Application, Advantages and Challenges of Human Biomonitoring in Exposure Assessment as a Part of Human Health Risk Assessment Process including Occupational Settings

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Abstract

Human biomonitoring (HBM) has a long tradition both in health care and public health with wide range of applications including occupational settings. Its advantage is the integration of all exposure routes and sources. Since HBM information is an integrated exposure finding, it offers the opportunity to trace and mimic a realistic exposure scenario. It reduces the number of assumptions that need to be done when estimating exposure, and thus helps to reduce the uncertainties in exposure science. In spite of some challenges, such as further harmonization in the area of HBM, necessity to derive equivalents of markers of external exposure, but also an addressing the ethical and political aspects of its application, HBM is an efficient and cost-effective way to measure the level of exposure of the human body to xenobiotics.

Key words: risk assessment, xenobiotics, exposure, mercury, human biomonitoring

ABBREVIATIONS:

HBM	human biomonitoring
IPCS/WHO	International Programme on Chemical Safety WHO
PFOS	perfluorooctane sulfonate
PCBs	polychlorinated biphenyls
PBPK model	physiologically based pharmacokinetic modelling
ADME	absorption, distribution, metabolism, excretion

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INTRODUCTION

People are exposed to thousands of chemicals in work and the environment via air, water, food and soil. More than 10,000 chemical contaminants can enter the human body through the mouth, the skin, by ingestion and respiration. The general population experiences uncontrolled multi-chemical exposure from many different sources at doses around or well below regulatory limits. The first exposure occurs already in the uterus (Kromerová and Bencko, 2017).

A plethora of chemicals from anthropogenic and natural origins enter animal feed, human food and water either as undesirable contaminants or as part of the components of a diet. Anthropogenic contaminants of public and animal health importance, include amongst others: persistent organic pollutants (i.e. dioxins, polychlorinated biphenyls, brominated flame retardants, perfluoroalkyl acids), Maillard reaction products (acrylamide, furans), phthalates, pharmaceuticals as well as residues from production aids and chemicals authorized for use following a pre-marketing approval in food and feed productions such as pesticides/biocides, and food and feed additives. Important classes of natural contaminants include heavy metals such as lead, cadmium, uranium, mercury and metalloids such as arsenic and natural toxins produced by bacteria, protozoa, algae, fungi, and plants (Dorne, 2013).

Risk is defined by IPCS/WHO (International Programme on Chemical Safety WHO) as „the probability of an adverse effect in an organism, system, or (sub)population caused under specified circumstances by exposure to an agent“ (IPCS, 2004). Complete elimination of the risk is an unrealistic objective and the circumstances and the level of exposure is an important aspect (Kromerová and Bencko, 2017).

There have been significant advances in techniques to obtain available data. Despite this development, however, exposure information for 95–99% of the 100,000 chemicals having toxicity information is still unavailable (Egeghy et al., 2012).

The National Research Council of the United States of America in 2002 defined human biomonitoring (hereinafter referred to as “HBM”) as a method for assessing human exposure to chemicals by measuring the chemicals or their metabolites in human tissues or specimens such as blood or urine” (CDC, 2005). HBM relies on the use of biomarkers, measurable indicators of changes, or events in biological systems. Biomarkers are measured concentrations of chemical substances, their metabolites or reaction products in human tissues or specimens, such as blood, urine, hair, adipose tissue, teeth, saliva, breast milk, and sperm. (Choi et al., 2015).

ADVANTAGES AND APPLICATION OF HUMAN BIOMONITORING

It was shown that heterogeneity in biological measurements is less likely to skew results than heterogeneity in external exposure (Fowler, 2013). Thus, HBM is a sound solution for addressing chemical ‘events’ and leading to fewer uncertainties (Dong, 2015).

