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Integration of biomonitoring data into risk assessment

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Abstract

Biomonitoring for environmental chemicals in human biological media has become an indispensible feature of the chemical risk assessment landscape. While the relevance of biomonitoring data to exposure assessment is obvious, biomonitoring is also playing a critical role as a fundamental component of environmental epidemiology. In this respect, biomonitoring data are increasingly becoming a primary basis for hazard identification as well as dose-response assessment. Biomonitoring data can also provide powerful information on the efficacy of risk management efforts. As the process of chemical risk assessment moves from a chemical-by-chemical approach to a broader focus on the landscape of tens of thousands of chemicals in commerce, biomonitoring is playing an increasing role in the development of high-throughput computational exposure models as well as in the interpretation and application of high-throughput toxicity testing data in a risk context. Finally, biomonitoring data are central to the development and implementation of the concept of the exposome, which will be increasingly important in the assessment and management of chemical risks.

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Biomonitoring, Risk assessment, Exposome, Dose-response.

1. Background

Biomonitoring — measurement of chemical concentrations in human biological media such as serum or urine — has been called the "gold standard" for assessing human exposure to environmental chemicals [1]. Exposure assessment is one of the fundamental components of the classic paradigm for chemical risk assessment [2]. Thus, the relevance of such data to this step of the risk assessment process is obvious [3]. But as the availability of biomonitoring data has grown, scientists and policy makers have also recognized the broader utility of these data in the hazard identification, dose-response assessment, and risk characterization phases of the core risk assessment paradigm. Further, risk assessment has evolved into a larger process that includes initial scoping steps to ensure fit-for-purpose assessments, community and stakeholder involvement, risk management actions, and iterative evaluation and interaction across the various risk assessment and risk management stages [4]. And the risk assessment community is increasingly focused on the challenges of assessing toxicity and potential risks of exposure to the broad landscape of tens of thousands of data-poor chemicals in commerce [5] as well as developing a broader understanding of the potential influences of the complex pattern of multiple chemical exposures across life stages on health. Biomonitoring data are relevant to and increasingly integrated into all of these aspects of the broader risk assessment process.

2. Exposure assessment

Population-representative biomonitoring data being generated by the National Health and Nutrition Examination Survey (NHANES) program and similar programs in Canada and elsewhere has been the subject of a great deal of interest in the risk assessment community [6,7]. While the general relevance of biomonitoring data to chemical exposure assessment is obvious, the disconnect between the typical approach to exposure assessment based on external exposure levels (mg/kg-d or mg/m^3) and the data produced in biomonitoring studies (concentrations in biological media such as blood or urine) poses challenges to direct integration of such data into the conventional risk assessment process [3,8]. These contrasting approaches to characterizing exposure can be related to one another through understanding of typical exposure pathways coupled with data or models of the absorption, distribution, metabolism and elimination (ADME) characteristics of chemicals. Quantitative description of these elements in simple or more elaborate statistical or toxicokinetic models provides tools for translation between external and internal dose metrics and for the integration of biomonitoring data in the conventional risk assessment paradigm [3,8–13].

Both simple and more complex toxicokinetic data and models, including data on urinary excretion fractions for non-persistent chemicals, have been developed for a relatively wide range of chemicals and can be used to predict the time course of blood, urine, or tissue concentrations of a chemical resulting from a specified external exposure. However, understanding the external

exposure profile leading to an observed distribution of biomarker concentrations in a population, termed "reverse dosimetry," is a more complex and computationally intense problem, and generally requires assumptions about the timing and population distribution of exposures [8,13–17]. Concentrations of non-persistent chemicals can vary widely within individuals both within and across days, as well as between individuals with different exposure profiles [18–20]. As a result, a variety of simplifying assumptions such as constant steady-state exposure rates or inference based on statistical characteristics of observed biomarker distributions have been used in order to estimate the distribution of exposures in an individual or population based on biomonitoring data sets [19,21–23]. Estimated exposures derived from biomonitoring data can be used for comparison and evaluation of external exposure estimates obtained from environmental monitoring data, potentially illuminating the existence of sources or pathways not previously identified, to identify populations with elevated exposures, and to characterize the degree of variability in population exposures [24,25].

3. Application of biomonitoring data in hazard assessment, dose–response assessment, and risk characterization

Biomonitoring has been used for more than a century for specific occupational environments and exposures [1]. Beginning in the second half of the 20th century, biomonitoring for selected environmental chemicals was initiated more widely in the general population, including through the National Human Adipose Tissue Survey (NHATS) and the NHANES program [3]. The continuous NHANES biomonitoring program, begun in 1999, heralded widespread expansion of the use of biomonitoring in environmental epidemiology. As analytical techniques have improved in sensitivity and cost, the field of environmental epidemiology, with studies of potential exposure-response relationships based on biomonitoring data in both cross sectional and longitudinal cohorts, has exploded.

The central focus of such studies is to test hypotheses about potential exposure-outcome relationships in human populations. The reliance on biomonitoring as a primary metric of exposure has led to increasing opportunities for using human data as a primary source of hazard identification and dose-response assessment in the context of risk assessment. The relationship between blood lead and childhood intelligence measures is the classic example of use of biomonitoring data in hazard identification and dose response assessment [26]; indeed, biomonitoring remains the primary basis for assessment of both exposure and response to lead. Increasingly, however, data from environmental epidemiology studies present opportunities to conduct risk assessment solely or primarily based on human biomonitoring data, either in parallel to or replacing assessments based on external exposure metrics.

A single biomonitoring-based study of exposure and response is unlikely to drive either hazard or dose-response assessment for a chemical, although some researchers have begun to use risk assessment tools such as benchmark dose estimation within their studies (see, for example, [27]). However, a body of literature evaluated in a systematic review [28] and integrated with supporting in vitro bioactivity or in vivo toxicity data may provide sufficient basis for identification of a point of departure and a risk assessment based on biomarker concentrations [29]. The US Environmental Protection Agency (US EPA) based its most recent assessment of the risks of dioxin-like compounds on human epidemiological studies that relied on serum dioxin levels as the exposure metric [30]. The French Agency for Food, Environment, and Occupational Safety and Health (ANSES) set an exposure limit for polychlorinated biphenyls in human serum based on human exposure-response studies [31].

The increasing use of toxicokinetic modeling in the dose-response assessment process based on animal toxicological data presents additional opportunities for integration of biomonitoring data into the risk assessment process [32]. Numerous dose-response assessments conducted over the past decade at the US EPA have relied upon measured or modeled blood concentrations at the point of departure in animal studies as the point of departure for estimating human equivalent doses. The animal blood concentrations at the point of departure represent an opportunity for direct comparison with human biomonitoring data for selected classes of chemicals. For example, the recent health advisories for perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate from EPA both estimated points of departure based on serum concentrations in animal studies [33,34]. These serum concentrations represent a natural target for comparison to biomonitoring data in the general population or targeted populations for assessment in a margin of exposure context, for example, as proposed in the Risk 21 framework [35].

Several approaches have been considered for the evaluation of population biomonitoring data [21]. The utility of toxicokinetic data and models for interpreting biomonitoring data in a risk assessment context has led to the development of the concept of Biomonitoring Equivalents (BEs), which are estimates of the biomarker concentrations consistent with risk assessment-based exposure guidance values [8,14,36]. Use of BE values for risk characterization based on biomonitoring data has been demonstrated for several dozen chemicals in the US, Canada, Australia, and Europe (reviewed in