Jusko et al. 2014; Nepomnaschy et al. 2009; Meeker et al. 2005; Perrier et al. 2016; Weiss et al. 2015; Morgan et al. 2015; Geens et al. 2015; Spaan et al. 2015; Reeves et al. 2014; Fisher et al. 2015; Ackerman et al. 2014; Guidry et al. 2015; Pollack et al. 2016; Romano et al. 2017); the biomarker concentrations obtained from multiple measures (preferably from collections at various times of the day and on multiple days during the study period) or pooled specimens would "average" the concentrations of the target chemicals during the study period.

Of interest, the reproducibility of such measurements will differ, depending on the chemical, the nature of the exposure, and the study population. For example, for nonpersistent compounds for which exposure is largely driven by use of personal care products (e.g., certain phthalates, parabens), the largest variability contributor will be interindividual, while for nonpersistent chemicals with mainly dietary sources that can change substantively from day to day and even within a day (e.g., bisphenol A [BPA], polycyclic aromatic hydrocarbons [PAHs]), large intraindividual differences are expected (Koch et al. 2014; Preau et al. 2010; Teeguarden et al. 2011; Ye et al. 2011; Frederiksen et al. 2013; Li et al. 2010; Lassen et al. 2013; Fromme et al. 2007; Bradman et al. 2013; Wielgomas 2013). For example, the intraclass correlation coefficient (ICC) describes the reliability of repeated measures over time and is defined as the ratio of between-subject variance to total (between-subject plus within-subject) variance. ICC ranges from zero (no reproducibility) to one (perfect reproducibility). Interestingly, ICCs of biomarker concentrations associated with episodic dietary exposures tend to be lower than for other exposures (e.g., use of personal care products), regardless of the study population (e.g., children, pregnant women, other adults) and the timeframe evaluated (days, months, years) (Ferguson et al. 2014; Adibi et al. 2008; Bertelsen et al. 2014; Braun et al. 2011, 2012; Cantonwine et al. 2014; Engel et al. 2014; Hauser et al. 2004; Irvin et al. 2010; Lewis et al. 2014, 2015; Mahalingaiah et al. 2008; Meeker et al. 2012; Peck et al. 2010; Philippat et al. 2013; Quiros-Alcala et al. 2013; Smith et al. 2012; Teitelbaum et al. 2008; Watkins et al. 2014; Whyatt et al. 2012; Baird et al. 2010; Valvi et al. 2015; Hoppin et al. 2002; Townsend et al. 2013; Heffernan et al. 2014; Jusko et al. 2014; Nepomnaschy et al. 2009; Meeker et al. 2005; Perrier et al. 2016; Weiss et al. 2015; Morgan et al. 2015; Geens et al. 2015; Spaan et al. 2015; Reeves et al. 2014; Fisher et al. 2015; Ackerman et al. 2014; Guidry et al. 2015; Dewalque et al. 2015). These findings suggest that short-term variability in biomarker concentrations may also apply to long-term variability because the associated exposures related to lifestyle habits do not change considerably over time (Calafat et al. 2015), particularly if commercial formulations of the chemicals do not change within the study timeframe and geographic location.

Sampling Strategies The use of spot urine samples (i.e., single, untimed urine specimen, voided spontaneously) is common in environmental epidemiology despite the well-recognized fact that spot concentrations for short-lived chemicals can show considerable inter- and intraindividual temporal variability, particularly for episodic exposures (Calafat et al. 2015; Aylward et al. 2014). Collecting spot

samples, including first morning voids, is easier than collecting 24-h samples and may facilitate compliance in epidemiologic studies.

In recent years, several investigations evaluated the suitability of spot samples, including first morning voids, and 24-h collections to categorize exposures to nonpersistent compounds such as plastic components (phthalates, BPA), personal care product chemicals (e.g., parabens, triclosan), pesticides, and PAHs from the biomarker urinary concentrations (Koch et al. 2014; Preau et al. 2010; Ye et al. 2011; Frederiksen et al. 2013; Li et al. 2010; Lassen et al. 2013; Bradman et al. 2013; Wielgomas 2013; Aylward et al. 2017). Interestingly, regardless of the collection strategy (spot, first morning, 24-h), urinary concentrations of the target biomarkers varied considerably during the 6–7 consecutive days of study, and the main contributors to the total variance differed. Specifically, biomarker urinary concentrations of chemicals with mainly dietary sources showed higher inter-day variability than those of chemicals with mostly non-dietary sources (e.g., use of personal care products) for which inter-person variability was most pronounced. These findings and the fact that the concentrations of biomarkers in first morning voids or spot samples correlated moderately to highly with those from 24-h composites suggest that, for exposure assessment, collecting 24-h voids may not be advantageous compared to multiple spot collections.

The nature of the exposures (diet vs other lifestyle factors) and timing of urine sampling to evaluate chemical exposures should be considered. This critical aspect is particularly relevant when evaluating exposures to chemical mixtures because the sources and timing of the exposures are likely to vary depending on the chemical. Changing the time of collection of spot samples and recording the time of urine collection and time since last void would provide useful information to interpret biomonitoring data for chemical mixtures.

Because not all sources of the more than 80,000 chemicals commercially used are known, understanding the details related to collecting and processing of biomonitoring specimens is also critical. Sampling must ensure that the biomarker concentrations reflect contact with the chemicals or their precursor(s) from a person's usual exposures over time (e.g., during pregnancy) and not from recent contact, such as from use of medical equipment or medical intervention or from specimen contamination (Calafat and Needham 2009; Calafat et al. 2015). Field or travel blanks are advantageous to identify potential external contamination during sample collection (Calafat and Needham 2009) but are inadequate to highlight contact with the chemical shortly before sampling. For example, during medical interventions people may be exposed to chemicals used in plastics such as DEHP and BPA (Huygh et al. 2015; Su et al. 2012; Weuve et al. 2006; Green et al. 2005; Calafat et al. 2004; Duty et al. 2013; Calafat et al. 2009). Concentrations of these chemicals or their metabolites in specimens collected soon after medical treatment would reflect true exposures (Calafat et al. 2015; Vandentorren et al. 2011; Yan et al. 2009), but would not be representative of typical daily exposures and, therefore, likely would be irrelevant in environmental epidemiology studies.

2.5 Population-Based Biomonitoring Surveys

Human biomonitoring data per se do not provide information on health effects (CDC 2009), but general population human biomonitoring programs are useful for investigating human exposure to chemical mixtures and are important tools for integrating environment and health (Angerer et al. 2006; National Research Council 2006; Bell and Edwards 2015; Sobus et al. 2015).