The main advantage of using biomarkers is intrinsic in their nature, representing an integrative measurement of exposure to a given agent (i.e. the internal dose), that results from complex pathways of human exposure and also incorporates toxicokinetic information and individual characteristics such as genetically based susceptibility. It takes into account processes like metabolism, bioaccumulation and excretion. Through the use of biomarkers, it is not only possible to monitor exposure, but it also becomes feasible to detect early health effects.

HBM can show geographical and socio-economic differences in exposure and body burdens. Another major advantage of HBM is the possibility to reduce the number of assumptions that have to be made regarding consumption rates. Thus, HBM helps to further reduce the uncertainties in exposure science.

Advantage is also the integration over all routes and sources that may elucidate exposures that have not been anticipated or have been neglected in external aggregate exposure assessments and/or models. For the complex health risk assessment for the general public, HBM surveys are the ideal tool to collect exposure data. For example, the Human Early Life Exposome (HELIX) project, measure environmental exposures of up to 32,000 European mother–child pairs and their consequent impact on the growth, development, and health of the children. It estimates prenatal and postnatal exposure to a broad range of chemical and physical exposures: persistent and non-persistent organic chemicals, metals, pesticides, environmental tobacco smoke, water contaminants, air pollutants, noise, UV radiation, and contact with green spaces. Part of the project is also the collection of extensive biomarker data for a subset of 1200 mother–child pairs (Choi et al., 2015).

However, biological measures of exposure should be preferred, if available, to environmental exposure data as they are closer to the target organ dose and provide greater precision in risk estimates and in dose–response relationships. HBM is often more specific and sensitive than environmental monitoring (e.g. food monitoring) in assessing the degree of recent and, by all means, also past exposure to chemicals from all routes (Manno et al., 2010). Internal doses, i.e. concentrations in fluids (urine, blood) or organs inside the body, are relevant to reflect the actual exposure. Internal doses are also more relevant than external doses to provide a link between exposure and effects. They account for the dose to which target organs or systems are actually exposed to. In the context of human predictive toxicology, there is an increase of the use of models coupling human toxicokinetic modelling and dose–response models relating internal dose and effects at target level, as shown, for instance by Péry et al. (2013) to predict acetaminophen hepatotoxicity in humans from effects measured in vitro on hepatic cell lines (Ciffroy et al., 2016).

Long-term external monitoring data are always lacking, and external exposure cannot be determined to completely account for internal exposure (Bernillon and Bois, 2000). HBM can be used for revealing long-term trends for contaminants in the population and indicate the likely environmental implications. For example, remarkable 13-fold increase for PFOS has been observed in females in China.

Furthermore, HBM can help develop PBPK models that understand the ADME process. Redding et al. used physiological parameters from a population cohort in Taiwan and reference values given in the literature to estimate partition coefficients based on chemical structure and lipid content in various body tissues (Redding et al., 2008). They also utilised exposure data from Japan to predict the acquired PCB-153 body burdens at an average child-bearing age of 25 years. Good agreement between HBM measurements and prediction indicated the feasibility of the application of biomonitoring data in human health risk assessment.

By reconstructing allocation of relevant pathways with advanced statistical techniques HBM may offer solutions for exposure minimisation or even elimination. (Dong, 2015). Modelling approaches from HBM data could be used for generating consistent input data for human exposure assessment. For example, Ulaszewska et al. (2012) used HBM data of PCBs levels in Italian women breast milk, and PBPK models to determine the most probable scenario of exposure: for each congener, the authors determined the most probable long-term history of PCBs emission in air, as well as concentrations in environmental receptor media and food, and estimated the time evolution of the daily intakes over the lifetime. As a result, they were able to reconstruct accurately the exposure and filled in data gaps on environmental concentrations over decades. Such reverse modelling that uses HBM data can generate data for human health risk assessment (Ciffroy et al., 2016). Since HBM information is an integrated exposure finding, it offers the opportunity to trace and mimic a realistic exposure scenario (Dong and Hu, 2011).

