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Discussion

Human biomonitoring as a tool to support chemicals regulation in the European Union

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At the World Summit on Sustainable Development in 2002 governments agreed "*to achieve, by 2020, that chemicals are used and producedin ways that lead to the minimization of significant adverse effects on human health and the environment*" (United Nations, 2002). This objective is reiterated in the European Union's (EU) 7th Environmental Action Programme (EU, 2013),

Recognising key gaps in the knowledge required to support actions on chemicals, the 7th Environmental Action Programme calls for efforts to address these gaps in order "*to accelerate decision making and to enable the further development of the chemicals-related acquis to better target areas of concern*". Human biomonitoring (HBM) is identifed as a tool that can serve the chemicals agenda by providing "*authorities with a more comprehensive view of actual exposure of the population to pollutants, especially sensitive groups such as children, and can provide better evidence from guiding appropriate responses*" (EU, 2013).

European citizens are exposed to a wide range of chemicals through their diet and through different environmental pathways, in their homes as well as through their use of consumer products and at the workplace. While not all chemicals pose a health risk, exposure to some can seriously damage human health (European Environment Agency (EEA) - Joint Research Centre (JRC), 2013).

Yet our current understanding of chemical risks to human health suffers limitations, both on the side of exposure and with regard to the associated health impacts. The effects of long-term and low-dose exposure to mixtures of chemicals still remain poorly understood. In addition, the potential human health impacts of chemicals used in large volumes deserve more attention. These knowledge gaps are particularly acute for a large number of emerging substances that are used in a wide range of products, some of which have been already detected in the environment (Brack et al., 2012).

HBM as a tool in understanding chemicals risk

HBM measures environmental chemicals and their metabolites in the human body, usually through analyses of blood, urine, hair, breast milk or tissues. It provides an aggregated measure of the level of exposure to chemicals through different exposure pathways. As such, HBM is an important tool for assessing exposures of the human population to chemicals, and in the case of harmful

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chemicals, estimating potential health risks linked to the exposure. Studies based on birth cohorts have the potential to elucidate causality between exposure to a particular pollutant and a health effect. Analysed over time, HBM data allow evaluation of trends in exposure and can be used to assess the efficiency of implemented policies (EEA-JRC, 2013).

The 7th Environmental Action Programme also recognises the increased vulnerability of sensitive population groups, such as children and pregnant women, to chemical risk and highlights the role that HBM can play in assessing the actual exposure of the population to pollutants (EU, 2013). HBM surveys can also provide evidence of elevated exposures in specific subpopulations, such as individuals in particular occupational settings, living close to pollution hot spots, or with specific dietary patterns (Lagerqvist et al., 2015). HBM has also been successfully applied in the early phases of disaster follow-up and aftercare to document any excess exposure among victims and relief workers (RIVM, 2001). Such evidence may inform the development of targeted new measures to protect specific sub-groups, ranging from awareness raising focused on exposure prevention to controls on upstream pollution sources.

In addition to clarifying and quantifying exposure to already known substances, HBM can also provide early warnings for exposure to emerging chemicals. New analytical and statistical tools can be implemented to identify emerging chemicals based on their physoicochemical properties or their biological actions. This can assist decision makers in managing chemical risks before they generate significant costs to health, through the prevention of large-scale exposure to toxic chemicals.

HBM also has the potential to enhance chemical risk assessments, by providing an important supplement to conventional sources of information (World Health Organization (WHO) Regional Office for Europe, 2015). Chemical risk assessors have traditionally used toxicological data from animal studies and safety assessment factors to derive intakes that can be associated with an acceptable level of risk. Risk assessment is then carried out by comparing these intake values, such as acceptable daily intake or tolerable daily intake (ADI/TDI), against intake values that are modelled based on measured or estimated exposure from inhalation, as well as from oral and dermal routes, where possible. HBM produces evidence of aggregate internal exposure from multiple routes and sources of exposure, so providing a basis for estimating total body burden. The application of HBM data to risk assessment can therefore help to reduce the uncertainty inherent in assessing exposure. In order to realise these benefits, collaborations between scientists involved in HBM, modellers and chemical risk assessors are required, to ensure that HBM data is tailored to serve risk assessments and to develop innovative risk assessment approaches. A recent review of the application of HBM to human exposure assessment for food safety identified potential added value, but found that further work is required to develop HBM-based guidance values and validated analytical methods, and to ensure that European surveys target substances of concern to policy makers (Choi et al., 2015).