For example, in the United States, the Centers for Disease Control and Prevention (CDC) conducts the National Health and Nutrition Examination Survey (NHANES) (CDC 2011, 2017). Beginning in 1971 and then yearly since 1999, NHANES collects detailed medical history and performs physical examinations on all survey participants, approximately 5000 per year—selected through a complex statistical process using the most current census information—and includes a biomonitoring component from participants 1 year of age and older (CDC 2017; Calafat 2012). Most NHANES biomonitoring data are based on the analysis of samples from representative subsets of participants (e.g., one-third sample); subset distributions often change with survey cycles. Of note, biomonitoring measurements in blood or blood serum are only available from participants 12 years and older, with the exception of lead, cadmium, mercury, and, since 2011, manganese and selenium (minimum age of 1 year), and cotinine (minimum age of 3 years); biomonitoring measurements in urine are available for persons 6 years (3 years starting in 2015) of age and older (CDC 2011; Calafat 2012). Since 1999, the number of chemicals measured in people's blood has increased from 27 to more than 300 (CDC 2017). The NHANES biomonitoring program provides the most comprehensive assessment of the U.S. general population's exposure to hundreds of environmental chemicals (CDC 2011, 2017). These data, which are representative of the U.S. population, have been used to establish population reference ranges, track exposure trends, identify populations with higher than background exposures, prioritize research needs, and, sometimes, inform chemical risk assessments (National Research Council 2012; Sobus et al. 2015). For example, several federal agencies in the United States have used NHANES biomonitoring data to support various research and regulatory activities, including, among others, the U.S. Environmental Protection Agency (EPA) decision to remove lead from gasoline and the reregistration of triclosan and the U.S. Consumer Products Safety Commission (CPSC) decision to prohibit the use of certain phthalates in children's toys and child care articles (Sobus et al. 2015; U.S. EPA 2008; CPSC 2017). More recently, EPA also used NHANES data for lead, mercury, perchlorate, and several organic compounds—polyfluoroalkyl and perfluoroalkyl substances, polychlorinated biphenyls, polybrominated diphenyl ethers, phthalates, and BPA—in its third edition of America's Children and the Environment (U.S. EPA 2013), a report which, among other goals, can help policymakers and the public track and understand the potential impacts of environmental contaminants on children's health and, ultimately, to identify and evaluate ways to minimize these impacts.

Nationwide human biomonitoring initiatives also exist in other countries, including Austria, Belgium (Flanders), Canada, Czech Republic, France, Germany, Israel, Japan, Korea, Slovenia, and Spain (Health Canada 2017; Kolossa-Gehring et al. 2012; Kawamoto et al. 2014; Perez-Gomez et al. 2013; Cerna et al. 2012; Frery et al. 2012; Schoeters et al. 2012; Perharic and Vracko 2012; Berman et al. 2012; Casteleyn et al. 2015; La Corte and Wuttke 2012; Hohenblum et al. 2012; Ha et al. 2014). Biological samples collected as part of these programs have been used to provide the most comprehensive assessment of these countries' general populations' exposure to select environmental chemicals (CDC 2017; Becker et al. 2009; Koch et al. 2007; Schulz et al. 2007; Haines and Murray 2012; Jeong et al. 2014; Geens et al. 2014; Saoudi et al. 2014; Puklova et al. 2010; Bartolome et al. 2015; Levine et al. 2015; Černá et al. 2017) and also have the potential to inform chemical risk assessments (Albertini et al. 2006).

In addition to nationwide general population programs, biomonitoring has been increasingly used in environmental epidemiology such as birth cohort studies as well as cohorts of specific population groups. The list of programs relying on biomonitoring measurements is so extensive that it can't be covered in this short chapter. The examples below are meant to illustrate the breadth and versatility of populations for which biomonitoring can provide useful information in environmental epidemiology research.

Birth cohort studies include, among many others, the U.S. National Institute of Environmental Health Sciences/EPA's Children's Centers for Environmental Health and Disease Prevention (https://www.epa.gov/research-grants/niehsepa-childrens-environmental-health-and-disease-prevention-research-centers), Project VIVA, The Infant Development and the Environment Study, the Mothers and Children's Environmental Health Study, the Norwegian Mother and Child Cohort Study, the Danish National Birth Cohort, and the Northern Norway Mother-and-Child Contaminant Cohort (Kim et al. 2009; Zeman et al. 2013; Ronningen et al. 2006; Guxens et al. 2012; Olsen 2012; Veyhe et al. 2015; Oken et al. 2015; Barrett et al. 2014). Cohorts of specific population groups include, among many, the Framingham Heart Study, the Nurses' Health Study, the Women's Health Initiative, the Childhood Autism Risks from Genetics and the Environment Study, the Shanghai Women's Health Study, and the Shanghai Men's Health Study (Zheng et al. 2005; Cupples et al. 2007; Colditz and Hankinson 2005; Hays et al. 2003; Hertz-Picciotto et al. 2006; Cai et al. 2007). Lactating women may be considered a special category within these specific population groups. Human milk is regarded as infants' best nutrition source (Landrigan et al. 2002). Nonetheless, environmental chemicals can also partition into breast milk (Lehmann et al. 2014), and breast milk monitoring programs can provide useful information to study early life exposures to environmental chemicals (Lehmann et al. 2014; Solomon and Weiss 2002; Berlin et al. 2005; Fenton et al. 2005; LaKind et al. 2005; Pan et al. 2010; LaKind et al. 2001; Colles et al. 2008; Li et al. 2009; Croes et al. 2012). Breast milk programs, for instance, albeit restricted to one specific sector of the population, have been useful to assess temporal trends to select persistent organic compounds (Solomon and Weiss 2002; Konishi et al. 2001; Kunisue et al. 2006; Raab et al. 2007; Abballe

et al. 2008; Polder et al. 2008; Lignell et al. 2009; Sundstrom et al. 2011; Fang et al. 2013; Vukavic et al. 2013; Darnerud et al. 2015).

For these population-based initiatives, biomonitoring can provide important exposure information as well as data to understand the potential impact of the environment, including chemical mixtures, among other factors, on various aspects of human health such as reproductive outcomes, development, behavior, and respiratory health. Age; diet and lifestyle; route, frequency, and intensity of the exposures; potential interactions among chemicals; and genetic factors, among others, are critical in determining health outcomes from exposures to chemical mixtures. In the context of environmental public health, the recent increase in studies linking biomonitoring exposure data and human health would benefit from the definition and implementation of best practices for analysis, interpretation, and communication of biomonitoring data (Sobus et al. 2015; LaKind et al. 2014).

2.6 Conclusions

Biomonitoring provides an integrated measure of exposure to chemicals from all sources and routes and can be reliably used to estimate internal doses. Because of technological advances, a vast amount of biomonitoring exposure data already exist, and the volume of studies including a biomonitoring component for exposure assessment and, most recently, for relating internal exposure to potential health effects continue to increase. The 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 critical to a successful biomonitoring initiative.

References

Abballe, A., T.J. Ballard, E. Dellatte, et al. 2008. Persistent environmental contaminants in human milk: Concentrations and time trends in Italy. *Chemosphere* 73: S220–S227.

Ackerman, J.M., R.E. Dodson, C.L. Engel, et al. 2014. Temporal variability of urinary di (2-ethylhexyl) phthalate metabolites during a dietary intervention study. *Journal of Exposure Science and Environmental Epidemiology* 24: 595–601.

Adetona, O., K. Horton, A. Sjodin, et al. 2013. Concentrations of select persistent organic pollutants across pregnancy trimesters in maternal and in cord serum in Trujillo, Peru. *Chemosphere* 91: 1426–1433.