HBM and biomarkers have a long tradition in health care. They are used in curative and preventive medicine in several domains, and may be applied in different context also in environmental health. In occupational medicine, HBM plays an important role within the measurement of the body burden of toxic substances and their metabolites for more than a century. HBM is also used in particular for detection of exposure and adverse health risk and for assessing the efficiency of preventive measures and for controlling working place limit values set. For certain industries and professions testing is mandatory. In public health, HBM is used in population screening to identify people at risk for developing a specific disease in an early stage. Tests are administered not only to individuals who have no apparent symptoms but also to population groups with potentially elevated risk. In environmental health, HBM is used together with other methods such as environmental monitoring and modelling for research, surveillance and awareness raising. In research studies, biomarkers are used to improve the knowledge on causal links between environmental factors and health, often addressing or including (early) effect biomarkers and genetic factors (biomarkers of susceptibility). HBM can support monitoring/surveillance of control the efficiency of political risk reduction measures, it can provide data for identification of needs and priority setting in policy, and contribute to a decision basis for management measures such as the establishment of limit values. (Choi et al., 2015).

HBM has become a primary tool for exposure assessment in a wide variety of contexts, including population monitoring at national level, and individual exposure assessments in the context of epidemiological research into potential adverse health effects of chemical exposures besides other due to improvements in analytical chemistry, including growing lab capacity and reductions in cost, coupled with the increasing focus on more subtle exposure levels that involve more complex exposure sources and routes of exposure (Aylward et al., 2014).

Occupational settings

When compared with environmental monitoring, biological monitoring provides additional information which can contribute for a more accurate occupational risk assessment at the individual and/or group level. Biomarkers are usually more specific and sensitive than most clinical tests, and therefore may be more effective for assessing a causal relationship between health impairment and chemical exposure when a change is first detected in exposed workers. Additionally, HBM can help to fill the gaps and give important information related to baseline exposure, or provide effect information needed to evaluate future exposure or health data. For instance, HBM before and after exposure can decide if exposure occurred, and if health monitoring should be conducted long-term due to possible health effects arising after a long period since exposure happened (Ladeira and Viegas, 2016).

HBM tools provide information for several actions related to occupational health interventions. Some of those are: determining if a specific exposure has occurred and if it implies a risk to workers' health, providing knowledge of exposure by all possible exposure routes, deciding if health outcomes can be expected from exposure; helping to clarify the results from clinical testing in some circumstances, recognizing the adequacy of control measures in place and helping to demonstrate the link between an occupational exposure and a health effect. Finally, the data obtained with HBM tools can support health monitoring and surveillance programmes, and identifying possible trends in exposure (Decker et al., 2013). HBM is useful in occupational health intervention, since it allows us to obtain detailed information about exposure and what can be expected regarding health effects resulting from exposure. Therefore, HBM can be considered an important tool for preventing exposure and exposure outcomes (Ladeira and Viegas, 2016).

HBM has a fundamental role in - but not limited to - occupational risk assessment. Experience in BM gained in the occupational setting has often been applied to assess (the effects of) human exposure to chemicals in the general environment. The use of biological fluids/tissues for the assessment of human exposure, effect or susceptibility to chemicals in the workplace represents, together with the underlying data (e.g. personal exposure and biological monitoring measurements, media-specific residue measurements, product use and time-activity information), a critical component of the occupational risk assessment process (ORA). Some of the most common benefits to ORA from the use of HBM data are the following: assessment of the total internal dose from all different routes of absorption (including inhalation, ingestion, dermal absorption) or from a single route of absorption when the others are excluded, quantitation of the internal dose from exposure to multiple chemicals, including assessment of interaction/competition in absorption, metabolism, excretion, separation between occupational and non-occupational exposure (e.g. pre-shift vs. post-shift values for volatile or, in general, short half-life chemicals), estimate of past exposure (e.g. PbU determination after Pb chelation by EDTA), assessment of protective equipment efficacy, ventilation, workplace amelioration, etc., assessment of individual susceptibility (e.g. genetic polymorphism, metabolic phenotype, DNA repair, etc.), assessment of early signs of disease (i.e. late biomarkers of effect) (Manno et al., 2010) .