The German HBM Commission derives HBM values with the aim of interpreting the HBM data in terms of the health impact of the exposure levels identified (Schulz et al., 2007; Umweltbundesamt 2016b). If necessary, HBM data may also be interpreted for specific sub-populations. The derivation of HBM values is based on both toxicological and epidemiological data. Two levels are defined, HBM I and HBM II. The HBM I value represents the concentration of a substance in human biological material below which, based on the current state of knowledge, there is no risk of adverse health effects. The HBM II value describes the concentration of a substance in human biological material above which adverse health effects are possible and, consequently, there is an acute need for the reduction of exposure based on biomedical advice. For levels between the HBM I value and the HBM II value, adverse health effects cannot be excluded anymore with a sufficient certainty. While HBM assessment values based on human exposure–response data remain the most highly valuable and interpretable assessment values, sufficient epidemiological data only exist for very few chemicals. As a consequence, efforts have been undertaken to translate substantiated tolerable intake values, such as ADI/TDI, provisional tolerable weekly intake (PTWI) and reference dose (RfD), into equivalent biomonitoring levels. Resulting HBM values allow for an assessment of the health impacts of the levels of pollutants or metabolites found in human samples, and can be used to assess whether regulatory or voluntary measures to reduce exposure are needed. In addition, HBM data can be used to assess whether existing risk management measures have actually resulted in reduced health risks for the European population (Apel et al., 2016).

HBM can also be used to better understand the health impacts that result from chemical exposure. By linking human biomonitoring data with data from health surveillance programmes, researchers can start to identify associations between chemical exposures and disease outcomes. Additional approaches, including longitudinal cohort studies, adverse outcome pathways and identification of biomarkers of effect, can be used to support a causal relationship between exposure and health effects. In cases where researchers find evidence of harm to health elicited by exposure to a chemical or a mixture of chemicals, such knowledge can provide powerful justification for actions to minimise exposure.

HBM as a tool to support policy making

In terms of how HBM can serve policy making, resulting evidence can be used to prioritise actions and measures for policy making, to evaluate the effectiveness of policy measures aimed at reducing exposure to hazardous substances, and to promote more comprehensive health impact assessments of policy options (Joas et al., 2012).

For example, the Global Monitoring Plan of the Stockholm Convention on persistent organic pollutants (United Nations Environment Programme (UNEP), 2016) aims to provide information for the assessment of long-term trends in the levels of POPs present in humans. In 2013, the WHO/UNEP Human Milk Survey provided results that indicate success in eliminating certain POP pesticides from human milk, linked to implementation of the Stockholm Convention on Persistent Organic Pollutants (UNEP, 2013).

At EU level, the Regulation concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) (EU, 2006) aims to improve the protection of human health and the environment through the better and earlier identification of the intrinsic properties of chemical substances. Information on exposure patterns and time trends in exposure across Europe for specific chemicals could be used to assess the efficacy of the restriction process under REACH. Restrictions may limit or ban the manufacture, placing on the market or use of a substance and serve to protect human health and the environment from unacceptable risks posed by chemicals.

Furthermore, under REACH health-based exposure limits known as Derived No-Effect Levels (DNELs) or Derived Minimal Effect Levels (DMELs) are to be derived for all substances subject to registration that are manufactured/imported/used in quantities of 10 tonnes or more per year. These are the levels above which humans should not be exposed. Researchers have suggested that these exposure limits might be translated into biomarker concentrations, known as biomonitoring equivalents (BEs) (Boogaard et al., 2012), which can then be used to interpret exposure levels on their potential impact on health on a population based level. As a prerequisite for using a DNEL/DMEL to derive a BE, the selection