Adibi, J.J., R.M. Whyatt, P.L. Williams, et al. 2008. Characterization of phthalate exposure among pregnant women assessed by repeat air and urine samples. *Environmental Health Perspectives* 116: 467–473.

Albertini, R., M. Bird, N. Doerrer, et al. 2006. The use of biomonitoring data in exposure and human health risk assessments. *Environmental Health Perspectives* 114: 1755–1762.

Angerer, J., M.G. Bird, T.A. Burke, et al. 2006. Strategic biomonitoring initiatives: Moving the science forward. *Toxicological Sciences* 93: 3–10.

Angerer, J., U. Ewers, and M. Wilhelm. 2007. Human biomonitoring: State of the art. *International Journal of Hygiene and Environmental Health* 210: 201–228.

Arnold, S.M., J. Angerer, P.J. Boogaard, et al. 2013. The use of biomonitoring data in exposure and human health risk assessment: Benzene case study. *Critical Reviews in Toxicology* 43: 119–153.

Axelsson, J., L. Rylander, A. Rignell-Hydbom, et al. 2015. Phthalate exposure and reproductive parameters in young men from the general Swedish population. *Environment International* 85: 54–60.

Aylward, L.L., S.M. Hays, R. Smolders, et al. 2014. Sources of variability in biomarker concentrations. *Journal of Toxicology and Environmental Health, Part B* 17: 45–61.

Aylward, L.L., S.M. Hays, and A. Zidek. 2017. Variation in urinary spot sample, 24 h samples, and longer-term average urinary concentrations of shortlived environmental chemicals: implications for exposure assessment and reverse dosimetry. *Journal of Exposure Science and Environmental Epidemiology* 27 (6): 582–590.

Baird, D.D., T.M. Saldana, P.A. Nepomnaschy, et al. 2010. Within-person variability in urinary phthalate metabolite concentrations: Measurements from specimens after long-term frozen storage. *Journal of Exposure Science and Environmental Epidemiology* 20: 169–175.

Barr, D.B., R. Bravo, G. Weerasekera, et al. 2004. Concentrations of dialkyl phosphate metabolites of organophosphorus pesticides in the US population. *Environmental Health Perspectives* 112: 186–200.

Barrett, E.S., S. Sathyanarayana, S. Janssen, et al. 2014. Environmental health attitudes and behaviors: Findings from a large pregnancy cohort study. *European Journal of Obstetrics & Gynecology and Reproductive Biology* 176: 119–125.

Bartolome, M., J.J. Ramos, F. Cutanda, et al. 2015. Urinary polycyclic aromatic hydrocarbon metabolites levels in a representative sample of the Spanish adult population: The BIOAMBIENT.ES project. *Chemosphere* 135: 436–446.

Becker, K., T. Goen, M. Seiwert, et al. 2009. GerES IV: Phthalate metabolites and bisphenol A in urine of German children. *International Journal of Hygiene and Environmental Health* 212: 685–692.

Bell, S.M., and S.W. Edwards. 2015. Identification and prioritization of relationships between environmental stressors and adverse human health impacts. *Environmental Health Perspectives* 123: 1193–1199.

Berlin, C.M., B.L. Crase, P. Furst, et al. 2005. Methodologic considerations for improving and facilitating human milk research. *Journal of Toxicology and Environmental Health, Part A* 68: 1803–1823.

Berman, T., Y. Amitai, S. Almog, et al. 2012. Human biomonitoring in Israel: Past, present, future. *International Journal of Hygiene and Environmental Health* 215: 138–141.

Bertelsen, R.J., S.M. Engel, T.A. Jusko, et al. 2014. Reliability of triclosan measures in repeated urine samples from Norwegian pregnant women. *Journal of Exposure Science and Environmental Epidemiology* 24: 517–521.

Birnbaum, L.S. 2010. Applying research to public health questions: Biologically relevant exposures. *Environmental Health Perspectives* 118: A152.

Bradman, A., K. Kogut, E.A. Eisen, et al. 2013. Variability of organophosphorous pesticide metabolite levels in spot and 24-hr urine samples collected from young children during 1 week. *Environmental Health Perspectives* 121: 118–124.

Braun, J.M., A.E. Kalkbrenner, A.M. Calafat, et al. 2011. Variability and predictors of urinary bisphenol A concentrations during pregnancy. *Environmental Health Perspectives* 119: 131–137.

Braun, J.M., K.W. Smith, P.L. Williams, et al. 2012. Variability of urinary phthalate metabolite and bisphenol A concentrations before and during pregnancy. *Environmental Health Perspectives* 120: 739–745.

Cai, H., W. Zheng, Y.B. Xiang, et al. 2007. Dietary patterns and their correlates among middle-aged and elderly Chinese men: A report from the Shanghai Men's Health Study. *British Journal of Nutrition* 98: 1006–1013.

Calafat, A.M. 2012. The U.S. National Health and Nutrition Examination Survey and human exposure to environmental chemicals. *International Journal of Hygiene and Environmental Health* 215: 99–101.

Calafat, A.M., and L.L. Needham. 2009. What additional factors beyond state-of-the-art analytical methods are needed for optimal generation and interpretation of biomonitoring data? *Environmental Health Perspectives* 117: 1481–1485.

Calafat, A.M., L.L. Needham, M.J. Silva, et al. 2004. Exposure to di-(2-ethylhexyl) phthalate among premature neonates in a neonatal intensive care unit. *Pediatrics* 113: e429–e434.

Calafat, A.M., X. Ye, M.J. Silva, et al. 2006. Human exposure assessment to environmental chemicals using biomonitoring. *International Journal of Andrology* 29: 166–171.

Calafat, A.M., J. Weuve, X.Y. Ye, et al. 2009. Exposure to bisphenol A and other phenols in neonatal intensive care unit premature infants. *Environmental Health Perspectives* 117: 639–644.

Calafat, A.M., L.Y. Wong, M.J. Silva, et al. 2011. Selecting adequate exposure biomarkers of diisononyl and diisodecyl phthalates: Data from the 2005-2006 National Health and Nutrition Examination Survey. *Environmental Health Perspectives* 119: 50–55.

Calafat, A.M., M.P. Longnecker, H.M. Koch, et al. 2015. Optimal exposure biomarkers for nonpersistent chemicals in environmental epidemiology. *Environmental Health Perspectives* 123: A166–A168.

Cantonwine, D.E., J.F. Cordero, L.O. Rivera-Gonzalez, et al. 2014. Urinary phthalate metabolite concentrations among pregnant women in Northern Puerto Rico: Distribution, temporal variability, and predictors. *Environment International* 62: 1–11.

Carlin, D.J., C.V. Rider, R. Woychik, et al. 2013. Unraveling the health effects of environmental mixtures: An NIEHS priority. *Environmental Health Perspectives* 121: A6–A8.

Casteleyn, L., B. Dumez, K. Becker, et al. 2015. A pilot study on the feasibility of European harmonized Human Biomonitoring: Strategies towards a common approach, challenges and opportunities. *Environmental Research* 141: 3–14.