CHALLENGES OF HUMAN BIOMONITORING

Ideally, both the biomarker of effect and the biomarker of exposure should be associated closely with the overall individual exposure so that it provides an exact measure of the internal dose or the individual health risk. It should be sensitive, specific, biologically relevant, feasible, practical, and inexpensive. Seldom does a biomarker meet all of these criteria - most biomarkers represent a compromise of these criteria (Choi et al., 2015).

As biomarker concentrations vary both within and between individuals, the variation in biomarker concentrations observed in a population biomonitoring study is not easy to interpret. In addition, the biological media selected for sampling affects biomarker concentrations independent of other factors. Finally, also disease states in particular renal or hepatic diseases impacts on biomarker variation (Aylward et al., 2014).

Benefits and limitations of different sample types, including blood, hair, urine or breast milk, have been well summarised (Paustenbach and Galbraith, 2006).

With low tissue levels in the ng/kg body weight range, the detection of biomarkers can be an analytical challenge that is additionally complicated by contamination and the potential instability of conjugates. With urine sampling, the type of sampling (spot urine, 24h urine or morning void) is an important factor as is the use of volume-based or creatinine-based urinary concentrations. Changes in protein/fat composition and enzyme activity impact on reliability of human milk samples. (Choi et al., 2015).

Internal concentrations, i.e. concentrations in fluids (urine, blood) or organs inside the body, are relevant to reflect the actual exposure (Ciffroy et al., 2016).

HBM data does not differentiate the exposure by source, and HBM alone cannot provide information about the source of exposure or how long a chemical has been in the body. For translation of HBM data into daily exposure estimates there is need of a detailed understanding of the potential analytical/methodological pitfalls and of the toxicokinetics of the individual chemical.

In addition, HBM raises important ethical and privacy issues due to the fact that it involves taking samples in humans and partly even needs to be invasive (blood samples) (Choi et al., 2015).

Occupational settings

HBM is one of the best, and probably the most rapidly growing, tool available today for the prevention of health effects resulting from occupational exposure to chemicals. Therefore, there is a growing attention towards scientific and ethical issues, and social implications that must include individual risk estimation, communication of epidemiological results, and translation of epidemiologic data into clinical or occupational health practice. The information about exposure and susceptibility gained by biological monitoring is personal and may predict health

impairments. Such information may therefore be discriminative and thus sensitive in relation to future opportunities in occupational health insurance. It is therefore of utmost importance to keep all information confidential. Since the primary purpose of biological monitoring is the protection of workers' health, situations must be avoided where the data gathered from exposure, effect or susceptibility biomarkers could result in an adverse impact on a worker's status of employment and/or quality of life. In principle, biological monitoring should not result in discrimination or reduction of job opportunities for the workers involved. (Ladeira and Viegas, 2016).

CONCLUSION

HBM is an efficient and cost-effective way to measure the level of exposure of the human body to xenobiotics, including occupational settings. Its advantage is the integration of all exposure routes and sources. Since HBM information is an integrated exposure finding, it offers the opportunity to trace and mimic a realistic exposure scenario. It reduces the number of assumptions that need to be done when estimating exposure, and thus helps to reduce the uncertainties in exposure science. Other advantages include the possibility of clarifying the human metabolism and mechanism of toxicity of contaminants, the possibility of its use in case of the majority of xenobiotics and the fact that it reflects the internal dose of the contaminant at the given point in time. However, further harmonization in the area of human biomonitoring is necessary to derive equivalents of markers of external exposure, and also to address the ethical and political aspects of its application. Nevertheless, the overall benefits of HBM in the context of a comprehensive approach to risk assessment as a step in the desired direction in minimizing the uncertainty and in approaching the real exposure are unquestionable.

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