CDC. 2009. Fourth National Report on Human Exposure to Environmental Chemicals, Centers for Disease Control and Prevention; National Center for Environmental Health; Division of Laboratory Sciences, Atlanta. https://www.cdc.gov/exposurereport/pdf/fourthreport.pdf. Accessed 9 Dec 2017.

———. 2011. NHANES environmental chemical data tutorial. National Center for Health Statistics. http://www.cdc.gov/nchs/tutorials/environmental/index.htm. Accessed 9 Dec 2017.

———. 2017. Fourth National Report on Human Exposure to Environmental Chemicals. Updated Tables, January 2017, Centers for Disease Control and Prevention; National Center for Environmental Health; Division of Laboratory Sciences, Atlanta. https://www.cdc.gov/exposurereport/. Accessed 9 Dec 2017.

Cerna, M., A. Krskova, M. Cejchanova, et al. 2012. Human biomonitoring in the Czech Republic: An overview. *International Journal of Hygiene and Environmental Health* 215: 109–119.

Černá, M., V. Puklová, L. Hanzlíková, et al. 2017. 25 years of HBM in the Czech Republic. *International Journal of Hygiene and Environmental Health* 220 (2): 3–5.

Colditz, G.A., and S.E. Hankinson. 2005. The Nurses' Health Study: Lifestyle and health among women. *Nature Reviews Cancer* 5: 388–396.

Colles, A., G. Koppen, V. Hanot, et al. 2008. Fourth WHO-coordinated survey of human milk for persistent organic pollutants (POPs): Belgian results. *Chemosphere* 73: 907–914.

CPSC. 2017. Prohibition of children's toys and child care articles containing specified phthalates. *Federal Register* 82: 49938–49982.

Croes, K., A. Colles, G. Koppen, et al. 2012. Persistent organic pollutants (POPs) in human milk: A biomonitoring study in rural areas of Flanders (Belgium). *Chemosphere* 89: 988–994.

Cupples, L.A., H.T. Arruda, E.J. Benjamin, et al. 2007. The Framingham Heart Study 100K SNP genome-wide association study resource: Overview of 17 phenotype working group reports. *BMC Medical Genetics* 8 (Suppl 1): S1.

Dales, R.E., L.M. Kauri, and S. Cakmak. 2018. The associations between phthalate exposure and insulin resistance, beta-cell function and blood glucose control in a population-based sample. *Science of The Total Environment* 612: 1287–1292.

Darnerud, P.O., S. Lignell, M. Aune, et al. 2015. Time trends of polybrominated diphenylether (PBDE) congeners in serum of Swedish mothers and comparisons to breast milk data. *Environmental Research* 138: 352–360.

Dewalque, L., C. Pirard, S. Vandepaer, et al. 2015. Temporal variability of urinary concentrations of phthalate metabolites, parabens and benzophenone-3 in a Belgian adult population. *Environmental Research* 142: 414–423.

Duggan, A., G. Charnley, W. Chen, et al. 2003. Di-alkyl phosphate biomonitoring data: Assessing cumulative exposure to organophosphate pesticides. *Regulatory Toxicology and Pharmacology* 37: 382–395.

Duty, S.M., K. Mendonca, R. Hauser, et al. 2013. Potential sources of bisphenol A in the neonatal intensive care unit. *Pediatrics* 131: 483–489.

Engel, L.S., J.P. Buckley, G. Yang, et al. 2014. Predictors and variability of repeat measurements of urinary phenols and parabens in a cohort of Shanghai women and men. *Environmental Health Perspectives* 122: 733–740.

Fang, J., E. Nyberg, A. Bignert, et al. 2013. Temporal trends of polychlorinated dibenzo-p-dioxins and dibenzofurans and dioxin-like polychlorinated biphenyls in mothers' milk from Sweden, 1972-2011. *Environment International* 60: 224–231.

Fenton, S.E., M. Condon, A.S. Ettinger, et al. 2005. Collection and use of exposure data from human milk biomonitoring in the United States. *Journal of Toxicology and Environmental Health, Part A* 68: 1691–1712.

Ferguson, K.K., T.F. McElrath, Y.A. Ko, et al. 2014. Variability in urinary phthalate metabolite levels across pregnancy and sensitive windows of exposure for the risk of preterm birth. *Environment International* 70: 118–124.

Fisher, M., T.E. Arbuckle, R. Mallick, et al. 2015. Bisphenol A and phthalate metabolite urinary concentrations: Daily and across pregnancy variability. *Journal of Exposure Science and Environmental Epidemiology* 25: 231–239.

Frederiksen, H., L. Aksglaede, K. Sorensen, et al. 2011. Urinary excretion of phthalate metabolites in 129 healthy Danish children and adolescents: Estimation of daily phthalate intake. *Environmental Research* 111: 656–663.

Frederiksen, H., S.K. Kranich, N. Jorgensen, et al. 2013. Temporal variability in urinary phthalate metabolite excretion based on spot, morning, and 24-h urine samples: Considerations for epidemiological studies. *Environmental Science & Technology* 47: 958–967.

Frery, N., S. Vandentorren, A. Etchevers, et al. 2012. Highlights of recent studies and future plans for the French human biomonitoring (HBM) programme. *International Journal of Hygiene and Environmental Health* 215: 127–132.

Fromme, H., G. Bolte, H.M. Koch, et al. 2007. Occurrence and daily variation of phthalate metabolites in the urine of an adult population. *International Journal of Hygiene and Environmental Health* 210: 21–33.

Geens, T., L. Bruckers, A. Covaci, et al. 2014. Determinants of bisphenol A and phthalate metabolites in urine of Flemish adolescents. *Environmental Research* 134: 110–117.

Geens, T., A.C. Dirtu, E. Dirinck, et al. 2015. Daily intake of bisphenol A and triclosan and their association with anthropometric data, thyroid hormones and weight loss in overweight and obese individuals. *Environment International* 76: 98–105.

Glynn, A., U. Berger, A. Bignert, et al. 2012. Perfluorinated alkyl acids in blood serum from primiparous women in Sweden: Serial sampling during pregnancy and nursing, and temporal trends 1996-2010. *Environmental Science & Technology* 46: 9071–9079.

Green, R., R. Hauser, A.M. Calafat, et al. 2005. Use of di(2-ethylhexyl) phthalate-containing medical products and urinary levels of mono(2-ethylhexyl) phthalate in neonatal intensive care unit infants. *Environmental Health Perspectives* 113: 1222–1225.

Guidry, V.T., M.P. Longnecker, H. Aase, 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. *Environmental Health Perspectives* 123: 705–711.

Guo, Y., J. Weck, R. Sundaram, et al. 2014. Urinary concentrations of phthalates in couples planning pregnancy and its association with 8-hydroxy-2'-deoxyguanosine, a biomarker of oxidative stress: Longitudinal Investigation of Fertility and the Environment Study. *Environmental Science & Technology* 48: 9804–9811.

Guxens, M., F. Ballester, M. Espada, et al. 2012. Cohort profile: The INMA--INfancia y Medio Ambiente--(environment and childhood) project. *International Journal of Epidemiology* 41: 930–940.

Ha, M., H.J. Kwon, J.H. Leem, et al. 2014. Korean Environmental Health Survey in Children and Adolescents (KorEHS-C): Survey design and pilot study results on selected exposure biomarkers. *International Journal of Hygiene and Environmental Health* 217: 260–270.

Haines, D.A., and J. Murray. 2012. Human biomonitoring of environmental chemicals--early results of the 2007-2009 Canadian Health Measures Survey for males and females. *International Journal of Hygiene and Environmental Health* 215: 133–137.

Hauser, R., J.D. Meeker, S. Park, et al. 2004. Temporal variability of urinary phthalate metabolite levels in men of reproductive age. *Environmental Health Perspectives* 112: 1734–1740.

Hays, J., J.R. Hunt, F.A. Hubbell, et al. 2003. The Women's Health Initiative recruitment methods and results. *Annals of Epidemiology* 13: S18–S77.

Health Canada. 2017. Fourth report on human biomonitoring of environmental chemicals in Canada: results of the Canadian Health Measures Survey Cycle 4 (2014–2015), Health Canada, Ottawa. https://www.canada.ca/en/health-canada/services/environmental-workplacehealth/reports-publications/environmental-contaminants/fourth-report-human-biomonitoring-environmental-chemicals-canada.html. Accessed 9 Dec 2017.

Heffernan, A.L., L.L. Aylward, A.J. Samidurai, et al. 2014. Short term variability in urinary bisphenol A in Australian children. *Environment International* 68: 139–143.

Hertz-Picciotto, I., L.A. Croen, R. Hansen, et al. 2006. The CHARGE study: An epidemiologic investigation of genetic and environmental factors contributing to autism. *Environmental Health Perspectives* 114: 1119–1125.

Hohenblum, P., P. Steinbichl, W. Raffesberg, et al. 2012. Pollution gets personal! A first population-based human biomonitoring study in Austria. *International Journal of Hygiene and Environmental Health* 215: 176–179.

Hooper, K., J. She, M. Sharp, et al. 2007. Depuration of polybrominated diphenyl ethers (PBDEs) and polychlorinated biphenyls (PCBs) in breast milk from California first-time mothers (primiparae). *Environmental Health Perspectives* 115: 1271–1275.

Hoppin, J.A., J.W. Brock, B.J. Davis, et al. 2002. Reproducibility of urinary phthalate metabolites in first morning urine samples. *Environmental Health Perspectives* 110: 515–518.

Huang, P.-C., C.-H. Tsai, W.-Y. Liang, et al. 2016. Early phthalates exposure in pregnant women is associated with alteration of thyroid hormones. *Plos One* 11 (7): e0159398.

Huygh, J., K. Clotman, G. Malarvannan, et al. 2015. Considerable exposure to the endocrine disrupting chemicals phthalates and bisphenol-A in intensive care unit (ICU) patients. *Environment International* 81: 64–72.

Irvin, E.A., A.M. Calafat, M.J. Silva, et al. 2010. An estimate of phthalate exposure among pregnant women living in Trujillo, Peru. *Chemosphere* 80: 1301–1307.

James-Todd, T., R. Stahlhut, J.D. Meeker, et al. 2012. Urinary phthalate metabolite concentrations and diabetes among women in the National Health and Nutrition Examination Survey (NHANES) 2001-2008. *Environmental Health Perspectives* 120: 1307–1313.

Jeong, S.W., C.K. Lee, C.H. Suh, et al. 2014. Blood lead concentration and related factors in Korea from the 2008 National Survey for Environmental Pollutants in the Human Body. *International Journal of Hygiene and Environmental Health* 217: 871–877.

Jusko, T.A., P.A. Shaw, C.A. Snijder, et al. 2014. Reproducibility of urinary bisphenol A concentrations measured during pregnancy in the Generation R Study. *Journal of Exposure Science and Environmental Epidemiology* 24: 532–536.

Kasper-Sonnenberg, M., H.M. Koch, J. Wittsiepe, et al. 2012. Levels of phthalate metabolites in urine among mother-child-pairs – results from the Duisburg birth cohort study, Germany. *International Journal of Hygiene and Environmental Health* 215: 373–382.

Kasper-Sonnenberg, M., J. Wittsiepe, K. Wald, et al. 2017. Pre-pubertal exposure with phthalates and bisphenol A and pubertal development. *Plos One* 12 (11): e0187922.

Kato, K., L.Y. Wong, A.M. Chen, et al. 2014. Changes in serum concentrations of maternal poly- and perfluoroalkyl substances over the course of pregnancy and predictors of exposure in a multiethnic cohort of Cincinnati, Ohio pregnant women during 2003-2006. *Environmental Science & Technology* 48: 9600–9608.

Kawamoto, T., H. Nitta, K. Murata, et al. 2014. Rationale and study design of the Japan environment and children's study (JECS). *BMC Public Health* 14: 25.

Kim, J.H., and Y.C. Hong. 2014. HSP70-hom gene polymorphisms modify the association of diethylhexyl phthalates with insulin resistance. *Environmental and Molecular Mutagenesis* 55: 727–734.

Kim, B.M., M. Ha, H.S. Park, et al. 2009. The mothers and children's environmental health (MOCEH) study. *European Journal of Epidemiology* 24: 573–583.

Kim, J.H., H.Y. Park, S. Bae, et al. 2013. Diethylhexyl phthalates is associated with insulin resistance via oxidative stress in the elderly: A panel study. *Plos One* 8: e71392.

Koch, H.M., and J. Angerer. 2007. Di-iso-nonylphthalate (DINP) metabolites in human urine after a single oral dose of deuterium-labelled DINP. *International Journal of Hygiene and Environmental Health* 210: 9–19.

Koch, H.M., and A.M. Calafat. 2009. Human body burdens of chemicals used in plastic manufacture. *Philosophical Transactions of the Royal Society of London B: Biological Sciences* 364: 2063–2078.

Koch, H.M., H.M. Bolt, and J. Angerer. 2004. Di(2-ethylhexyl)phthalate (DEHP) metabolites in human urine and serum after a single oral dose of deuterium-labelled DEHP. *Archives of Toxicology* 78: 123–130.

Koch, H.M., H.M. Bolt, R. Preuss, et al. 2005. New metabolites of di(2-ethylhexyl)phthalate (DEHP) in human urine and serum after single oral doses of deuterium-labelled DEHP. *Archives of Toxicology* 79: 367–376.

Koch, H.M., K. Becker, M. Wittassek, et al. 2007. Di-n-butylphthalate and butylbenzylphthalate – urinary metabolite levels and estimated daily intakes: Pilot study for the German Environmental Survey on children. *Journal of Exposure Science and Environmental Epidemiology* 17: 378–387.

Koch, H.M., K.L.Y. Christensen, V. Harth, et al. 2012. Di-n-butyl phthalate (DnBP) and diisobutyl phthalate (DiBP) metabolism in a human volunteer after single oral doses. *Archives of Toxicology* 86: 1829–1839.

Koch, H.M., A. Schutze, C. Palmke, et al. 2013. Metabolism of the plasticizer and phthalate substitute diisononyl-cyclohexane-1,2-dicarboxylate (DINCH) in humans after single oral doses. *Archives of Toxicology* 87: 799–806.

Koch, H.M., L.L. Aylward, S.M. Hays, et al. 2014. Inter- and intra-individual variation in urinary biomarker concentrations over a 6-day sampling period. Part 2: Personal care product ingredients. *Toxicology Letters* 231: 261–269.

Kolossa-Gehring, M., K. Becker, A. Conrad, et al. 2012. Environmental surveys, specimen bank and health related environmental monitoring in Germany. *International Journal of Hygiene and Environmental Health* 215: 120–126.

Konishi, Y., K. Kuwabara, and S. Hori. 2001. Continuous surveillance of organochlorine compounds in human breast milk from 1972 to 1998 in Osaka, Japan. *Archives of Environmental Contamination and Toxicology* 40: 571–578.

Kunisue, T., M. Muraoka, M. Ohtake, et al. 2006. Contamination status of persistent organochlorines in human breast milk from Japan: Recent levels and temporal trend. *Chemosphere* 64: 1601–1608.

La Corte, E., and S. Wuttke. 2012. The First Nations Biomonitoring Initiative-FNBI. *International Journal of Hygiene and Environmental Health* 215: 168–171.

LaKind, J.S., C.M. Berlin, and D.Q. Naiman. 2001. Infant exposure to chemicals in breast milk in the United States: What we need to learn from a breast milk monitoring program. *Environmental Health Perspectives* 109: 75–88.

LaKind, J.S., R.L. Brent, M.L. Dourson, et al. 2005. Human milk biomonitoring data: Interpretation and risk assessment issues. *Journal of Toxicology and Environmental Health, Part A* 68: 1713–1769.

LaKind, J.S., J.R. Sobus, M. Goodman, et al. 2014. A proposal for assessing study quality: Biomonitoring, Environmental Epidemiology, and Short-lived Chemicals (BEES-C) instrument. *Environment International* 73: 195–207.

Landrigan, P.J., B. Sonawane, D. Mattison, et al. 2002. Chemical contaminants in breast milk and their impacts on children's health: An overview. *Environmental Health Perspectives* 110: A313–A315.

Larsson, K., K.L. Bjorklund, B. Palm, et al. 2014. Exposure determinants of phthalates, parabens, bisphenol A and triclosan in Swedish mothers and their children. *Environment International* 73: 323–333.

Lassen, T.H., H. Frederiksen, T.K. Jensen, et al. 2013. Temporal variability in urinary excretion of bisphenol A and seven other phenols in spot, morning, and 24-h urine samples. *Environmental Research* 126: 164–170.

Lehmann, G.M., M.A. Verner, B. Luukinen, et al. 2014. Improving the risk assessment of lipophilic persistent environmental chemicals in breast milk. *Critical Reviews in Toxicology* 44: 600–617.

Leng, G., U. Ranft, D. Sugiri, et al. 2003. Pyrethroids used indoors--biological monitoring of exposure to pyrethroids following an indoor pest control operation. *International Journal of Hygiene and Environmental Health* 206: 85–92.

Levine, H., T. Berman, R. Goldsmith, et al. 2015. Urinary concentrations of polycyclic aromatic hydrocarbons in Israeli adults: Demographic and life-style predictors. *International Journal of Hygiene and Environmental Health* 218: 123–131.

Lewis, R.C., D.E. Cantonwine, L.V. Anzalota Del Toro, et al. 2014. Urinary biomarkers of exposure to insecticides, herbicides, and one insect repellent among pregnant women in Puerto Rico. *Environmental Health* 13: 97.

———. 2015. Distribution and determinants of urinary biomarkers of exposure to organophosphate insecticides in Puerto Rican pregnant women. *Science of The Total Environment* 15: 337–344.

Li, J., L. Zhang, Y. Wu, et al. 2009. A national survey of polychlorinated dioxins, furans (PCDD/Fs) and dioxin-like polychlorinated biphenyls (dl-PCBs) in human milk in China. *Chemosphere* 75: 1236–1242.

Li, Z., L.C. Romanoff, M.D. Lewin, et al. 2010. Variability of urinary concentrations of polycyclic aromatic hydrocarbon metabolite in general population and comparison of spot, first-morning, and 24-h void sampling. *Journal of Exposure Science and Environmental Epidemiology* 20: 526–535.

Lignell, S., M. Aune, P.O. Darnerud, et al. 2009. Persistent organochlorine and organobromine compounds in mother's milk from Sweden 1996-2006: Compound-specific temporal trends. *Environmental Research* 109: 760–767.

Mahalingaiah, S., J.D. Meeker, K.R. Pearson, et al. 2008. Temporal variability and predictors of urinary bisphenol a concentrations in men and women. *Environmental Health Perspectives* 116: 173–178.

Makey, C.M., M.D. McClean, A. Sjodin, et al. 2014. Temporal variability of polybrominated diphenyl ether (PBDE) serum concentrations over one year. *Environmental Science & Technology* 48: 14642–14649.

Meeker, J.D., D.B. Barr, L. Ryan, et al. 2005. Temporal variability of urinary levels of nonpersistent insecticides in adult men. *Journal of Exposure Science and Environmental Epidemiology* 15: 271–281.

Meeker, J.D., S.A. Missmer, L. Altshul, et al. 2009. Serum and follicular fluid organochlorine concentrations among women undergoing assisted reproduction technologies. *Environmental Health* 8: 32.

Meeker, J.D., A.M. Calafat, and R. Hauser. 2012. Urinary phthalate metabolites and their biotransformation products: Predictors and temporal variability among men and women. *Journal of Exposure Science and Environmental Epidemiology* 22: 376–385.

Mervish, N., K.J. McGovern, S.L. Teitelbaum, et al. 2014. Dietary predictors of urinary environmental biomarkers in young girls, BCERP, 2004-7. *Environmental Research* 133: 12–19.

Morello-Frosch, R., J. Varshavsky, M. Liboiron, et al. 2015. Communicating results in post-Belmont era biomonitoring studies: Lessons from genetics and neuroimaging research. *Environmental Research* 136: 363–372.

Morgan, M., P. Jones, and J. Sobus. 2015. Short-term variability and predictors of urinary pentachlorophenol levels in Ohio preschool children. *International Journal of Environmental Research and Public Health* 12: 800–815.

National Research Council. 2006. *Human biomonitoring for environmental chemicals*. Washington, DC: The National Academies Press. https://doi.org/10.17226/11700. Accessed 9 Dec 2017.

———. 2012. Exposure science in the 21st century: A vision and a strategy. National Academies Press (US), Washington (DC). http://www.nap.edu/catalog/13507/exposure-science-in-the-21st-century-a-vision-and-a. Accessed 9 Dec 2017.

Needham, L.L., and K. Sexton. 2000. Assessing children's exposure to hazardous environmental chemicals: An overview of selected research challenges and complexities. *Journal of Exposure Analysis & Environmental Epidemiology* 10: 611–629.

Needham, L.L., D.B. Barr, and A.M. Calafat. 2005a. Characterizing children's exposures: Beyond NHANES. *Neurotoxicology* 26: 547–553.

Needham, L.L., H. Ozkaynak, R.M. Whyatt, et al. 2005b. Exposure assessment in the National Children's Study: Introduction. *Environmental Health Perspectives* 113: 1076–1082.

Needham, L.L., D.G. Patterson, D.B. Barr, et al. 2005c. Uses of speciation techniques in biomonitoring for assessing human exposure to organic environmental chemicals. *Analytical and Bioanalytical Chemistry* 381: 397–404.

Needham, L.L., A.M. Calafat, and D.B. Barr. 2007. Uses and issues of biomonitoring. *International Journal of Hygiene and Environmental Health* 210: 229–238.

———. 2008. Assessing developmental toxicant exposures via biomonitoring. *Basic & Clinical Pharmacology & Toxicology* 102: 100–108.

Nepomnaschy, P.A., D.D. Baird, C.R. Weinberg, et al. 2009. Within-person variability in urinary bisphenol A concentrations: Measurements from specimens after long-term frozen storage. *Environmental Research* 109: 734–737.

Oken, E., A.A. Baccarelli, D.R. Gold, et al. 2015. Cohort profile: Project viva. *International Journal of Epidemiology* 44: 37–48.

Olsen, J. 2012. Nine months that last a lifetime. Experience from the Danish National Birth Cohort and lessons learned. *International Journal of Hygiene and Environmental Health* 215: 142–144.

Pan, I.J., J.L. Daniels, A.H. Herring, et al. 2010. Lactational exposure to polychlorinated biphenyls, dichlorodiphenyltrichloroethane, and dichlorodiphenyldichloroethylene and infant

growth: An analysis of the Pregnancy, Infection, and Nutrition Babies Study. *Paediatric and Perinatal Epidemiology* 24: 262–271.

Park, H.Y., J.H. Kim, Y.H. Lim, et al. 2013. Influence of genetic polymorphisms on the association between phthalate exposure and pulmonary function in the elderly. *Environmental Research* 122: 18–24.

Peck, J.D., A.M. Sweeney, E. Symanski, et al. 2010. Intra- and inter-individual variability of urinary phthalate metabolite concentrations in Hmong women of reproductive age. *Journal of Exposure Science and Environmental Epidemiology* 20: 90–100.

Perez-Gomez, B., R. Pastor-Barriuso, M. Cervantes-Amat, et al. 2013. BIOAMBIENT.ES study protocol: Rationale and design of a cross-sectional human biomonitoring survey in Spain. *Environmental Science and Pollution Research* 20: 1193–1202.

Perharic, L., and P. Vracko. 2012. Development of national human biomonitoring programme in Slovenia. *International Journal of Hygiene and Environmental Health* 215: 180–184.

Perrier, F., L. Giorgis-Allemand, R. Slama, et al. 2016. Within-subject pooling of biological samples to reduce exposure misclassification in biomarker-based studies. *Epidemiology* 27: 378–388.

Philippat, C., M.S. Wolff, A.M. Calafat, et al. 2013. Prenatal exposure to environmental phenols: Concentrations in amniotic fluid and variability in urinary concentrations during pregnancy. *Environmental Health Perspectives* 121: 1225–1231.

Pirkle, J.L., L.L. Needham, and K. Sexton. 1995. Improving exposure assessment by monitoring human tissues for toxic chemicals. *Journal of Exposure Analysis and Environmental Epidemiology* 5: 405–424.

Pollack, A.Z., N.J. Perkins, L. Sjaarda, et al. 2016. Variability and exposure classification of urinary phenol and paraben metabolite concentrations in reproductive-aged women. *Environmental Research* 151: 513–520.

Polder, A., C. Thomsen, G. Lindstrom, et al. 2008. Levels and temporal trends of chlorinated pesticides, polychlorinated biphenyls and brominated flame retardants in individual human breast milk samples from Northern and Southern Norway. *Chemosphere* 73: 14–23.

Preau, J.L., L.Y. Wong, M.J. Silva, et al. 2010. Variability over 1 week in the urinary concentrations of metabolites of diethyl phthalate and di(2-ethylhexyl) phthalate among eight adults: An observational study. *Environmental Health Perspectives* 118: 1748–1754.

Puklova, V., A. Krskova, M. Cerna, et al. 2010. The mercury burden of the Czech population: An integrated approach. *International Journal of Hygiene and Environmental Health* 213: 243–251.

Quiros-Alcala, L., B. Eskenazi, A. Bradman, et al. 2013. Determinants of urinary bisphenol A concentrations in Mexican/Mexican-American pregnant women. *Environment International* 59: 152–160.

Raab, U., U. Schwegler, U. Preiss, et al. 2007. Bavarian breast milk survey--pilot study and future developments. *International Journal of Hygiene and Environmental Health* 210: 341–344.

Reeves, K.W., J. Luo, S.E. Hankinson, et al. 2014. Within-person variability of urinary bisphenol-A in postmenopausal women. *Environmental Research* 135: 285–288.

Romano, M.E., N.L. Hawley, M. Eliot, et al. 2017. Variability and predictors of urinary concentrations of organophosphate flame retardant metabolites among pregnant women in Rhode Island. *Environmental Health* 16 (1).

Romero-Franco, M., R.U. Hernandez-Ramirez, A.M. Calafat, et al. 2011. Personal care product use and urinary levels of phthalate metabolites in Mexican women. *Environment International* 37: 867–871.

Ronningen, K.S., L. Paltiel, H.M. Meltzer, et al. 2006. The biobank of the Norwegian Mother and Child Cohort Study: A resource for the next 100 years. *European Journal of Epidemiology* 21: 619–625.

Saah, A.J., and D.R. Hoover. 1997. “Sensitivity” and “specificity” reconsidered: The meaning of these terms in analytical and diagnostic settings. *Annals of Internal Medicine* 126: 91–94.

Saoudi, A., N. Frery, A. Zeghnoun, et al. 2014. Serum levels of organochlorine pesticides in the French adult population: The French National Nutrition and Health Study (ENNS), 2006-2007. *Science of The Total Environment* 472: 1089–1099.

Sathyanarayana, S., R. Grady, E.S. Barrett, et al. 2016. First trimester phthalate exposure and male newborn genital anomalies. *Environmental Research* 151: 777–782.

Schoeters, G., H.E. Den, A. Colles, et al. 2012. Concept of the Flemish human biomonitoring programme. *International Journal of Hygiene and Environmental Health* 215: 102–108.

Schulz, C., A. Conrad, K. Becker, et al. 2007. Twenty years of the German Environmental Survey (GerES): Human biomonitoring – temporal and spatial (West Germany/East Germany) differences in population exposure. *International Journal of Hygiene and Environmental Health* 210: 271–297.

Sexton, K., L.L. Needham, and J.L. Pirkle. 2004. Human biomonitoring of environmental chemicals. *Am Sci* 92: 38–45.

Smith, K.W., J.M. Braun, P. Williams, et al. 2012. Predictors and variability of urinary paraben concentrations in men and women, including before and during pregnancy. *Environmental Health Perspectives* 120: 1538–1543.

Sobus, J.R., R.S. DeWoskin, Y.M. Tan, et al. 2015. Uses of NHANES biomarker data for chemical risk assessment: Trends, challenges, and opportunities. *Environmental Health Perspectives* 123: 919–927.

Solomon, G.M., and P.M. Weiss. 2002. Chemical contaminants in breast milk: Time trends and regional variability. *Environmental Health Perspectives* 110: A339–A347.

Spaan, S., A. Pronk, H.M. Koch, et al. 2015. Reliability of concentrations of organophosphate pesticide metabolites in serial urine specimens from pregnancy in the Generation R Study. *Journal of Exposure Science and Environmental Epidemiology* 25: 286–294.

Su, P.H., Y.Z. Chang, H.P. Chang, et al. 2012. Exposure to di(2-ethylhexyl) phthalate in premature neonates in a neonatal intensive care unit in Taiwan. *Pediatric Critical Care Medicine* 13: 671–677.

Sundstrom, M., D.J. Ehresman, A. Bignert, et al. 2011. A temporal trend study (1972-2008) of perfluorooctanesulfonate, perfluorohexanesulfonate, and perfluorooctanoate in pooled human milk samples from Stockholm, Sweden. *Environment International* 37: 178–183.

Teeguarden, J.G., A.M. Calafat, X.Y. Ye, et al. 2011. Twenty-four hour human urine and serum profiles of bisphenol A during high-dietary exposure. *Toxicological Sciences* 123: 48–57.

Teitelbaum, S.L., J.A. Britton, A.M. Calafat, et al. 2008. Temporal variability in urinary concentrations of phthalate metabolites, phytoestrogens and phenols among minority children in the United States. *Environmental Research* 106: 257–269.

Teitelbaum, S.L., N. Mervish, E.L. Moshier, et al. 2012. Associations between phthalate metabolite urinary concentrations and body size measures in New York City children. *Environmental Research* 112: 186–193.

Tellez-Rojo, M.M., A. Cantoral, D.E. Cantonwine, et al. 2013. Prenatal urinary phthalate metabolites levels and neurodevelopment in children at two and three years of age. *Science of The Total Environment* 461: 386–390.

Townsend, M.K., A.A. Franke, X.N. Li, et al. 2013. Within-person reproducibility of urinary bisphenol A and phthalate metabolites over a 1 to 3 year period among women in the Nurses' Health Studies: A prospective cohort study. *Environmental Health* 12: 80.

UNEP. 2013. Global chemicals outlook – Towards sound management of chemicals. https://sustainabledevelopment.un.org/content/documents/1966Global%20Chemical.pdf. Accessed 9 Dec 2017.

Upson, K., S. Sathyanarayana, A.J. De Roos, et al. 2013. Phthalates and risk of endometriosis. *Environmental Research* 126: 91–97.

U.S. EPA. 1985. Lead poisoning: A historical perspective. https://archive.epa.gov/epa/aboutepa/lead-poisoning-historical-perspective.html. Accessed 9 Dec 2017.

———. 2008. 5-Chloro-2-(2,4-dichlorophenoxy) phenol (Triclosan): Risk Assessment for the Reregistration Eligibility Decision (RED) Document. Case No 2340. DP Barcode 343544. PC

Code: 054901, U.S. Environmental Protection Agency. https://archive.epa.gov/pesticides/reregistration/web/html/index-316.html. Accessed 9 Dec 2017.

———. 2013. America's children and the environment, Third Edition (ACE3). http://www.epa.gov/ace/index.html. Accessed 9 Dec 2017.

Valvi, D., N. Monfort, R. Ventura, et al. 2015. Variability and predictors of urinary phthalate metabolites in Spanish pregnant women. *International Journal of Hygiene and Environmental Health* 218: 220–231.

Vandentorren, S., F. Zeman, L. Morin, et al. 2011. Bisphenol-A and phthalates contamination of urine samples by catheters in the Elfe pilot study: Implications for large-scale biomonitoring studies. *Environmental Research* 111: 761–764.

Veyhe, A.S., D. Hofoss, S. Hansen, et al. 2015. The Northern Norway Mother-and-Child Contaminant Cohort (MISA) Study: PCA analyses of environmental contaminants in maternal sera and dietary intake in early pregnancy. *International Journal of Hygiene and Environmental Health* 218: 254–264.

Vukavic, T., M.M. Vojinovic, I. Mihajlovic, et al. 2013. Human milk POPs and neonatal risk trend from 1982 to 2009 in the same geographic region in Serbia. *Environment International* 54: 45–49.

Waldron, H.A. 1973. Lead poisoning in the ancient world. *Medical History* 17: 391–399.

Watkins, D.J., M. Eliot, S. Sathyanarayana, et al. 2014. Variability and predictors of urinary concentrations of phthalate metabolites during early childhood. *Environmental Science & Technology* 48: 8881–8890.

Weiss, L., T.E. Arbuckle, M. Fisher, et al. 2015. Temporal variability and sources of triclosan exposure in pregnancy. *International Journal of Hygiene and Environmental Health* 218: 507–513.

Weuve, J., B.N. Sanchez, A.M. Calafat, et al. 2006. Exposure to phthalates in neonatal intensive care unit infants: Urinary concentrations of monoesters and oxidative metabolites. *Environmental Health Perspectives* 114: 1424–1431.

WHO. 2011. Toxicological and health aspects of bisphenol A. Report of Joint FAO/WHO Expert Meeting 2–5 November 2010 and Report of Stakeholder Meeting on Bisphenol A 1 November 2010. http://whqlibdoc.who.int/publications/2011/97892141564274_eng.pdf. Accessed 9 Dec 2017.

Whyatt, R.M., X.H. Liu, V.A. Rauh, et al. 2012. Maternal prenatal urinary phthalate metabolite concentrations and child mental, psychomotor, and behavioral development at 3 years of age. *Environmental Health Perspectives* 120: 290–295.

Wielgomas, B. 2013. Variability of urinary excretion of pyrethroid metabolites in seven persons over seven consecutive days-implications for observational studies. *Toxicology Letters* 221: 15–22.

Yan, X., A. Calafat, S. Lashley, et al. 2009. Phthalates biomarker identification and exposure estimates in a population of pregnant women. *Human and Ecological Risk Assessment* 15: 565–578.

Ye, X.Y., L.Y. Wong, A.M. Bishop, et al. 2011. Variability of urinary concentrations of bisphenol A in spot samples, first morning voids, and 24-hour collections. *Environmental Health Perspectives* 119: 983–988.

Zeman, F.A., C. Boudet, K. Tack, et al. 2013. Exposure assessment of phthalates in French pregnant women: Results of the ELFE pilot study. *International Journal of Hygiene and Environmental Health* 216: 271–279.

Zhang, Y.H., X.Z. Meng, L. Chen, et al. 2014. Age and sex-specific relationships between phthalate exposures and obesity in Chinese children at puberty. *Plos One* 9: e104852.

Zheng, W., W.H. Chow, G. Yang, et al. 2005. The Shanghai Women's Health Study: Rationale, study design, and baseline characteristics. *American Journal of Epidemiology* 162: 1123–1131.